



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 NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/945,588	07/31/2020	Ariane Lozac'hmeur	123138-5013-US	8972
43850	7590	09/25/2025	EXAMINER	
Morgan, Lewis & Bockius LLP (SF)			BAILEY, STEVEN WILLIAM	
One Market, Spear Street Tower, Suite 2800			ART UNIT	PAPER NUMBER
San Francisco, CA 94105			1687	
			NOTIFICATION DATE	DELIVERY MODE
			09/25/2025	ELECTRONIC

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

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

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

donald.mixon@morganlewis.com
sfipdocketing@morganlewis.com

Office Action Summary

Application No.

16/945,588

Applicant(s)

Lozac'hmeur et al.

Examiner

STEVEN W BAILEY

Art Unit

1687

AIA (First Inventor to File) 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 11 April 2025.

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

2a) ☐ This action is **FINAL**.

2b) ☒ This action is non-final.

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

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

Disposition of Claims*

5) ☒ Claim(s) 1-12,16,19-25,154-155,159 and 161-163 is/are pending in the application.

5a) Of the above claim(s) ____ is/are withdrawn from consideration.

6) ☐ Claim(s) ____ is/are allowed.

7) ☒ Claim(s) 1-12,16,19-25,154-155,159 and 161-163 is/are rejected.

8) ☒ Claim(s) 5,10,21 and 23 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)

3) ☐ Interview Summary (PTO-413)

Paper No(s)/Mail Date ____.

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)

4) ☐ Other: ____.

Paper No(s)/Mail Date ____.

DETAILED ACTION

1. The Applicant's response, received 11 April 2025 has been fully considered. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Notice of Pre-AIA or AIA Status

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

Continued Examination Under 37 CFR 1.114

3. 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.

4. Applicant's submission filed on 11 April 2025 has been entered.

Status of the Claims

5. Claims 1-12, 16, 19-25, 154, 155, 159, and 161-163 are pending.
6. Claims 1-12, 16, 19-25, 154, 155, 159, and 161-163 are rejected.
7. Claims 5, 10, 21, and 23 are objected to.

Priority

8. The effective filing date of the claimed invention is 01 August 2019.
9. Claims 1-12, 16, 19-25, 154, 155, 159, and 161-163 are given the benefit for priority to Provisional Application No. 62/881,845, filed 01 August 2019, Provisional Application No. 62/931,600, filed 06 November 2019, and Provisional Application No. 62/978,130, filed 18 February 2020.

Claim Interpretation

10. Claim 1 at step (D) is interpreted as reciting a product-by-process limitation with the product being the data of respective microsatellite loci obtained from biological samples of a cohort of at least 200 subjects, wherein the cohort consists of healthy subjects or subjects with stable microsatellite cancer. The claim is further interpreted to not require the processing steps of producing the product.

Claim Objections

11. The objection to claim 165 in the Office action mailed 13 January 2025 is withdrawn in view of the amendment received 11 April 2025.
12. The amendment received 11 April 2025 has been fully considered, however after further consideration new grounds for objection are raised in view of the amendment.
13. Claims 5 and 10 are objected to because of the following informalities: The claims recite "the subject" in line four, however claim 1, from which they depend, recites "test subject." Therefore, claims 5 and 10 should be amended to recite "the test subject."

Art Unit: 1687

14. Claim 21 is objected to because of the following informalities: The claim references the symbol or marker "(iii)" with regard the biological samples from the cohort, however claim 1 at step (D) does not recite the symbols ore markers "(i)" or "(ii)."
15. Claim 23 is objected to because of the following informalities: The claim references the "(F) determining" step, however the claim should be referencing the "(H) determining" step in view of the amendment.
16. Appropriate correction is required.

Claim Rejections - 35 USC § 112

17. The amendment received 11 April 2025 has been fully considered, however after further consideration new grounds for rejection are raised in view of the amendment.
18. 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.
19. 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.
20. Claims 2, 21, and 161 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.
21. Claim 2 recites the limitation "the human reference genome" in nine. There is insufficient antecedent basis for this limitation in the claim.
22. Claim 21 is indefinite for reciting the limitation "wherein the biological samples from the cohort further include (iii) solid tumor samples from training subjects with

unstable microsatellite cancer” because claim 1 recites “wherein the cohort **consists** of healthy subjects or subjects with stable microsatellite cancer” (emphasis added) and therefore claim 1 is closed to other types of subjects, i.e., unstable microsatellite cancer, and thus, it is unclear as to whether claim 21 is referencing the same cohort as recited at step (D) of claim 1, or else a different cohort altogether, or else the cohort at step (D) does not consist of healthy or stable microsatellite cancer subjects.

23. Claim 161 recites the limitation “the human microsatellite loci selected from the group” in two. There is insufficient antecedent basis for this limitation in the claim.

24. The following is a quotation of 35 U.S.C. 112(d):

(d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

25. The following is a quotation of pre-AIA 35 U.S.C. 112, fourth paragraph:

Subject to the following paragraph [i.e., the fifth paragraph of pre-AIA 35 U.S.C. 112], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

26. Claims 21 and 154 are rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C.

112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends.

27. Claim 21 recites “wherein the biological samples from the cohort further include (iii) solid tumor samples from training subjects with unstable microsatellite cancer,” and therefore is of improper dependent form for no longer requiring that the cohort at step

Art Unit: 1687

(D) of claim 1 “consists of the healthy and stable cancer subjects,” because claim 21 is requiring that the cohort includes subjects with unstable cancer.

28. Claim 154 recites limitations that are recited at step (A) in claim 1, and therefore is of improper dependent form for failing to further limit the subject matter of the claim upon which it depends.

29. Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

Claim Rejections - 35 USC § 101

30. The rejection of claims 1-12, 16, 19-25, 154, 155, 159, and 161-165 under 35 U.S.C. 101 in the Office action mailed 13 January 2025 is maintained with modification in view of the amendment received 11 April 2025.

31. 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.

32. Claims 1-12, 16, 19-25, 154, 155, 159, and 161-163 are rejected under 35 U.S.C. 101 because the claimed invention is directed to an abstract idea and a law of nature without significantly more. The claims recite: (a) mathematical concepts, (e.g., mathematical relationships, formulas or equations, mathematical calculations); (b) mental processes, i.e., concepts performed in the human mind, (e.g., observation, evaluation, judgement, opinion); and (c) a law of nature (naturally occurring relationship).

33. Subject matter eligibility evaluation in accordance with MPEP 2106.

34. **Eligibility Step 1:** Claims 1-12, 16, 19-25, 154, 155, 159, and 161-163 are directed to a method (process) of determining a microsatellite instability (MSI) status of a test subject.

35. Therefore, the claims are encompassed by the categories of statutory subject matter, and thus satisfy subject matter eligibility requirements under Eligibility Step 1.

36. **[Step 1: YES]**

37. **Eligibility Step 2A:** First it is determined in Prong One whether a claim recites a judicial exception, and if so, then it is determined in Prong Two whether the recited judicial exception is integrated into a practical application of that exception.

38. **Eligibility Step 2A Prong One:** In determining whether a claim is directed to a judicial exception, examination is performed that analyzes whether the claim recites a judicial exception, i.e., whether a law of nature, natural phenomenon, or abstract idea is set forth or described in the claim.

39. Independent claim 1 recites the following steps which fall within the mental processes and/or mathematical concepts groupings of abstract ideas:

- at step (C) mapping the set of raw sequence reads against a reference genome for the species of the test subject, thereby obtaining a plurality of aligned nucleotide sequences, wherein the plurality of aligned nucleotide sequences comprises at least 15,000 nucleotide sequences mapped to a respective predetermined microsatellite loci in the plurality of predetermined microsatellite loci and wherein the plurality of aligned nucleotide sequences has an average length of at least 50 nucleotides (i.e., mental processes);

- at step (D) determining, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, a corresponding density estimate of a number of repeat units in the respective microsatellite locus using a number of repeat units in each nucleotide sequence in a corresponding plurality of nucleotide sequences that map to the respective microsatellite locus obtained from biological samples of a cohort of at least 200 subjects, wherein the cohort consists of healthy subjects or subjects with stable microsatellite cancer, thereby determining at least 30 density estimates (i.e., mental processes and mathematical concepts);
- at step (E) converting each corresponding nucleotide sequence in the plurality of aligned nucleotide sequences to a likelihood score using (i) the corresponding density estimate of a number of repeat units in the respective microsatellite locus, which the corresponding nucleotide sequence maps to, from among the at least 30 density estimates and (ii) a number of repeat units in the corresponding nucleotide sequence, thereby obtaining a plurality of likelihood scores, each likelihood score in the plurality of likelihood scores associated with a corresponding microsatellite locus in the plurality of predetermined microsatellite loci (i.e., mental processes and mathematical concepts);
- at step (F) determining a respective value for a likelihood of microsatellite locus stability for each respective microsatellite locus in the plurality of predetermined microsatellite loci by taking a measure of central tendency of those likelihood scores in the plurality of likelihood scores that are associated with the respective microsatellite locus (i.e., mental processes and mathematical concepts);

- at step (G) using one or more corresponding metric values for one or more metrics for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the one or more metrics including the likelihood of microsatellite locus stability of the respective microsatellite locus, to determine a proportion of the plurality of predetermined microsatellite loci that are unstable (i.e., mental processes and mathematical concepts); and
- at step (H) determining the MSI status of the test subject from the proportion of the plurality of predetermined microsatellite loci that are unstable (i.e., mental processes and mathematical concepts).

40. Independent claim 1 recites a law of nature by associating an individual's genomic data (microsatellites, i.e., short, repeated sequences of DNA) with a phenotype (microsatellite instability), i.e., a genotype-phenotype correlation (MPEP 2106.04(b)).

41. Dependent claims 2-12, 16, 19-25, 161, and 162 recite the following steps which fall within the mental processes and/or mathematical concepts groupings of abstract ideas, as noted below.

42. Dependent claim 2 further recites:

- wherein the mapping at step (C) comprises:
 - aligning each respective raw sequence read in the set of raw sequence reads to the reference genome for the test subject, thereby obtaining a corresponding set of aligned raw sequence reads for the respective DNA fragment (i.e., mental processes); and

- collapsing the corresponding set of aligned raw sequence reads for the respective DNA fragment into a corresponding nucleotide sequence for the respective DNA fragment that has been aligned to the human reference genome, thereby obtaining the plurality of aligned nucleotide sequences (i.e., mental processes).

43. Dependent claim 3 further recites:

- the plurality of aligned nucleotide sequences comprises at least 250,000 aligned nucleotide sequences (i.e., mental processes).

44. Dependent claim 4 further recites:

- the one or more metrics further comprises a percentage score (i.e., mental processes and mathematical concepts); and
- the corresponding metric value for the percentage score is the percentage of aligned nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus (i.e., mental processes and mathematical concepts).

45. Dependent claim 5 further recites:

- for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject (i.e., mental processes).

46. Dependent claim 6 further recites:

- for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values, wherein each respective reference value in the plurality of reference values is determined at least in part based on a distribution of the number of repeat units at the respective microsatellite locus in a respective reference sample in a plurality of reference standards (i.e., mental processes and mathematical concepts).

47. Dependent claim 7 further recites:

- for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus (i.e., mental processes and mathematical concepts).

48. Dependent claim 8 further recites:

- the one or more metrics further comprises a lower mean score (i.e., mental processes and mathematical concepts); and
- the corresponding metric value for the lower mean score is determined at least in part by the mean number of repeat units in aligned nucleotide sequences, in the plurality of aligned nucleotides, mapping to the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat

units representative of a stable construct at the respective microsatellite locus (i.e., mental processes and mathematical concepts).

49. Dependent claim 9 further recites:

- the mean number of repeat units is normalized by the reference number of repeat units representative of a stable construct at the respective microsatellite locus (i.e., mental processes and mathematical concepts).

50. Dependent claim 10 further recites:

- for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject (i.e., mental processes and mathematical concepts).

51. Dependent claim 11 further recites:

- for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values, wherein each respective reference value in the plurality of reference values is determined at least in part based on a distribution of the number of repeat units at the respective microsatellite locus in a respective reference sample in a plurality of reference samples (i.e., mental processes and mathematical concepts).

52. Dependent claim 12 further recites:

- for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable

construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus (i.e., mental processes and mathematical concepts).

53. Dependent claim 16 further recites:

- the one or more corresponding metric values further comprises a corresponding standard deviation of the number of repeat units in the aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, mapping to the respective microsatellite locus (i.e., mental processes and mathematical concepts).

54. Dependent claim 19 further recites:

- the using (G) comprises inputting, for each respective microsatellite locus in the plurality of microsatellite loci, the corresponding metric value for each of the one or more metrics to a classifier that distinguishes between stable and unstable microsatellite loci (mental processes).

55. Dependent claim 20 further recites:

- the biological samples from the cohort include both (i) solid tumor samples from training subjects with stable microsatellite cancer and (ii) normal tissue samples (i.e., mental processes).

56. Dependent claim 21 further recites:

- the biological samples from the cohort further include (iii) solid tumor samples from training subjects with unstable microsatellite cancer (i.e., mental processes).

57. Dependent claim 22 further recites:

Art Unit: 1687

- the classifier comprises a k-nearest neighbors classifier (i.e., mental processes and mathematical concepts).

58. Dependent claim 23 further recites:

- the classifier assigns a stability status selected from unstable and stable to each respective microsatellite locus in the plurality of predetermined microsatellite loci (i.e., mental processes), and the (F) determining classifies the subject as having a high level of microsatellite instability when at least a threshold proportion of microsatellite loci are assigned a status of unstable (i.e., mental processes and mathematical concepts).

59. Dependent claim 24 further recites:

- the threshold proportion of microsatellite loci is at least 30% of the plurality of predetermined microsatellite loci (i.e., mental processes and mathematical concepts).

60. Dependent claim 25 further recites:

- the threshold proportion of microsatellite loci is at least 50% of the plurality of predetermined microsatellite loci (i.e., mental processes and mathematical concepts).

61. Dependent claim 161 further recites:

- the plurality of predetermined microsatellite loci comprises at least 10 of the human microsatellite loci selected from the group listed in the claim (i.e., mental processes).

62. Dependent claim 162 further recites:

- the plurality of predetermined microsatellite loci comprises at least all of the human microsatellite loci from the group listed in the claim (i.e., mental processes).

63. The abstract ideas recited in the claims are evaluated under the broadest reasonable interpretation (BRI) of the claim limitations when read in light of and consistent with the specification. As noted in the foregoing section, the claims are determined to contain limitations that can practically be performed in the human mind with the aid of a pen and paper (e.g., mapping sequence data to a reference sequence; determining density estimations; and calculating likelihood scores; are steps that can be practically performed in the human mind with the aid of pen and paper), and therefore recite judicial exceptions from the mental process grouping of abstract ideas.

Additionally, the recited limitations that are identified as judicial exceptions from the mathematical concepts grouping of abstract ideas (e.g., determining density estimations; generating likelihood scores; measuring central tendencies of the likelihood scores; and determining a proportion of loci that are unstable (e.g., Specification at para. [0397])) are abstract ideas irrespective of whether or not the limitations are practical to perform in the human mind. Furthermore, a law of nature correlating a genotype-phenotype association is identified at Eligibility Step 2A Prong One.

64. Therefore, claims 1-12, 16, 19-25, 154, 155, 159, and 161-163 recite an abstract idea and a law of nature.

65. **[Step 2A Prong One: YES]**

66. **Eligibility Step 2A Prong Two:** In determining whether a claim is directed to a judicial exception, further examination is performed that analyzes if the claim recites additional elements that when examined as a whole integrates the judicial exception(s) into a practical application (MPEP 2106.04(d)). A claim that integrates a judicial exception into a practical application will apply, rely on, or use the judicial exception in a manner that imposes a meaningful limit on the judicial exception. The claimed additional elements are analyzed to determine if the abstract idea is integrated into a practical application (MPEP 2106.04(d)(I); MPEP 2106.05(a-h)). If the claim contains no additional elements beyond the abstract idea, the claim fails to integrate the abstract idea into a practical application (MPEP 2106.04(d)(III)).

67. The judicial exceptions identified in Eligibility Step 2A Prong One are not integrated into a practical application because of the reasons noted below.

68. Dependent claims 2-12, 16, 19-25, 161, and 162 do not recite any elements in addition to the judicial exception, and thus are part of the judicial exception.

69. The additional elements in independent claim 1 include:

- step (A) hybridizing cell-free DNA fragments from a liquid biopsy sample from a test subject to a plurality of nucleic acid capture probes to generate a plurality of cell-free DNA fragments enriched, relative to all cell-free DNA fragments in the liquid biopsy sample, for a set of cell-free DNA fragments encompassing a plurality of predetermined microsatellite loci, wherein the plurality of nucleic acid capture probes collectively hybridize to at least 30 predetermined microsatellite loci and wherein a number of repeats within each microsatellite locus in the

plurality of predetermined microsatellite loci in the germ line of the test subject is unknown;

- step (B) sequencing the plurality of cell-free DNA fragments to generate a set of raw sequence reads; and
- step (D) a computer system comprising at least one processor and a memory for storing.

70. The additional elements in dependent claims 154, 155, 159, and 163 include:

- the plurality of cell-free DNA fragments from the liquid biopsy sample are enriched, relative to all cell-free DNA fragments in the liquid biopsy sample, for a set of cell-free DNA fragments that comprises the plurality of predetermined microsatellite loci (claim 154);
- the plurality of aligned sequence reads represents, on average, greater than 1000X sequence depth for each microsatellite locus in the plurality of predetermined microsatellite loci and the plurality of aligned nucleotide sequences comprises at least 30000 nucleotide sequences (claim 155);
- the liquid biopsy sample is a blood or blood plasma sample (claim 159); and
- the subject is a human (claim 163).

71. The additional element of a computer system comprising at least one processor and a memory for storing (claim 1) invokes a computer merely as a tool for use in the claimed process, i.e., performing the abstract ideas, and therefore is not an improvement to computer functionality itself, or an improvement to any other technology or technical field, and therefore, does not integrate the judicial exceptions into a practical application (see MPEP 2106.04(d)(1)).

Art Unit: 1687

72. The additional elements of hybridizing cell-free DNA fragments from a liquid biopsy sample from a test subject to a plurality of nucleic acid capture probes to generate a plurality of cell-free DNA fragments enriched, relative to all cell-free DNA fragments in the liquid biopsy sample, for a set of cell-free DNA fragments encompassing a plurality of predetermined microsatellite loci (claims 1 and 154); sequencing the plurality of cell-free DNA fragments to generate a set of raw sequence reads (claim 1); the plurality of aligned sequence reads represents, on average, greater than 1000X sequence depth for each microsatellite locus in the plurality of predetermined microsatellite loci and the plurality of aligned nucleotide sequences comprises at least 30000 nucleotide sequences (claim 155); the liquid biopsy sample is a blood or blood plasma sample (claim 159); and the subject is a human (claim 163); are steps in the process of gathering data for use in the claimed process, and therefore do not add more than insignificant extra-solution activity to the recited judicial exceptions (see MPEP 2106.05(g)).

73. Thus, the additionally recited elements merely invoke a computer as a tool, and/or amount to insignificant extra-solution data gathering activity, and as such, when all limitations in claims 1-12, 16, 19-25, 154, 155, 159, and 161-163 have been **considered as a whole**, the claims are deemed to not recite any additional elements that would integrate a judicial exception into a practical application, and therefore claims 1-12, 16, 19-25, 154, 155, 159, and 161-163 are directed to an abstract idea (MPEP 2106.04(d)).

74. **[Step 2A Prong Two: NO]**

75. **Eligibility Step 2B:** Because the claims recite an abstract idea, and do not integrate that abstract idea into a practical application, the claims are probed for a specific inventive concept. The judicial exception alone cannot provide that inventive concept or practical application (MPEP 2106.05). Identifying whether the additional elements beyond the abstract idea amount to such an inventive concept requires considering the additional elements individually and in combination to determine if they amount to significantly more than the judicial exception (MPEP 2106.05A i-vi).

76. The claims do not include any additional elements that are sufficient to amount to significantly more than the judicial exception(s) because of the reasons noted below.

77. Dependent claims 2-12, 16, 19-25, 161, and 162 do not recite any elements in addition to the judicial exceptions.

78. The additional elements recited in independent claim 1 and dependent claims 154, 155, 159, and 163 are identified above, and carried over from Step 2A: Prong Two along with their conclusions for analysis at Step 2B. Any additional element or combination of elements that was considered to be insignificant extra-solution activity at Step 2A: Prong Two was re-evaluated at Step 2B, because if such re-evaluation finds that the element is unconventional or otherwise more than what is well-understood, routine, conventional activity in the field, this finding may indicate that the additional element is no longer considered to be insignificant; and all additional elements and combination of elements were evaluated to determine whether any additional elements or combination of elements are other than what is well-understood, routine, conventional activity in the field, or simply append well-understood, routine,

Art Unit: 1687

conventional activities previously known to the industry, specified at a high level of generality, to the judicial exception, per MPEP 2106.05(d).

79. The additional elements of a computer system comprising at least one processor and a memory for storing (claim 1); are conventional (see MPEP at 2106.05(b) and 2106.05(d)(II) regarding conventionality of computer components and computer processes).

80. The additional element of hybridizing cell-free DNA fragments from a liquid biopsy sample from a test subject to a plurality of nucleic acid capture probes to generate a plurality of cell-free DNA fragments enriched, relative to all cell-free DNA fragments in the liquid biopsy sample; is conventional. Evidence for the conventionality is shown by Osumi et al. (Cancer Science, 2019 (First published 11 February 2019), Vol. 110, No. 4, pp. 1148-1155, newly cited). Osumi et al. reviews the clinical utility of circulating tumor DNA (ctDNA) for colorectal cancer (Title) and provides an overview of the characteristics of ctDNA with a focus on detection methods for ctDNA, and the feasibility of use of ctDNA to monitor tumor dynamics for patients with colorectal cancer (Abstract). Osumi et al. further shows that the measurement of biomarkers before treatment is of importance in the optimum management of patients with colorectal cancer (CRC) and that tissue-based biomarkers such as *RAS* mutation, *BRAF* mutation, *HER2* amplification, and microsatellite instability are used to determine prognosis and guide systemic therapy (page 1148, col. 1, Introduction). Osumi et al. further shows that compared with a classic biopsy, liquid biopsies are more convenient, and present minimal procedural risk to the patient, and that ctDNA has potential clinical utility as a key component of liquid biopsies (page 1148, col. 2, Introduction). Osumi et al. further

Art Unit: 1687

shows that capture-based next generation sequencing (NGS) has the ability to enrich genomic regions of interest by hybridizing target genes/regions to antisense oligonucleotides before sequence, and that this approach allows for the agnostic analysis of large portions of the genome and can identify multiple mutations with increased sensitivity (page 1150, col. 1, para. 1) and further shows various technologies for detecting ctDNA using targeted sequencing approaches (Table 2).

81. The additional elements of sequencing the plurality of cell-free DNA fragments to generate a set of raw sequence reads (claim 1); the plurality of aligned sequence reads represents, on average, greater than 1000X sequence depth for each microsatellite locus in the plurality of predetermined microsatellite loci and the plurality of aligned nucleotide sequences comprises at least 30000 nucleotide sequences (claim 155); the liquid biopsy sample is a blood or blood plasma sample (claim 159); and the subject is a human (claim 163); are conventional. Evidence for the conventionality is shown by Morganti et al. (Critical Reviews in Oncology, 2019 (Published January 2019), Vol. 133, pp. 171-182, as cited in the Office action mailed 20 September 2023). Morganti et al. reviews the complexity of genome sequencing and reporting, particularly focusing on next-generation sequencing (NGS) technologies and the implementation of precision medicine (Title; and Abstract). Morganti et al. shows that NGS technologies allow for the obtainment of extensive genetic information from liquid biopsies, and the obtainment of genetic material for sequencing from circulating tumor cells (CTCs) and circulating cell-free tumor DNA (ctDNA; page 172, col. 2, para, 1; and page 177, col. 2, Section 4.3). Morganti et al. further reviews NGS sequencing (page 173, Section 2.2) and NGS methods (page 174, Section 3), and further still, reviews advantages of NGS

Art Unit: 1687

methodology with regard to microsatellite instability analyses (page 177, col. 1, Section 4.2.2). Morganti et al. further shows that liquid biopsies are non-invasive blood tests (page 177, col. 2, Section 4.3); next-generation sequencing platforms that produce at least 30,000 reads per run (Table 2); and genome analysis by targeted sequencing, in which specific regions of interest are isolated and sequenced, and gene panels allowing selected genes to be sequence with a 500-1000X coverage (page 174, col. 2, para. 2).

82. Therefore, when taken alone, all additional elements in claims 1-12, 16, 19-25, 154, 155, 159, and 161-163 do not amount to significantly more than the above-identified judicial exception(s). Even when evaluated as a combination, the additional elements fail to transform the exception(s) into a patent-eligible application of that exception. Thus, claims 1-12, 16, 19-25, 154, 155, 159, and 161-163 are deemed to not contribute an inventive concept, i.e., amount to significantly more than the judicial exception(s) (MPEP 2106.05(II)).

83. **[Step 2B: NO]**

Response to Arguments

84. The Applicant's arguments/remarks received 11 April 2025 have been fully considered, but are not persuasive.

85. The Applicant states on page 12 of the Remarks (para. 2) that the claims of the present application are not directed to an abstract idea and are thus patent eligible because (i) they integrate any alleged abstract idea into the practical application of a non-invasive determination of the MSI status of a cancer in a test subject from a liquid biopsy sample, and (ii) they improve the technical field of laboratory diagnostic testing by adding specific limitations and/or adding unconventional steps that confine the claims

Art Unit: 1687

to the particular useful application and provide personalized, precision medicine based laboratory diagnostic testing results. The Applicant further states (para. 3) that the claimed method includes a series of steps and specific limitations that result in a non-invasive determination of the MSI status of a cancer in a test subject. The Applicant further states that while the claimed method may involve judicial exceptions, the result of these judicial exceptions is a non-invasive determination of the MSI status of a cancer in a test subject, and that this has nothing to do with the identified judicial exceptions, and that moreover, the process that enables the non-invasive determination of the MSI status of a cancer in a test subject is not an insignificant extra-solution activity because, as discussed below, conventional processes do not satisfactorily allow determination of the MSI status of a cancer from a liquid biopsy sample. The Applicant further presents (pages 12-14) claim 1 with bolded passages because of their significance in the Applicant's arguments for patentability of the claim. The Applicant further states (page 14, para. 2) that as can be seen, claim 1 is directed to a non-invasive determination of the MSI status of a test subject from a liquid biopsy sample, and that the claimed invention integrates the alleged judicial exception into a practical application that addresses technical problem(s) in the field of diagnostic testing, and provides enhancement in the technical field of personalizing diagnostic testing results. On pages 14-16 of the Remarks, the Applicant points to the Specification at paragraphs [0008] – [0013] for explanations of the challenges and technical problems addressed by claim 1, and further states (page 16, para. 2) that claim 1 addresses the technical problems described in the Applicant's specification and thus enables the practical

Art Unit: 1687

application of determining the MSI status of a cancer in a test subject in a non-invasive fashion.

86. These arguments are not persuasive, because first, regarding the Applicant's assertion that the instant claims provide an improvement that integrates the recited judicial exceptions into a practical application (i.e., Eligibility Step 2A Prong Two), the evaluation of whether a claim as a whole integrates the recited judicial exception into a practical application of the exception requires determining whether the claim as a whole applies, relies on, or uses the judicial exception(s) in a manner that imposes a meaningful limit on the judicial exception by: (1) identifying whether there are any additional elements recited in the claim beyond the judicial exception(s); and (2) evaluating those additional elements individually and in combination to determine whether they integrate the exception into a practical application, using one or more of the considerations introduced in MPEP 2106.04(d) subsection I, and discussed in more detail in MPEP §§ 2106.04(d)(1), 2106.04(d)(2), 2106.05(a) through (c) and 2106.05(e) through (h). As noted in the rejection above, the additional elements recited at steps (A) and (B) of claim 1 are steps used in the gathering of the data for use in the claimed process, and the additional elements recited at step (D) of claim 1 merely invoke computer components for executing the judicial exceptions recited in the claimed process. Second, the additional elements recited at steps (A) and (B) of the claimed process, e.g., liquid biopsies (as opposed to tissue biopsies) and hybrid-capture enrichment of cell-free DNA fragments, are conventional additional elements, as discussed in the rejection above. Third, an indication that the claimed invention provides an improvement can include a discussion in the specification that identifies a technical

Art Unit: 1687

problem and explains the details of an unconventional technical solution expressed in the claim, or identifies technical improvements realized by the claim over the prior art (MPEP 2106.05(a)), however as previously noted in this response to arguments and also in the discussion at 2B in the above rejection, the instant claims do not recite any additional elements that are unconventional, and thus, the instant claimed improvement to the technical field of laboratory diagnostic testing is a purported improvement to the abstract idea (determining microsatellite instability (MSI) status), and not an improvement to computer functionality itself, or an improvement to another technology or technical field.

87. On page 16 of the Remarks, the Applicant points to the MPEP at 2106.05 (i.e., Eligibility Step 2B) and states on page 17 (para. 2) that thus, the claim has to be considered as a whole and evaluated as an ordered combination. The Applicant further states (para. 3) that in the instant case, claim 1 recites a series of steps in an order and includes specific elements (e.g., hybridizing cell-free DNA fragments to capture probes to enrich for cell-free DNA fragments encompassing a plurality of microsatellite loci, sequencing the enriched cell-free DNA fragments, mapping sequence reads, etc.) that interact and impact each other, and that these steps, in particular when viewed in the ordered combination and along with the specific elements recited in these steps, imposes a meaningful limit on any recited judicial exception, sufficiently limiting the use of the recited judicial exception to the practical application of non-invasively determining the MSI status of a cancer in a test subject. The Applicant further states (para. 4) that accordingly, when viewed as a whole, the claimed method integrates any alleged judicial exception into a practical application that improves clinical oncology by reducing

Art Unit: 1687

the time, cost, and invasiveness of testing for MSI status, and therefore claim 1 is patent eligible under the second prong of Step 2A because the claim is not directed to an abstract idea.

88. These arguments are not persuasive, because first, with regard to Eligibility Step 2A Prong Two (addressed in the foregoing response to arguments), when claim 1 is considered as a whole, there are no additional elements that would integrate the recited judicial exceptions into a practical application because the additional elements recited at steps (A) and (B) of claim 1 are steps used in the gathering of the data for use in the claimed process, and the additional elements recited at step (D) of claim 1 merely invoke computer components for executing the judicial exceptions recited in the claimed process. Second, the additional elements recited at steps (A) and (B) of the claimed process, e.g., liquid biopsies (as opposed to tissue biopsies) and hybrid-capture enrichment of cell-free DNA fragments, are conventional additional elements, as discussed in the rejection above, and thus, the instant claimed improvement to clinical oncology by reducing the time, cost, and invasiveness of testing for MSI status is a purported improvement to the abstract idea (determining microsatellite instability (MSI) status), and not an improvement to computer functionality itself, or an improvement to another technology or technical field. Third, regarding Eligibility Step 2B, whether a claim amounts to significantly more involves the search for an inventive concept, and an inventive concept is furnished by an element of combination of elements that is recited in the claim in addition to (beyond) the judicial exception, and is sufficient to ensure that the claim as a whole amounts to significantly more than the judicial exception itself (MPEP 2106.05 I.). Step 2B asks: Does the claim recite additional elements that

Art Unit: 1687

amount to significantly more than the judicial exception? Examiners should answer this question by first identifying whether there are any additional elements (features/limitations/steps) recited in the claim beyond the judicial exception(s), and then evaluating those additional elements individually **and in combination** to determine whether they contribute an inventive concept (*i.e.*, amount to significantly more than the judicial exception(s)). As noted in the rejection above, and in the foregoing responses to arguments, the additional elements recited at steps (A) and (B) of claim 1 are steps used in the gathering of the data for use in the claimed process, and the additional elements recited at step (D) of claim 1 merely invoke computer components for executing the judicial exceptions recited in the claimed process, and thus, when the additional elements are evaluated individually and in combination (*i.e.*, as an ordered combination), the claim is determined to not recite any additional elements that would amount to an inventive concept, *i.e.*, amount to significantly more than the judicial exceptions (MPEP 2106.05(II)). Therefore, the instant claimed ordered combination of steps in determining the MSI status of a cancer in a test subject is a purported improvement to the abstract idea (determining microsatellite instability (MSI) status), and not an improvement to computer functionality itself, or an improvement to another technology or technical field.

89. The Applicant states on page 18 (paras. 1 and 2) of the Remarks that the claims recite non-routine and unconventional processes that add inventive concepts and amount to significantly more than any alleged judicial exception and are thus patentable under at least Step 2B. The Applicant further reiterates (paras. 3-5) the claim 1 limitations at steps (A), (B), and (C) and further states (para. 4) that as an initial matter,

Art Unit: 1687

the mere use of a liquid biopsy assay for determining the MSI status of a cancer in a patient was unconventional at the time the present application was filed, as evidenced by paragraphs [0008] and [0024] of the Applicant's specification, which state that at the time the present application was filed, determining the MSI status of a cancer was conventionally performed by evaluating DNA from a solid tumor biopsy sample. The Applicant further states (page 19, bottom) that considered alone, the use of a liquid biopsy sample to generate data that can be used to determine the MSI status of a cancer in a test subject, as recited in the ordered combination of steps (A)-(C) of amended claim 1, add inventive concepts and amount to significantly more than any alleged judicial exception. The Applicant further states that moreover, the additional recitations in step (A) of amended claim 1 detailing how this data is generated further evidences the non-conventionality of these steps. The Applicant further states that specifically, step (A) recites use of a plurality of nucleic acid capture probes that collectively hybridize to at least 30 predetermined microsatellite loci and wherein a number of repeats within each microsatellite locus in the plurality of predetermined microsatellite loci in the germ line of the test subject is unknown, and that both the use of capture probes against a plurality of microsatellite loci to enrich for cell-free DNA fragments encompassing microsatellite loci and the determination of MSI status in the absence of knowledge about the number of repeats within each microsatellite locus in the germ line of the subject were non-conventional at the time of the filing of the present application. The Applicant points to *Bascom Global Internet Services v. AT&T Mobility*, and further states (page 20, para. 2) that an inventive concept can be found in the non-conventional and non-generic arrangement of known conventional pieces, and that

Art Unit: 1687

representative claim 1 as a whole recites a unique and non-invasive method for determining the MSI status of a cancer in a test subject, and the claimed method solves the various problems associated with conventional determination of MSI status using solid tumor samples, and that additionally, the claims amount to an inventive concept because they are not taught by the relevant art. Finally, the Applicant states (para. 3) that for at least the reasons stated in *Bascom Global Internet Services v. AT&T Mobility*, the claims are patent-eligible because the particular arrangements of elements is a technical improvement over prior ways, which results in a non-invasive method for determining the MSI status of a cancer in a test subject.

90. These arguments are not persuasive, because first, the additional elements recited at steps (A), (B), and (D) of claim 1 are conventional additional elements, as discussed at Step 2B in the rejection above, and further discussed in the Osumi et al. reference. Second, step (C) of claim 1 does not recite any additional elements, also as shown in the rejection above. Third, regarding the argument that using a liquid biopsy assay for determining the MSI status of a cancer in a patient was unconventional at the time the present application was filed, as evidenced by paragraphs [0008] and [0024] of the Applicant's specification, which states that at the time the present application was filed, determining the MSI status of a cancer was conventionally performed by evaluating DNA from a solid tumor biopsy sample, it is noted that the discussion in the foregoing responses to arguments and in the above rejection explain that a liquid biopsy is conventional, as is a targeted-capture sequencing assay that is utilized to sequence particular identified genomic loci. Additionally, it is further noted that the actual loci being targeted are part of the law of nature and the sequenced data of the targeted loci

comprise the abstract idea. Fourth, and as discussed above, an inventive concept is furnished by an element or combination of elements that is recited in the claim in addition to (beyond) the judicial exception (i.e., an additional element), and is sufficient to ensure that the claim as a whole amounts to significantly more than the judicial exception itself. However, the additional elements recited in claim 1, (hybrid-capture targeted enrichment of cell-free DNA fragments obtained from a liquid biopsy and genomic sequencing) when considered individually and as an ordered combination, are conventional additional elements, and therefore do not provide an inventive concept, as discussed above. Fifth, the judicial exceptions (i.e., determining MSI status) whether considered individually or as an ordered combination, cannot provide the inventive concept (MPEP 2106.05 I.). Sixth, the search for an inventive concept is different from an anticipation analysis under 35 U.S.C. 102 or an obviousness analysis under 35 U.S.C. 103, and because there are separate and distinct requirements from eligibility, patentability of the claimed invention under 35 U.S.C. 102 and 103 with respect to the prior art is neither required for, nor a guarantee of, patent eligibility under 35 U.S.C. 101 (MPEP 2106.05(I)). Seventh, the claimed technical improvement in the particular arrangement of elements is a purported improvement to the abstract idea (determining microsatellite instability (MSI) status), and not an improvement to computer functionality itself, or an improvement to another technology or technical field.

Conclusion

91. **No claims are allowed.**

Art Unit: 1687

92. This Office action is a Non-Final action. A shortened statutory period for reply to this action is set to expire **THREE MONTHS** from the mailing date of this application.

Inquiries

93. Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN W. BAILEY whose telephone number is (571)272-8170. The examiner can normally be reached Mon - Fri. 1000 - 1800.

94. 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>.

95. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, KARLHEINZ 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.

96. 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

Art Unit: 1687

(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.

/S.W.B./

Examiner, Art Unit 1687

/KAITLYN L MINCHELLA/

Primary Examiner, Art Unit 1685

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A method of determining a microsatellite instability (MSI) status of a test subject, the method comprising:

~~at a computer system having one or more processors, and memory storing one or more programs for execution by the one or more processors:~~

(A) hybridizing cell-free DNA fragments from a liquid biopsy sample from a test subject to a plurality of nucleic acid capture probes to generate a plurality of cell-free DNA fragments enriched, relative to all cell-free DNA fragments in the liquid biopsy sample, for a set of cell-free DNA fragments encompassing a plurality of predetermined microsatellite loci, wherein the plurality of nucleic acid capture probes collectively hybridize to at least 30 predetermined microsatellite loci and wherein a number of repeats within each microsatellite locus in the plurality of predetermined microsatellite loci in the germ line of the test subject is unknown;

(B) sequencing the plurality of cell-free DNA fragments to generate a set of raw sequence reads;

(C) mapping the set of raw sequence reads against a reference genome for the species of the test subject, thereby obtaining a plurality of aligned nucleotide sequences, wherein the plurality of aligned nucleotide sequences comprises at least 15,000 nucleotide sequences mapped to a respective predetermined microsatellite loci in the plurality of predetermined microsatellite loci and wherein the plurality of aligned nucleotide sequences has an average length of at least 50 nucleotides;

~~(A) obtaining, for each respective cell-free DNA fragment in a plurality of cell-free DNA fragments from a liquid biopsy sample from the test subject, a corresponding nucleotide sequence that has been mapped to a microsatellite locus in a plurality of predetermined microsatellite loci in a reference genome for the species of the test subject, wherein the plurality of predetermined microsatellite loci comprises 30 or more loci and wherein a number of repeats within each microsatellite locus in the plurality of predetermined microsatellite loci in the germ line of the test subject is unknown, thereby obtaining a plurality of aligned nucleotide sequences;~~

~~wherein the plurality of aligned nucleotide sequences comprises at least 15,000 nucleotide sequences and wherein the plurality of aligned nucleotide sequences has an average length of at least 50 nucleotides;~~

[(B)] (D) determining, at a computer system comprising at least one processor and a memory storing at least one program for execution by the at least one processor, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, a corresponding density estimate of a number of repeat units in the respective microsatellite locus using a number of repeat units in each nucleotide sequence in a corresponding plurality of nucleotide sequences that map to the respective microsatellite locus obtained from biological samples of a cohort of at least 200 subjects, wherein the cohort consists of healthy subjects or subjects with stable microsatellite cancer, thereby determining at least 30 density estimates;

[(C)] (E) converting each corresponding nucleotide sequence in the plurality of aligned nucleotide sequences to a likelihood score using (i) the corresponding density estimate of a number of repeat units in the respective microsatellite locus, which the corresponding nucleotide sequence maps to, from among the at least 30 density estimates and (ii) a number of repeat units in the corresponding nucleotide sequence, thereby obtaining a plurality of likelihood scores, each likelihood score in the plurality of likelihood scores associated with a corresponding microsatellite locus in the plurality of predetermined microsatellite loci;

[(D)] (F) determining a respective value for a likelihood of microsatellite locus stability for each respective microsatellite locus in the plurality of predetermined microsatellite loci by taking a measure of central tendency of those likelihood scores in the plurality of likelihood scores that are associated with the respective microsatellite locus;

[(E)] (G) using one or more corresponding metric values for one or more metrics for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the one or more metrics including the likelihood of microsatellite locus stability of the respective microsatellite locus, to determine a proportion of the plurality of predetermined microsatellite loci that are unstable; and

[(F)] (H) determining the MSI status of the test subject from the proportion of the plurality of predetermined microsatellite loci that are unstable.

2. (Currently Amended) The method of claim 1, wherein the mapping (C) ~~obtaining (A)~~ comprises, ~~for each respective DNA fragment in the plurality of DNA fragments:~~
 ~~obtaining a corresponding set of raw sequence reads for the respective DNA fragment;~~
 aligning each respective raw sequence read in the set of raw sequence reads to the reference genome for the test subject, thereby obtaining a corresponding set of aligned raw sequence reads for the respective DNA fragment; and
 collapsing the corresponding set of aligned raw sequence reads for the respective DNA fragment into a corresponding nucleotide sequence for the respective DNA fragment that has been aligned to the human reference genome, thereby obtaining the plurality of aligned nucleotide sequences.
3. (Previously Presented) The method of claim 1, wherein the plurality of aligned nucleotide sequences comprises at least 250,000 aligned nucleotide sequences.
4. (Previously Presented) The method of claim 1, wherein:
 the one or more metrics further comprises a percentage score, and
 the corresponding metric value for the percentage score is the percentage of aligned nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus.
5. (Original) The method of claim 4, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject.
6. (Original) The method of claim 4, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values, wherein each respective reference value in the plurality of reference values is determined at least in part

based on a distribution of the number of repeat units at the respective microsatellite locus in a respective reference sample in a plurality of reference standards.

7. (Original) The method of claim 4, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus.

8. (Previously Presented) The method of claim 1, wherein:
the one or more metrics further comprises a lower mean score, and
the corresponding metric value for the lower mean score is determined at least in part by the mean number of repeat units in aligned nucleotide sequences, in the plurality of aligned nucleotides, mapping to the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus.

9. (Original) The method of claim 8, wherein the mean number of repeat units is normalized by the reference number of repeat units representative of a stable construct at the respective microsatellite locus.

10. (Previously Presented) The method of claim 8, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject.

11. (Previously Presented) The method of claim 8, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values, wherein each respective reference value in the plurality of reference values is determined

at least in part based on a distribution of the number of repeat units at the respective microsatellite locus in a respective reference sample in a plurality of reference samples.

12. (Previously Presented) The method of claim 8, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus.

13-15. (Cancelled)

16. (Previously Presented) The method of claim 1, wherein the one or more corresponding metric values further comprises a corresponding standard deviation of the number of repeat units in the aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, mapping to the respective microsatellite locus.

17-18. (Cancelled)

19. (Currently Amended) The method of claim 1, wherein the using [(E)] (G) comprises inputting, for each respective microsatellite locus in the plurality of microsatellite loci, the corresponding metric value for each of the one or more metrics to a classifier that distinguishes between stable and unstable microsatellite loci.

20. (Previously Presented) The method of claim 1, wherein the biological samples from the cohort include both (i) solid tumor samples from training subjects with stable microsatellite cancer and (ii) normal tissue samples.

21. (Previously Presented) The method of claim 1, wherein the biological samples from the cohort further include (iii) solid tumor samples from training subjects with unstable microsatellite cancer.

22. (Previously Presented) The method of claim 19, wherein the classifier comprises a k-nearest neighbors classifier.

23. (Previously Presented) The method of claim 19, wherein the classifier assigns a stability status selected from unstable and stable to each respective microsatellite locus in the plurality of predetermined microsatellite loci, and the (F) determining classifies the subject as having a high level of microsatellite instability when at least a threshold proportion of microsatellite loci are assigned a status of unstable.

24. (Previously Presented) The method of claim 23, wherein the threshold proportion of microsatellite loci is at least 30% of the plurality of predetermined microsatellite loci.

25. (Previously Presented) The method of claim 23, wherein the threshold proportion of microsatellite loci is at least 50% of the plurality of predetermined microsatellite loci.

Claims 26-153. (Canceled)

154. (Previously Presented) The method of claim 1, wherein the plurality of cell-free DNA fragments from the liquid biopsy sample are enriched, relative to all cell-free DNA fragments in the liquid biopsy sample, for a set of cell-free DNA fragments that comprises the plurality of predetermined microsatellite loci.

155. (Previously Presented) The method of claim 1, wherein the plurality of aligned sequence reads represents, on average, greater than 1000X sequence depth for each microsatellite locus in the plurality of predetermined microsatellite loci and the plurality of aligned nucleotide sequences comprises at least 30000 nucleotide sequences.

156-158. (Cancelled)

159. (Previously Presented) The method of claim 1, wherein the liquid biopsy sample is a blood or blood plasma sample.

160. (Cancelled)

161. (Previously Presented) The method of claim 1, wherein the plurality of predetermined microsatellite loci comprises at least 10 of the human microsatellite loci selected from the group consisting of chr18:649874-649899, chr14:73959698-73959724, chr8:23712061-23712083, chr3:71008336-71008359, chr4:39501717-39501745, chr3:113377476-113377497, chr19:14104683-14104707, chr11:63149665-63149686, chr6:11714634-11714658, chr1:47325294-47325317, chr3:130733041-130733062, chr3:30691866-30691886, chr11:115047027-115047051, chr1:149900980-149901006, chrX:101409249-101409275, chr8:79629733-79629757, chr11:125763605-125763628, chr5:67584507-67584529, chr3:164905643-164905664, chr5:58270452-58270474, chr2:211179760-211179781, chr1:237060940-237060965, chr3:123332870-123332896, chr18:319939-319960, chr2:64069272-64069297, chr12:13364421-13364441, chr4:83785669-83785697, chr5:88018364-88018386, chr5:88018383-88018406, chr21:30339200-30339221, chr17:1326749-1326773, chr5:161494985-161495007, chr15:37391747-37391769, chr6:43021971-43021993, chr7:94989250-94989277, chr2:99614590-99614613, chr2:152236040-152236064, chr11:65268474-65268496, chr2:118854089-118854112, and chr18:649874-649899.

162. (Previously Presented) The method of claim 1, wherein the plurality of predetermined microsatellite loci comprises at least all of the human microsatellite loci of chr18:649874-649899, chr14:73959698-73959724, chr8:23712061-23712083, chr3:71008336-71008359, chr4:39501717-39501745, chr3:113377476-113377497, chr19:14104683-14104707, chr11:63149665-63149686, chr6:11714634-11714658, chr1:47325294-47325317, chr3:130733041-130733062, chr3:30691866-30691886, chr11:115047027-115047051, chr1:149900980-149901006, chrX:101409249-101409275, chr8:79629733-79629757, chr11:125763605-125763628, chr5:67584507-67584529, chr3:164905643-164905664, chr5:58270452-58270474, chr2:211179760-211179781, chr1:237060940-237060965, chr3:123332870-123332896, chr18:319939-319960, chr2:64069272-64069297, chr12:13364421-13364441, chr4:83785669-83785697, chr5:88018364-88018386,

chr5:88018383-88018406, chr21:30339200-30339221, chr17:1326749-1326773,
chr5:161494985-161495007, chr15:37391747-37391769, chr6:43021971-43021993,
chr7:94989250-94989277, chr2:99614590-99614613, chr2:152236040-152236064,
chr11:65268474-65268496, chr2:118854089-118854112, and chr18:649874-649899.

163. (Previously Presented) The method of claim 1, wherein the subject is a human.

164. (Canceled)

165. (Canceled)

Remarks/Arguments

Status of the Claims

Claims 1-13, 16, 19-25, 154, 155, and 159, 161-165 were previously pending in the application.

With this Response, claims 164-165 are canceled without prejudice.

With this Response, claim 1 is amended to include a step of enriching for cell-free DNA fragments encompassing a plurality of microsatellite loci using a plurality of nucleic acid capture probes. Support for the recital can be found throughout the application, for example at paragraphs [0104], [0245]-[0251], and [574]-[0575], as well as claim 154, as originally filed.

With this Response, claim 1 is amended to include a step of sequencing cell-free DNA fragments. Support for the recital can be found throughout the application, for example at paragraphs [0264]-[0269], as originally filed.

With this Response, claim 1 is amended to include a step of mapping raw sequence reads against a reference genome. Support for the recital can be found throughout the application, for example at paragraphs [0282]-[0289], as originally filed.

With this Response, claims 1, 2, and 19 are amended for informalities and/or clarity.

Accordingly, the claim amendments do not introduce any new matter. Applicant respectfully requests entry of the claim amendments.

Upon entry of the present amendment, claims 1-13, 16, 19-25, 154, 155, and 159, 161-164 will be pending for examination with claim 1 being independent.

Interview Summary

An Examiner interview took place on March 17, 2025, between representatives for Applicant, Brett Lovejoy and Andrew Antczak, and Examiners Steven Bailey and Kaitlyn Minchella (hereinafter, “the Interview”). Applicant thanks the Examiners for the courtesies extended during the Interview.

During the interview, the outstanding 35 U.S.C. § 101 rejection of the claims was discussed. Specifically, amendments reciting additional elements were discussed that could integrate any judicial exceptions into a practical application when the claim was considered as a whole, or that would amount to significantly more than any judicial exception. No agreement was reached as to the eligibility of any proposed amended claim.

The claim objection should be withdrawn

The Office Action objects to claim 165 for formalities. In an earnest attempt to expedite prosecution, and without acquiescing as to the merits of the rejection, Applicant has canceled claim 165, rendering the rejection moot.

The rejection under 35 U.S.C. § 101 should be withdrawn

Claims 1-12, 16, 19-25, 154, 155, and 159, 161-165 stand rejected under 35 U.S.C. § 101 as allegedly being directed to an abstract idea without significantly more, and specifically to mental processes and/or mathematical concepts. To the extent that the rejection is asserted to apply to the amended claims, Applicant respectfully disagrees for at least the following reasons.

(A) The claims are not directed to an abstract idea within the meaning of Alice.

MPEP § 2106.05 states: “claims that integrate [abstract ideas, natural phenomenon, and laws of nature] into ***an inventive concept*** are thereby transformed into patent-eligible inventions.” MPEP § 2106.04(a)(I)(II) also states: “[s]ome claims reciting an abstract idea are not directed to the abstract idea because they also recite additional elements (***such as an improvement***) demonstrating that the claims as a whole clearly do not seek to tie up the abstract idea”.

Similarly, the 2019 Guidance states: “[i]n Prong Two, examiners should evaluate whether the claim as a whole integrates the recited judicial exception into a practical application of the exception. A claim that integrates a judicial exception into a practical application will apply, rely on, or use the judicial exception in a manner that imposes a meaningful limit on the judicial exception, such that the claim is more than a drafting effort designed to monopolize the judicial

exception.” Moreover, the 2019 Guidance Update states at page 11: “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. No further analysis is required. The claim is eligible at Step 2A.”

The claims of the present application *are not directed to* an abstract idea and are thus patent eligible under 35 U.S.C. § 101 because (i) they integrate any alleged abstract idea into the practical application of a non-invasive determination of the MSI status of a cancer in a test subject from a liquid biopsy sample and (ii) they improve the technical field of laboratory diagnostic testing by adding specific limitations and/or adding unconventional steps that confine the claims to the particular useful application and provide personalized, precision medicine based laboratory diagnostic testing results.

The claimed method includes a series of steps and specific limitations that result in a non-invasive determination of the MSI status of a cancer in a test subject. While the claimed method may involve judicial exceptions, the result of these judicial exceptions is a non-invasive determination of the MSI status of a cancer in a test subject. This has nothing to do with the identified judicial exceptions. Moreover, the process that enables the non-invasive determination of the MSI status of a cancer in a test subject is not an insignificant extra-solution activity because, as discussed below, conventional processes do not satisfactorily allow determination of the MSI status of a cancer from a liquid biopsy sample. For discussion purposes, claim 1 is presented below with bolded passages recited in claim 1 because of their significance in Applicant’s arguments for patentability of the claim under 35 U.S.C. § 101 provided in this response:

1. A method of **determining a microsatellite instability (MSI) status of a test subject**, the method comprising:

(A) **hybridizing cell-free DNA fragments from a liquid biopsy sample from a test subject to a plurality of nucleic acid capture probes to generate a plurality of cell-free DNA fragments enriched, relative to all cell-free DNA fragments in the liquid biopsy sample, for a set of cell-free DNA fragments encompassing a plurality of predetermined microsatellite loci, wherein the plurality of nucleic acid capture probes that collectively hybridize to at least 30 predetermined microsatellite**

loci and wherein a number of repeats within each microsatellite locus in the plurality of predetermined microsatellite loci in the germ line of the test subject is unknown;

(B) **sequencing the plurality of cell-free DNA fragments** to generate a set of raw sequence reads;

(C) **mapping the set of raw sequence reads against a reference genome for the species of the test subject**, thereby obtaining a plurality of aligned nucleotide sequences, wherein the plurality of aligned nucleotide sequences comprises at least 15,000 nucleotide sequences mapped to a respective predetermined microsatellite loci in the plurality of predetermined microsatellite loci and wherein the plurality of aligned nucleotide sequences has an average length of at least 50 nucleotides;

(D) determining, at a computer system comprising at least one processor and a memory storing at least one program for execution by the at least one processor, **for each respective microsatellite locus in the plurality of predetermined microsatellite loci, a corresponding density estimate of a number of repeat units in the respective microsatellite locus using a number of repeat units in each nucleotide sequence in a corresponding plurality of nucleotide sequences that map to the respective microsatellite locus obtained from biological samples of a cohort of at least 200 subjects**, wherein the cohort consists of healthy subjects or subjects with stable microsatellite cancer, thereby determining at least 30 density estimates;

(E) converting each corresponding nucleotide sequence in the plurality of aligned nucleotide sequences to a likelihood score using (i) the corresponding density estimate of a number of repeat units in the respective microsatellite locus, which the corresponding nucleotide sequence maps to, from among the at least 30 density estimates and (ii) a number of repeat units in the corresponding nucleotide sequence, thereby obtaining a plurality of likelihood scores, each likelihood score in the plurality of likelihood scores associated with a corresponding microsatellite locus in the plurality of predetermined microsatellite loci;

(F) determining a respective value for a likelihood of microsatellite locus stability for each respective microsatellite locus in the plurality of predetermined microsatellite loci by taking a measure of central tendency of those likelihood scores in the plurality of likelihood scores that are associated with the respective microsatellite locus;

(G) using one or more corresponding metric values for one or more metrics for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the one or more metrics including the likelihood of microsatellite locus stability of the respective microsatellite

locus, to determine a proportion of the plurality of predetermined microsatellite loci that are unstable; and

(H) **determining the MSI status of the test subject** from the proportion of the plurality of predetermined microsatellite loci that are unstable.

Amended claim 1, emphasis added.

As can be seen, claim 1 is directed to a non-invasive determination of the MSI status of a test subject from a liquid biopsy sample. The claimed invention integrates the alleged judicial exception into a practical application that addresses technical problem(s) in the field of diagnostic testing, and provides enhancement in the technical field of personalizing diagnostic testing results.

The specification explains the challenges and technical problems addressed by claim 1. For instance, paragraphs [0008]-[0013] of the specification state:

[0008] MSI detection is typically performed by subjecting tumor tissue (“solid biopsy”) to clinical next-generation sequencing or specific assays, such as MMR IHC or MSI PCR. However, **collection of solid tumor biopsies is an invasive procedure. Moreover, the sample material recovered from the biopsy is only representative of the portion of the individual tumor sampled. This is particularly problematic in cancer patients with multiple tumors and patients with cancers having high tumor mutational burdens, because different tumors—and even different sections of the same tumor—can have different genomic, epigenetic, and transcriptomic profiles.** Circulating cell-free tumor DNA (cfDNA) testing (“liquid biopsy”) is rapidly emerging as a less invasive method for cancer detection and monitoring disease progression. However, liquid biopsy methodologies are hampered by the fact that DNA fragments from both cancerous and non-cancerous cells are present in blood plasma. In addition, the ratio of DNA from cancerous and non-cancerous cells varies from patient to patient, based on the tumor burden of the patient.

[0009] The use of large NGS genomic analysis is growing in order to address the need for more comprehensive characterization of an individual’s cancer genome. See, for example, Fernandes GS et al., Clinics, 72(10):588-94. Recent studies indicate that of the patients for which large NGS genomic analysis is performed, 30-40% then receive clinical care based on the assay results, which is limited by at least the identification of actionable genomic alterations, the availability of medication for treatment of identified actionable genomic alterations, and the clinical condition of the subject. See, Ross JS et al., JAMA Oncol.,

1(1):40-49 (2015); Ross JS et al., Arch. Pathol. Lab Med., 139:642-49 (2015); Hirshfield KM et al., Oncologist, 21(11):1315-25 (2016); and Groisberg R. et al., Oncotarget, 8:39254-67 (2017).

[0010] However, these large NGS genomic analyses are conventionally performed on solid tumor samples. For instance, each of the studies referenced in the paragraph above performed NGS analysis of FFPE tumor blocks from patients. Solid tissue biopsies remain the gold standard for diagnosis and identification of predictive biomarkers because they represent well-known and validated methodologies that provide a high degree of accuracy. Nevertheless, there are significant limitations to the use of solid tissue material for large NGS genomic analyses of cancers. For example, **tumor biopsies are subject to sampling bias caused by spatial and/or temporal genetic heterogeneity, e.g., between two regions of a single tumor and/or between different cancerous tissues (such as between primary and metastatic tumor sites or between two different primary tumor sites).** Such intertumor or intratumor heterogeneity can cause subclonal or emerging mutations to be overlooked when using localized tissue biopsies, with the potential for sampling bias to be exacerbated over time as subclonal populations further evolve and/or shift in predominance.

[0011] Additionally, **the acquisition of solid tissue biopsies often requires invasive surgical procedures, e.g., when the primary tumor site is located at an internal organ. These procedures can be expensive, time consuming, and carry a significant risk to the patient, e.g., when the patient's health is poor and may not be able to tolerate invasive medical procedures and/or the tumor is located in a particularly sensitive or inoperable location, such as in the brain or heart.** Further, the amount of tissue, if any, that can be procured depends on multiple factors, including the location of the tumor, the size of the tumor, the fragility of the patient, and the risk of comorbidities related to biopsies, such as bleeding and infections. For instance, recent studies report that tissue samples in a majority of advanced non-small cell lung cancer patients are limited to small biopsies, and cannot be obtained at all in up to 31% of patients. Ilie and Hofman, Transl. Lung Cancer Res., 5(4):420-23 (2016). Even when a tissue biopsy is obtained, the sample may be too scant for comprehensive testing.

[0012] Further, **the method of tissue collection, preservation (e.g., formalin fixation), and/or storage of tissue biopsies can result in sample degradation and variable quality DNA.** This, in turn, leads to inaccuracies in downstream assays and analysis, including next-generation sequencing (NGS) for the identification of biomarkers. Ilie and Hofman, Transl Lung Cancer Res., 5(4):420-23 (2016).

[0013] In addition, **the invasive nature of the biopsy procedure, the time and cost associated with obtaining the sample, and the compromised state of cancer patients receiving therapy render repeat testing of cancerous tissues impracticable, if not impossible.** As a result, solid tissue biopsy analysis is **not amenable to many monitoring schemes that would benefit cancer patients**, such as disease progression analysis, treatment efficacy evaluation, disease recurrence monitoring, and other techniques that require data from several time points.

Applicant's specification at paragraph [0008]-[0013], emphasis added

Claim 1 addresses the above-described technical problem(s) and thus enables the practical application of determining the MSI status of a cancer in a test subject in a non-invasive fashion.

To determine the patent eligibility under 35 U.S.C. § 101, MPEP §2106.05 states:

The full scope of the claim under the BRI should be considered to determine if the claim reflects an improvement in technology (e.g., the improvement described in the specification). In making this determination, it is critical that examiners **look at the claim “as a whole,”** in other words, the claim should be evaluated **“as an ordered combination,”** without ignoring the requirements of the individual steps.” When performing this evaluation, examiners should be **“careful to avoid oversimplifying the claims”** by looking at them generally and failing to account for the specific requirements of the claims. *McRO*, 837 F.3d at 1313, 120 USPQ2d at 1100.

Evaluating additional elements to determine whether they amount to an inventive concept requires considering them both individually and in combination to ensure that they amount to significantly more than the judicial exception itself. Because this approach considers all claim elements, the Supreme Court has noted that “it is consistent with the general rule that patent claims ‘**must be considered as a whole.**’” *Alice Corp.*, 573 U.S. at 218 n.3, 110 USPQ2d at 1981 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188, 209 USPQ 1, 8-9 (1981)). **Consideration of the elements in combination is particularly important**, because even if an additional element does not amount to significantly more on its own, it can still amount to significantly more when considered in combination with the other elements of the claim. See, e.g., *Rapid Litig. Mgmt. v. CellzDirect*, 827 F.3d 1042, 1051, 119 USPQ2d 1370, 1375 (Fed. Cir. 2016) (process reciting combination of individually well-known freezing and thawing steps was “far from routine and conventional” and thus eligible); *BASCOM Global Internet Servs. v. AT&T Mobility LLC*, 827 F.3d 1341, 1350, 119 USPQ2d 1236, 1242 (Fed. Cir. 2016) (**inventive concept may be found in the**

non-conventional and non-generic arrangement of components that are individually well-known and conventional).

Even if one or more additional elements are well-understood, routine, conventional activity when considered individually, the combination of additional elements may amount to an inventive concept. *Diamond v. Diehr*, 450 U.S. at 188, 209 USPQ at 9 (1981) (“[A] new combination of steps in a process may be patentable even though all the constituents of the combination were well known and in common use before the combination was made.”).

MPEP §2106.05, emphasis added.

Thus, the claim has to be considered as a whole and evaluated as an ordered combination. Examiners should be “careful to avoid oversimplifying the claims” by looking at them generally and failing to account for the specific requirements of the claims. Even if one or more additional elements are well-understood, routine, conventional activity when considered individually, the combination of additional elements may amount to an inventive concept.

In the instant case, claim 1 recites a series of steps in an order and includes specific elements (*e.g.*, hybridizing cell-free DNA fragments to capture probes to enrich for cell-free DNA fragments encompassing a plurality of microsatellite loci, sequencing the enriched cell-free DNA fragments, mapping sequence reads, etc.) that interact and impact each other. These steps, in particular when viewed in the ordered combination and along with the specific elements recited in these steps, imposes a meaningful limit on any recited judicial exception, sufficiently limiting the use of the recited judicial exception to the practical application of non-invasively determining the MSI status of a cancer in a test subject.

Accordingly, when viewed as a whole, the claimed method integrates any alleged judicial exception into a practical application that improves clinical oncology by reducing the time, cost, and invasiveness of testing for MSI status. Thus, for at least the reasons above, claim 1 is patent eligible under the second prong of Step 2A of the *Alice* analysis because the claim is not directed to an abstract idea.

(B) The claims recite non-routine and unconventional processes that add inventive concepts and amount to significantly more than any alleged judicial exception.

Even if the amended claims are found to be directed to an abstract idea—and Applicant contends they are not for at least the reasoning above—Applicant respectfully submits that the claims recite non-routine and unconventional processes that add inventive concepts and amount to significantly more than any alleged judicial exception and are thus patentable under at least Step 2B of the Guidance.

Specifically, step (A) of amended claim 1 recites hybridizing cell-free DNA fragments from a liquid biopsy sample from a test subject to a plurality of nucleic acid capture probes to generate a plurality of cell-free DNA fragments enriched, relative to all cell-free DNA fragments in the liquid biopsy sample, for a set of cell-free DNA fragments encompassing a plurality of predetermined microsatellite loci, wherein the plurality of nucleic acid capture probes comprises probes that collectively hybridize to at least 30 predetermined microsatellite loci and wherein a number of repeats within each microsatellite locus in the plurality of predetermined microsatellite loci in the germ line of the test subject is unknown.

Step (B) of amended claim 1 recites sequencing the plurality of cell-free DNA fragments to generate a set of raw sequence reads.

Step (C) of amended claim 1 recites mapping the set of raw sequence reads against a reference genome for the species of the test subject, thereby obtaining a plurality of aligned nucleotide sequences, wherein the plurality of aligned nucleotide sequences comprises at least 15,000 nucleotide sequences mapped to a respective predetermined microsatellite loci in the plurality of predetermined microsatellite loci and wherein the plurality of aligned nucleotide sequences has an average length of at least 50 nucleotides.

As an initial matter, the mere use of a liquid biopsy assay for determining the MSI status of a cancer in a patient was unconventional at the time the present application was filed. This is evidenced by paragraphs [0008] and [0024] of Applicant's specification, which state that at the time the present application was filed, determining the MSI status of a cancer was conventionally performed by evaluating DNA from a solid tumor biopsy sample:

[0008] **MSI detection is typically performed by subjecting tumor tissue (“solid biopsy”) to clinical next-generation sequencing or specific assays, such as MMR IHC or MSI PCR.** However, collection of solid tumor biopsies is an invasive procedure. Moreover, the sample material recovered from the biopsy is only representative of the portion of the individual tumor sampled. This is particularly problematic in cancer patients with multiple tumors and patients with cancers having high tumor mutational burdens, because different tumors—and even different sections of the same tumor—can have different genomic, epigenetic, and transcriptomic profiles. Circulating cell-free tumor DNA (cfDNA) testing (“liquid biopsy”) is rapidly emerging as a less invasive method for cancer detection and monitoring disease progression. However, liquid biopsy methodologies are hampered by the fact that DNA fragments from both cancerous and non-cancerous cells are present in blood plasma. In addition, the ratio of DNA from cancerous and non-cancerous cells varies from patient to patient, based on the tumor burden of the patient.

* * *

[0024] Microsatellite instability is a clinically actionable genomic indication for cancer immunotherapy. In microsatellite instability-high (MSI-H) tumors, defects in DNA mismatch repair (MMR) can cause a hypermutated phenotype where alterations accumulate in the repetitive microsatellite regions of DNA. **MSI detection is conventionally performed by subjecting tumor tissue (“solid biopsy”) to clinical next-generation sequencing or specific assays, such as MMR IHC or MSI PCR.** Circulating cell-free tumor DNA (cfDNA) testing (“liquid biopsy”) is rapidly emerging as a less invasive method for cancer detection and monitoring disease progression. Disclosed herein are methods and systems for detecting MSI using a cfDNA MSI detection assay with high specificity.

Applicant’s specification at paragraph [0008] and [0024], emphasis added.

Considered alone, the use of a liquid biopsy sample to generate data that can be used to determine the MSI status of a cancer in a test subject, as recited in the ordered combination of steps (A)-(C) of amended claim 1, add inventive concepts and amount to significantly more than any alleged judicial exception. Moreover, the additional recitations in step (A) of amended claim 1 detailing how this data is generated further evidence the non-conventionality of these steps. Specifically, step (A) recites use of a plurality of nucleic acid capture probes that collectively hybridize to at least 30 predetermined microsatellite loci and wherein a number of repeats within each microsatellite locus in the plurality of predetermined microsatellite loci in the germ line of the test subject is unknown. Both the use of capture probes against a plurality of

microsatellite loci to enrich for cell-free DNA fragments encompassing microsatellite loci and the determination of MSI status in the absence of knowledge about the number of repeats within each microsatellite locus in the germ line of the subject were non-conventional at the time of filing of the present application.

An inventive concept can be found in the non-conventional and non-generic arrangement of known conventional pieces. *Bascom Global Internet Services v. AT&T Mobility*, 827, F.3d, 1341, 1350 (Fed. Cir. 2016). Representative claim 1 as a whole recites a unique and non-invasive method for determining the MSI status of a cancer in a test subject. The claimed method solves the various problems associated with conventional determination of MSI status using solid tumor samples, as described above. Additionally, Applicant's claims amount to an "inventive concept" because they are not taught by the relevant art.

For at least the reasons stated in *BASCOM Glob. Internet Servs. v. AT&T Mobility LLC*, 827 F.3d 1341 (Fed. Cir. 2016), the claims are patent-eligible because "the particular arrangements of elements is a technical improvement over prior ways," which results in a non-invasive method for determining the MSI status of a cancer in a test subject. Accordingly, claim 1 qualifies as eligible subject matter under 35 U.S.C. § 101. All other pending claims rejected under 35 U.S.C. § 101 depend from claim 1 and thus are patentable under 35 U.S.C. § 101 for at least the same reason as claim 1. Applicant therefore respectfully requests that the 35 U.S.C. § 101 rejection be withdrawn.

CONCLUSION

All the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn.

Applicant believes that a full and complete reply has been made to the outstanding Office Action, and as such, the present application is in condition for allowance. 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.

Except for issue fees payable under 37 CFR § 1.18, the Commissioner is hereby authorized by this paper to charge any necessary fees during the entire pendency of this application including fees due under 37 CFR §§ 1.16 and 1.17, which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310 (Order No.: 123138-5013-US).

Prompt and favorable consideration of this Amendment and Response is respectfully requested.

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS LLP

Dated: <u>April 11, 2025</u> Customer No.: 43850 Morgan, Lewis & Bockius LLP One Market, Spear Street Tower San Francisco, CA 94105 Telephone: (415) 442-1000 Facsimile: (415) 442-1001	By: <u>/ Andrew J. Antczak /</u> Andrew J. Antczak, Reg. No. 70,871
---	--



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 NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/945,588	07/31/2020	Ariane Lozac'hmeur	123138-5013-US	8972
43850	7590	03/21/2025		
Morgan, Lewis & Bockius LLP (SF) One Market, Spear Street Tower, Suite 2800 San Francisco, CA 94105			EXAMINER BAILEY, STEVEN WILLIAM	
			ART UNIT	PAPER NUMBER
			1687	
			NOTIFICATION DATE	DELIVERY MODE
			03/21/2025	ELECTRONIC

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

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

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

donald.mixon@morganlewis.com
sfipdocketing@morganlewis.com

<i>Applicant-Initiated Interview Summary</i>	Application No. 16/945,588	Applicant(s) Lozac'hmeur et al.		
	Examiner STEVEN W BAILEY	Art Unit 1687	AIA (First Inventor to File) Status Yes	Page 1 of 2

All Participants (applicant, applicants representative, PTO personnel)	Title	Type
STEVEN W BAILEY	Examiner	Video Conference
KAITLYN MINCHELLA	Primary Examiner	
BRETT A. LOVEJOY	Attorney of Record	
ANDREW J. ANTCZAK	Attorney of Record	

Date of Interview: 17 March 2025

Issues Discussed:

35 U.S.C. 101

The Applicants and the Examiners discussed the rejection under 35 U.S.C. 101 in the Office action mailed 13 January 2025, in particular with regard to potential amendments that would recite additional elements that could integrate the judicial exceptions at Eligibility Step 2A: Prong Two when the claims are considered as a whole, or that would amount to significantly more than the judicial exceptions when the additional elements are considered individually and in combination at Eligibility Step 2B. No agreement was reached.

Other

The Applicant's gave a brief overview of the invention. The Applicant's did not provide a meeting agenda or proposed amendment.

/STEVEN W. BAILEY/ Examiner, Art Unit 1687	/KAITLYN L MINCHELLA/ Primary Examiner, Art Unit 1685
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

<i>Applicant-Initiated Interview Summary</i>	Application No. 16/945,588	Applicant(s) Lozac'hmeur et al.		
	Examiner STEVEN W BAILEY	Art Unit 1687	AIA (First Inventor to File) Status Yes	Page 2 of 2

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.



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 NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/945,588	07/31/2020	Ariane Lozac'hmeur	123138-5013-US	8972
43850	7590	01/13/2025		
Morgan, Lewis & Bockius LLP (SF) One Market, Spear Street Tower, Suite 2800 San Francisco, CA 94105			EXAMINER BAILEY, STEVEN WILLIAM	
			ART UNIT	PAPER NUMBER
			1687	
			NOTIFICATION DATE	DELIVERY MODE
			01/13/2025	ELECTRONIC

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

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

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

donald.mixon@morganlewis.com
sfipdocketing@morganlewis.com

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Status of the Claims

2. Claims 1-12, 16, 19-25, 154, 155, 159, and 161-165 are pending.
3. Claims 1-12, 16, 19-25, 154, 155, 159, and 161-165 are rejected.
4. Claim 165 is objected to.

Priority

5. Claims 1-12, 16, 19-25, 154, 155, 159, and 161-165 are given the benefit for priority to Provisional Application No. 62/881,845, filed 01 August 2019, Provisional Application No. 62/931,600, filed 06 November 2019, and Provisional Application No. 62/978,130, filed 18 February 2020.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on 21 November 2024 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Interpretation

7. Claim 1 at step (A) is interpreted as reciting a product-by-process limitation with the product being the data of a plurality of aligned nucleotide sequences that are mapped to a microsatellite locus in a plurality of predetermined microsatellite loci in a reference genome. The claim is further interpreted to not require the processing steps of producing the product.

8. Claim 1 at step (B) is interpreted as reciting a product-by-process limitation with the product being the data of respective microsatellite loci obtained from biological samples of a cohort of at least 200 subjects, wherein the cohort consists of healthy subjects or subjects with stable microsatellite cancer. The claim is further interpreted to not require the processing steps of producing the product.

9. Claim 154 is interpreted as reciting a product-by-process limitation with the product being the data for enriched cell-free DNA fragments that comprises the plurality of predetermined microsatellite loci. The claim is further interpreted to not require the processing steps of producing the product.

Claim Objections

10. The rejection to claim 25 in the Office action mailed 21 May 2024 is withdrawn in view of the amendment received 21 November 2024.

11. The amendment received 21 November 2024 has been fully considered, however after further consideration new grounds for objection are raised in view of the amendment.

12. Claim 165 is objected to because of the following informalities: The claim identifies two separate limitations with the same label – (B), i.e., lines 5-17 are labeled as step (B) with an indentation, and lines 18-25 are labeled as step (B) with an indentation.

13. Appropriate correction is required.

Claim Rejections - 35 USC § 112

14. The rejection of claim 162 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, in the Office action mailed 21 May 2024 is withdrawn in view of the amendment received 21 November 2024.

Claim Rejections - 35 USC § 101

15. The rejection of claims 1-12, 16, 19-25, 154, 155, 159, and 161-164 under 35 U.S.C. 101 in the Office action mailed 21 May 2024 is maintained with modification in view of the amendment received 21 November 2024.

16. 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.

17. Claims 1-12, 16, 19-25, 154, 155, 159, and 161-165 are rejected under 35 U.S.C. 101 because the claimed invention is directed to an abstract idea without significantly more. The claims recite: (a) mathematical concepts, (e.g., mathematical relationships, formulas or equations, mathematical calculations); and (b) mental processes, i.e., concepts performed in the human mind, (e.g., observation, evaluation, judgement, opinion).

18. Following the flowchart in MPEP 2106:

Eligibility Step 1

19. Claims 1-12, 16, 19-25, 154, 155, 159, and 161-165 are directed to a method (process) of determining a microsatellite instability (MSI) status of a test subject. Therefore, these claims are encompassed by the categories of statutory subject matter, and thus satisfy the subject matter eligibility requirements under Eligibility Step 1.

Eligibility Step 2A: Prong One

20. In determining whether a claim is directed to a judicial exception, examination is performed that analyzes whether the claim recites a judicial exception, i.e., whether a law of nature, natural phenomenon, or abstract idea is set forth or described in the claim.

21. **Independent claim 1** recites:

a mental process at step (A) of considering data, for each respective cell-free DNA fragment in a plurality of cell-free DNA fragments from a liquid biopsy sample from the test subject, of a corresponding nucleotide sequence that has been mapped to a microsatellite locus in a plurality of predetermined microsatellite loci in a reference genome for the species of the test subject, wherein the plurality of predetermined microsatellite loci comprises 30 or more loci and wherein a number of repeats within each microsatellite locus in the plurality of predetermined microsatellite loci in the germ line of the test subject is unknown, thereby obtaining a plurality of aligned nucleotide sequences, wherein the plurality of aligned nucleotide sequences comprises at least 15,000 nucleotide sequences and wherein the plurality of aligned nucleotide sequences has an average length of at least 50 nucleotides;

a mental process and a mathematical concept at step (B) of considering data for determining, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, a corresponding density estimate of a number of repeat units in the respective microsatellite locus using a number of repeat units in each nucleotide sequence in a corresponding plurality of nucleotide sequences that map to the respective microsatellite locus obtained from biological samples of a cohort of at least

Art Unit: 1687

200 subjects, wherein the cohort consists of healthy subjects or subjects with stable microsatellite cancer, thereby determining at least 30 density estimates;

a mental process and a mathematical concept at step (C) of considering data for converting each corresponding nucleotide sequence in the plurality of aligned nucleotide sequences to a likelihood score using

(i) the corresponding density estimate of a number of repeat units in the respective microsatellite locus, which the corresponding nucleotide sequence maps to, from among the at least 30 density estimates and

(ii) a number of repeat units in the corresponding nucleotide sequence, thereby obtaining a plurality of likelihood scores, each likelihood score in the plurality of likelihood scores associated with a corresponding microsatellite locus in the plurality of predetermined microsatellite loci;

a mental process and a mathematical concept at step (D) of considering data for determining a respective value for a likelihood of microsatellite locus stability for each respective microsatellite locus in the plurality of predetermined microsatellite loci by taking a measure of central tendency of those likelihood scores in the plurality of likelihood scores that are associated with the respective microsatellite locus;

a mental process and a mathematical concept at step (E) of considering data for using one or more corresponding metric values for one or more metrics for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the one or more metrics including the likelihood of microsatellite locus stability of the respective microsatellite locus, to determine a proportion of the plurality of predetermined microsatellite loci that are unstable; and

a mental process at step (F) of considering data for determining the MSI status of the test subject from the proportion of the plurality of predetermined microsatellite loci that are unstable.

22. **Independent claim 165** recites:

a mental process at step (A) of considering data of a set of raw sequence reads;

a mathematical concept at step (B; lines 5-17) for aligning each respective raw sequence read in the set of raw sequence reads to a reference genome for the test subject, thereby obtaining a corresponding set of aligned raw sequence reads for the respective DNA fragment; a mental process of considering data for collapsing the corresponding set of aligned raw sequence reads for the respective DNA fragment into a corresponding nucleotide sequence for the respective DNA fragment, thereby obtaining a plurality of aligned nucleotide sequences mapping to a microsatellite locus in a plurality of predetermined microsatellite loci in the reference genome for the species of the test subject, wherein the plurality of predetermined microsatellite loci comprises 30 or more loci, wherein a number of repeats within each microsatellite locus in the plurality of predetermined microsatellite loci in the germ line of the test subject is unknown, wherein the plurality of aligned nucleotide sequences comprises at least 15000 nucleotide sequences; and a mental process and a mathematical concept of considering data wherein the plurality of aligned nucleotide sequences has an average length of at least 50 nucleotides;

a mental process and a mathematical concept at step (B; lines 18-25) of considering data for determining, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, a corresponding density estimate of a number of

Art Unit: 1687

repeat units in the respective microsatellite locus using a number of repeat units in each nucleotide sequence in a corresponding plurality of nucleotide sequences that map to the respective microsatellite locus obtained from biological samples of a cohort of at least 200 subjects, wherein the cohort consists of healthy subjects or subjects with stable microsatellite cancer, thereby determining at least 30 density estimates;

a mental process and a mathematical concept at step (C) of considering data for converting each corresponding nucleotide sequence in the plurality of aligned nucleotide sequences to a likelihood score using

(i) the corresponding density estimate of a number of repeat units in the respective microsatellite locus, which the corresponding nucleotide sequence maps to, from among the at least 30 density estimates and

(ii) a number of repeat units in the corresponding nucleotide sequence, thereby obtaining a plurality of likelihood scores, each likelihood score in the plurality of likelihood scores associated with a corresponding microsatellite locus in the plurality of predetermined microsatellite loci;

a mental process and a mathematical concept at step (D) of considering data for determining a respective value for a likelihood of microsatellite locus stability for each respective microsatellite locus in the plurality of predetermined microsatellite loci by taking a measure of central tendency of those likelihood scores in the plurality of likelihood scores that are associated with the respective microsatellite locus;

a mental process and a mathematical concept at step (E) of considering data for using one or more corresponding metric values for one or more metrics for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the

Art Unit: 1687

one or more metrics including the likelihood of microsatellite locus stability of the respective microsatellite locus, to determine a proportion of the plurality of predetermined microsatellite loci that are unstable; and

a mental process at step (F) of considering data for determining the MSI status of the test subject from the proportion of the plurality of predetermined microsatellite loci that are unstable.

23. **Dependent claim 2** further recites a mental process of considering data for a corresponding set of raw sequence reads for the respective DNA fragment; a mathematical concept for aligning each respective raw sequence read in the set of raw sequence reads to the reference genome for the test subject, thereby obtaining a corresponding set of aligned raw sequence reads for the respective DNA fragment; a mental process and a mathematical concept of collapsing the corresponding set of aligned raw sequence reads for the respective DNA fragment into a corresponding nucleotide sequence for the respective DNA fragment that has been aligned to the human reference genome, thereby obtaining the plurality of aligned nucleotide sequences.

24. **Dependent claim 3** further recites a mental process of considering data wherein the plurality of aligned nucleotide sequences comprises at least 250,000 aligned nucleotide sequences.

25. **Dependent claim 4** further recites a mental process and a mathematical concept of considering data wherein the one or more metrics further comprises a percentage score; a mental process and a mathematical concept of considering data wherein the corresponding metric value for the percentage score is the percentage of aligned

Art Unit: 1687

nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus.

26. **Dependent claim 5** further recites a mental process of considering data wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject.

27. **Dependent claim 6** further recites a mental process and a mathematical concept of considering data wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values, wherein each respective reference value in the plurality of reference values is determined at least in part based on a distribution of the number of repeat units at the respective microsatellite locus in a respective reference sample in a plurality of reference standards.

28. **Dependent claim 7** further recites a mental process and a mathematical concept of considering data wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus.

29. **Dependent claim 8** further recites a mental process and a mathematical concept of considering data wherein the one or more metrics further comprises a lower mean score; and a mental process and mathematical concept of considering data wherein the corresponding metric value for the lower mean score is determined at least in part by the mean number of repeat units in aligned nucleotide sequences, in the plurality of aligned nucleotides, mapping to the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus.

30. **Dependent claim 9** further recites a mental process and a mathematical concept of considering data wherein the mean number of repeat units is normalized by the reference number of repeat units representative of a stable construct at the respective microsatellite locus.

31. **Dependent claim 10** further recites a mental process and a mathematical concept of considering data wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject.

32. **Dependent claim 11** further recites a mental process and a mathematical concept of considering data wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values, wherein each respective reference value in the plurality of reference values is determined at least in part based on a distribution of the number of repeat

units at the respective microsatellite locus in a respective reference sample in a plurality of reference samples.

33. **Dependent claim 12** further recites a mental process and a mathematical concept of considering data wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus.

34. **Dependent claim 16** further recites a mental process and a mathematical concept of considering data wherein the one or more corresponding metric values further comprises a corresponding standard deviation of the number of repeat units in the aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, mapping to the respective microsatellite locus.

35. **Dependent claim 19** further recites a mental process at step (E) of considering data of the corresponding metric value for each of the one or more metrics for each respective microsatellite locus in the plurality of microsatellite loci; and a mental process and a mathematical concept of considering data for using a classifier that distinguishes between data of stable and unstable microsatellite loci.

36. **Dependent claim 20** further recites a mental process of considering data wherein the biological samples from the cohort include both (i) solid tumor samples from training subjects with stable microsatellite cancer and (ii) normal tissue samples.

37. **Dependent claim 21** further recites a mental process of considering data wherein the biological samples from the cohort further include (iii) solid tumor samples from training subjects with unstable microsatellite cancer.
38. **Dependent claim 22** further recites a mental process and a mathematical concept wherein the classifier comprises a k-nearest neighbors classifier.
39. **Dependent claim 23** further recites a mental process and a mathematical concept of considering data wherein the classifier assigns a stability status selected from unstable and stable to each respective microsatellite locus in the plurality of predetermined microsatellite loci, and a mental process and a mathematical concept of considering data wherein the (F) determining classifies the subject as having a high level of microsatellite instability when at least a threshold proportion of microsatellite loci are assigned a status of unstable.
40. **Dependent claim 24** further recites a mental process and a mathematical concept of considering data wherein the threshold proportion of microsatellite loci is at least 30% of the plurality of predetermined microsatellite loci.
41. **Dependent claim 25** further recites a mental process and a mathematical concept of considering data wherein the threshold proportion of microsatellite loci is at least 50% of the plurality of predetermined microsatellite loci.
42. **Dependent claim 154** further recites a mental process of considering data wherein the plurality of cell-free DNA fragments from the liquid biopsy sample are enriched, relative to all cell-free DNA fragments in the liquid biopsy sample, for a set of cell-free DNA fragments that comprises the plurality of predetermined microsatellite loci.

43. **Dependent claim 155** further recites a mental process of considering data wherein the plurality of aligned sequence reads represents, on average, greater than 1000X sequence depth for each microsatellite locus in the plurality of predetermined microsatellite loci and the plurality of aligned nucleotide sequences comprises at least 30000 nucleotide sequences.
44. **Dependent claim 159** further recites a mental process of considering data wherein the liquid biopsy sample is a blood or blood plasma sample.
45. **Dependent claim 161** further recites a mental process of considering that the plurality of predetermined microsatellite loci comprises at least 10 of the human microsatellite loci selected from the group listed in the claim.
46. **Dependent claim 162** further recites a mental process of considering the plurality of predetermined microsatellite loci comprises at least all of the human microsatellite loci from the group listed in the claim.
47. **Dependent claim 163** further recites a mental process of considering data from a subject, wherein the subject is a human.
48. **Dependent claim 164** further recites a mental process of considering data of a plurality of cell-free nucleotide sequences.
49. The abstract ideas recited in the claims are evaluated under the broadest reasonable interpretation (BRI) of the claim limitations when read in light of and consistent with the specification, and determined to be directed to the analysis of data that in the simplest embodiments (sequence reads that are mapped to predetermined loci) are mental processes that are not too complex to be performed in the human mind with the aid of a pencil and paper. Additionally, the recited limitations that are identified

as judicial exceptions from the mathematical concepts grouping of abstract ideas are abstract ideas regardless of whether or not the limitations are practical to perform in the human mind.

Eligibility Step 2A: Prong Two

50. In determining whether a claim is directed to a judicial exception, further examination is performed that analyzes if the claim recites additional elements that when examined as a whole integrates the judicial exception(s) into a practical application (MPEP 2106.04(d)). A claim that integrates a judicial exception into a practical application will apply, rely on, or use the judicial exception in a manner that imposes a meaningful limit on the judicial exception. The claimed additional elements are analyzed to determine if the abstract idea is integrated into a practical application (MPEP 2106.04(d)(I); MPEP 2106.05(a-h)). If the claim contains no additional elements beyond the abstract idea, the claim fails to integrate the abstract idea into a practical application (MPEP 2106.04(d)(III)).

51. The judicial exceptions noted above are not integrated into a practical application because the additional elements of a computer system having one or more processors, and memory, in **independent claim 1**; a first computer system having one or more processors, and memory, and a second computer system having one or more processors, and memory, in **independent claim 165**; do not result in an improvement to computer functionality itself, and therefore do not integrate the recited judicial exceptions into a practical application. The additional elements of sequencing a plurality of cell-free DNA fragments from a liquid biopsy sample in **dependent claim 164**; sequencing a plurality of cell-free DNA fragments from a liquid biopsy sample from a

Art Unit: 1687

test subject in **independent claim 165**; and obtaining a corresponding set of raw sequence reads for the respective DNA fragment in **dependent claim 2**; are data gathering steps used in the recited judicial exceptions, and therefore do not integrate the recited judicial exceptions into a practical application. The additional element of obtaining data at steps (A) and (B) in **independent claim 1** is an insignificant extra-solution activity that is part of the data gathering process used in the recited judicial exceptions, and therefore does not integrate the recited judicial exceptions into a practical application. The additional element of inputting data in **dependent claim 19** is an insignificant extra-solution activity that is part of the data gathering process used in the recited judicial exceptions, and therefore does not integrate the recited judicial exception into a practical application.

52. All limitations in claims 1-12, 16, 19-25, 154, 155, 159, and 161-165 have been **considered as a whole**, and are deemed to not recite any additional elements that would integrate a judicial exception into a practical application (MPEP 2106.04(d)).

Eligibility Step 2B

53. Because the claims recite an abstract idea, and do not integrate that abstract idea into a practical application, the claims are probed for a specific inventive concept. The judicial exception alone cannot provide that inventive concept or practical application (MPEP 2106.05). Identifying whether the additional elements beyond the abstract idea amount to such an inventive concept requires considering the additional elements individually and in combination to determine if they amount to significantly more than the judicial exception (MPEP 2106.05A i-vi).

Art Unit: 1687

54. The claims do not include additional elements that are sufficient to amount to significantly more than the judicial exception(s) because the additional elements of a computer system having one or more processors, and memory, in **independent claim 1**; a first computer system having one or more processors, and memory, and a second computer system having one or more processors, and memory, in **independent claim 165**; obtaining data at steps (A) and (B) in **independent claim 1**; and inputting data in **dependent claim 19**; are conventional (**see MPEP at 2106.05(b) and 2106.05(d)(II) regarding conventionality of computer components and computer processes**).

55. The additional elements of sequencing a plurality of cell-free DNA fragments from a liquid biopsy sample in **dependent claim 164**; sequencing a plurality of cell-free DNA fragments from a liquid biopsy sample from a test subject in **independent claim 165**; and obtaining a corresponding set of raw sequence reads for the respective DNA fragment in **dependent claim 2**; are conventional. Evidence for the conventionality is shown by Morganti et al. (Critical Reviews in Oncology, 2019 (Published January 2019), Vol. 133, pp. 171-182, as cited in the Office action mailed 20 September 2023).

Morganti et al. reviews the complexity of genome sequencing and reporting, particularly focusing on next-generation sequencing (NGS) technologies and the implementation of precision medicine (Title; and Abstract). Morganti et al. shows that NGS technologies allow for the obtainment of extensive genetic information from liquid biopsies, and the obtainment of genetic material for sequencing from circulating tumor cells (CTCs) and circulating cell-free tumor DNA (ctDNA; page 172, column 2, para. 1; and page 177, column 2, Section 4.3). Morganti et al. further reviews NGS sequencing (page 173, Section 2.2) and NGS methods (page 174, Section 3), and further still, reviews

Art Unit: 1687

advantages of NGS methodology with regard to microsatellite instability analyses (page 177, column 1, Section 4.2.2).

56. Furthermore, all additional elements in claims 1-12, 16, 19-25, 154, 155, 159, and 161-165 have been evaluated individually **and in combination**, and are deemed to not contribute an inventive concept, i.e., amount to significantly more than the judicial exceptions (MPEP 2106.05(II)).

Response to Arguments

57. The Applicant's arguments/remarks received 21 November 2024 have been fully considered, but are not persuasive.

58. The Applicant states on page 13 of the Remarks (para. 3) that the claims are patent eligible under the first prong of Step 2A because the claims do not recite limitations that can be practically performed in the human mind. The Applicant further states (para. 4) that the Office seems to misinterpret the complexity of the claimed method, and further states that claim 1 expressly requires analysis of at least 15,000 sequences, and it would not be practical or possible for a human mind to perform the recited steps with respect to the analysis of at least 15,000 nucleotide sequences. The Applicant further states (para. 5) that with respect to newly presented claim 165, the claim recites a step of mapping raw sequence reads against a reference genome, which cannot be performed mentally.

59. These arguments are not persuasive, because first, with respect to newly presented claim 165, the step of mapping raw sequence reads against a reference genome is identified at Eligibility Step 2A: Prong One as a judicial exception from the mathematical concept grouping of abstract ideas in the rejection above, but is not

identified as a mental process. Second, with respect to the complexity of the claimed method, the claim limitations identified as judicial exceptions from the mental process grouping of abstract ideas at Eligibility Step 2A: Prong One in the rejection above are directed to the analysis of data that in the simplest embodiments are able to be performed mentally, or with paper and pencil. Although the amount of data may be considered to be significantly large and take considerable time and effort to process manually, the use of a general-purpose computer to perform the claimed method at a rate and accuracy that can far outstrip the mental performance of a skilled artisan does not change the nature of the activity being performed (i.e., an abstract idea), and therefore does not materially alter the patent eligibility of the claimed subject matter.

60. The Applicant states on page 14 (para. 1) that regardless of whether the claims permissibly involve or are based on mathematical concepts, the claims do not recite mathematical concepts, as outlined in Applicant's prior response filed February 20, 2024. The Applicant further states (para. 2) that the Office's explanation for why steps (B), (C), (D), and (E) in claim 1 recite mathematical concepts is a conclusory statement that does not provide the Applicant any basis for rebutting the analysis. The Applicant further states (para. 3) that all of the identified steps are merely based on or involve a mathematical concept, and analogizes (Remarks, page 14, para. 4, and page 15, para(s). 2-3) instant claim 1 with Example 38 of the USPTO Subject Matter Eligibility Examples (the "PEG Training Examples") that does not explicitly recite mathematical concepts, and contrasts instant claim 1 with PEG Training Examples 41, 43, and 45 that do explicitly recite mathematical concepts (Remarks, page 15, para. 1).

61. These arguments are not persuasive, because first, it is important to note that a mathematical concept need not be expressed in mathematical symbols, because words used in a claim operating on data to solve a problem can serve the same purpose as a formula or equation (MPEP 2106.04(a)(2)(I)). A claim that recites a mathematical calculation, when the claim is given its broadest reasonable interpretation in light of the specification, will be considered as falling within the "mathematical concepts" grouping. A mathematical calculation is a mathematical operation (such as multiplication), or an act of calculating using mathematical methods to determine a variable or number, e.g., performing an arithmetic operation such as exponentiation. There is no particular word or set of words that indicates a claim recites a mathematical calculation. That is, a claim does not have to recite the word "calculating" in order to be considered a mathematical calculation. For example, a step of "determining" a variable or number using mathematical methods or "performing" a mathematical operation may also be considered mathematical calculations when the broadest reasonable interpretation of the claim in light of the specification encompasses a mathematical calculation (MPEP 2106.04(a)(2)(C)). Second, the Eligibility Examples are hypothetical and only intended to be illustrative of the claim analysis performed using MPEP 2106, and of the particular issues noted in the Example. The Examples should be interpreted based on the fact patterns set forth in a particular Example, as other fact patterns may have different eligibility outcomes, as evidenced in the rejection above.

62. The Applicant states on page 16 of the Remarks (para. 2) that regardless of whether the amended claims recite an abstract idea, the claims are not directed to an abstract idea when properly viewed as a whole, and for at least this reason, the claims

Art Unit: 1687

are patent eligible. The Applicant further states (para. 4) that claim 1, as amended, represents an improvement in the field of clinical oncology, specifically, that facilitates determination of the microsatellite instability (MSI) status of a subject from a liquid biopsy assay, improving the diagnosis and treatment of cancer patients by both reducing the time and cost required to determine MSI status and by doing so in a less invasive way than conventional methods requiring testing of a solid tumor sample. The Applicant further points to evidence of the claimed improvements (page 16, para. 5 through page 17) in contrast to conventional methods (page 18, para. 1), and further points (page 18, para. 2, through page 19, para. 1) to the Applicant's specification at para(s). [0016] & [0017] for description of the advantages of using liquid biopsy procedures over solid tumor biopsies. The Applicant states on page 19 of the Remarks (para. 3) that accordingly, when viewed as a whole, the claimed method integrates any alleged judicial exception into a practical application that improves clinical oncology by reducing the time, cost, and invasiveness of testing for MSI status, and thus, for at least these reasons, claim 1 is patent eligible under the second prong of Step 2A.

63. These arguments are not persuasive, because first, evaluating whether judicial exceptions are integrated into a practical application comprises: (1) identifying whether there are any additional elements recited in the claim beyond the judicial exception(s); and (2) evaluating those additional elements individually and in combination to determine whether they integrate the exception into a practical application, using one or more of the considerations introduced in subsection I at 2106.04(d) of the MPEP, and discussed in more detail in MPEP §§ 2106.04(d)(1), 2106.04(d)(2), 2106.05(a) through (c) and 2106.05(e) through (h). As noted in the rejection above, when all limitations in

Art Unit: 1687

claims 1-12, 16, 19-25, 154, 155, 159, and 161-165 have been **considered as a whole**, they are deemed to not recite any additional elements that would integrate a judicial exception into a practical application (MPEP 2106.04(d)). Second, the instant claimed improvement in the field of clinical oncology is a purported improvement to the abstract idea (data analysis), and not an improvement to computer functionality itself, or an improvement to another technology or technical field.

Conclusion

64. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

65. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

66. Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN W. BAILEY whose telephone number is (571)272-8170. The examiner can normally be reached Mon - Fri. 1000 - 1800.

67. Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an

Art Unit: 1687

interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

68. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, KARLHEINZ 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.

69. 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.

/S.W.B./
Examiner, Art Unit 1687

/Karlheinz R. Skowronek/
Supervisory Patent Examiner, Art
Unit 1687

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A method of determining a microsatellite instability (MSI) status of a test subject, the method comprising:

at a computer system having one or more processors, and memory storing one or more programs for execution by the one or more processors:

(A) obtaining, for each respective cell-free DNA fragment in a plurality of cell-free DNA fragments from a liquid biopsy sample from the test subject, a corresponding nucleotide sequence that has been mapped to a microsatellite locus in a plurality of predetermined microsatellite loci in a reference genome for the species of the test subject, wherein the plurality of predetermined microsatellite loci comprises 30 or more loci and wherein a number of repeats within each microsatellite locus in the plurality of predetermined microsatellite loci in the germ line of the test subject is unknown, thereby obtaining a plurality of aligned nucleotide sequences, wherein the plurality of aligned nucleotide sequences comprises at least 15,000 nucleotide sequences and wherein the plurality of aligned nucleotide sequences has an average length of at least 50 nucleotides;

(B) determining, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, a corresponding density estimate of a number of repeat units in the respective microsatellite locus using a number of repeat units in each nucleotide sequence in a corresponding plurality of nucleotide sequences that map to the respective microsatellite locus obtained from biological samples of a cohort of at least 200 subjects, wherein the cohort consists of healthy subjects or subjects with stable microsatellite cancer, thereby determining at least 30 density estimates;

(C) converting each corresponding nucleotide sequence in the plurality of aligned nucleotide sequences to a likelihood score using (i) the corresponding density estimate of a number of repeat units in the respective microsatellite locus, which the corresponding nucleotide sequence maps to, from among the at least 30 density estimates and (ii) a number of repeat units in the corresponding nucleotide sequence, thereby obtaining a plurality of likelihood scores, each

likelihood score in the plurality of likelihood scores associated with a corresponding microsatellite locus in the plurality of predetermined microsatellite loci;

(D) determining a respective value for a likelihood of microsatellite locus stability for each respective microsatellite locus in the plurality of predetermined microsatellite loci by taking a measure of central tendency of those likelihood scores in the plurality of likelihood scores that are associated with the respective microsatellite locus;

(E) using one or more corresponding metric values for one or more metrics for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the one or more metrics including the likelihood of microsatellite locus stability of the respective microsatellite locus, to determine a proportion of the plurality of predetermined microsatellite loci that are unstable; and

(F) determining the MSI status of the test subject from the proportion of the plurality of predetermined microsatellite loci that are unstable.

2. (Previously Presented) The method of claim 1, wherein the obtaining (A) comprises, for each respective DNA fragment in the plurality of DNA fragments:

obtaining a corresponding set of raw sequence reads for the respective DNA fragment;
aligning each respective raw sequence read in the set of raw sequence reads to the reference genome for the test subject, thereby obtaining a corresponding set of aligned raw sequence reads for the respective DNA fragment; and

collapsing the corresponding set of aligned raw sequence reads for the respective DNA fragment into a corresponding nucleotide sequence for the respective DNA fragment that has been aligned to the human reference genome, thereby obtaining the plurality of aligned nucleotide sequences.

3. (Previously Presented) The method of claim 1, wherein the plurality of aligned nucleotide sequences comprises at least 250,000 aligned nucleotide sequences.

4. (Previously Presented) The method of claim 1, wherein:
the one or more metrics further comprises a percentage score, and

the corresponding metric value for the percentage score is the percentage of aligned nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus.

5. (Original) The method of claim 4, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject.

6. (Original) The method of claim 4, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values, wherein each respective reference value in the plurality of reference values is determined at least in part based on a distribution of the number of repeat units at the respective microsatellite locus in a respective reference sample in a plurality of reference standards.

7. (Original) The method of claim 4, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus.

8. (Previously Presented) The method of claim 1, wherein:
the one or more metrics further comprises a lower mean score, and
the corresponding metric value for the lower mean score is determined at least in part by the mean number of repeat units in aligned nucleotide sequences, in the plurality of aligned nucleotides, mapping to the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus.

9. (Original) The method of claim 8, wherein the mean number of repeat units is normalized by the reference number of repeat units representative of a stable construct at the respective microsatellite locus.

10. (Previously Presented) The method of claim 8, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject.

11. (Previously Presented) The method of claim 8, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values, wherein each respective reference value in the plurality of reference values is determined at least in part based on a distribution of the number of repeat units at the respective microsatellite locus in a respective reference sample in a plurality of reference samples.

12. (Previously Presented) The method of claim 8, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus.

13-15. (Cancelled)

16. (Previously Presented) The method of claim 1, wherein the one or more corresponding metric values further comprises a corresponding standard deviation of the number of repeat units in the aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, mapping to the respective microsatellite locus.

17-18. (Cancelled)

19. (Previously Presented) The method of claim 1, wherein the using (E) comprises inputting, for each respective microsatellite locus in the plurality of microsatellite loci, the corresponding metric value for each of the one or more metrics to a classifier that distinguishes between stable and unstable microsatellite loci.
20. (Previously Presented) The method of claim 1, wherein the biological samples from the cohort include both (i) solid tumor samples from training subjects with stable microsatellite cancer and (ii) normal tissue samples.
21. (Previously Presented) The method of claim 1, wherein the biological samples from the cohort further include (iii) solid tumor samples from training subjects with unstable microsatellite cancer.
22. (Previously Presented) The method of claim 19, wherein the classifier comprises a k-nearest neighbors classifier.
23. (Previously Presented) The method of claim 19, wherein the classifier assigns a stability status selected from unstable and stable to each respective microsatellite locus in the plurality of predetermined microsatellite loci, and the (F) determining classifies the subject as having a high level of microsatellite instability when at least a threshold proportion of microsatellite loci are assigned a status of unstable.
24. (Previously Presented) The method of claim 23, wherein the threshold proportion of microsatellite loci is at least 30% of the plurality of predetermined microsatellite loci.
25. (Currently Amended) The method of claim 23, wherein the threshold proportion of microsatellite loci is at least 50% of the ~~the~~ plurality of predetermined microsatellite loci.

Claims 26-153. (Canceled)

154. (Previously Presented) The method of claim 1, wherein the plurality of cell-free DNA fragments from the liquid biopsy sample are enriched, relative to all cell-free DNA fragments in the liquid biopsy sample, for a set of cell-free DNA fragments that comprises the plurality of predetermined microsatellite loci.

155. (Previously Presented) The method of claim 1, wherein the plurality of aligned sequence reads represents, on average, greater than 1000X sequence depth for each microsatellite locus in the plurality of predetermined microsatellite loci and the plurality of aligned nucleotide sequences comprises at least 30000 nucleotide sequences.

156-158. (Cancelled)

159. (Previously Presented) The method of claim 1, wherein the liquid biopsy sample is a blood or blood plasma sample.

160. (Cancelled)

161. (Previously Presented) The method of claim 1, wherein the plurality of predetermined microsatellite loci comprises at least 10 of the human microsatellite loci selected from the group consisting of chr18:649874-649899, chr14:73959698-73959724, chr8:23712061-23712083, chr3:71008336-71008359, chr4:39501717-39501745, chr3:113377476-113377497, chr19:14104683-14104707, chr11:63149665-63149686, chr6:11714634-11714658, chr1:47325294-47325317, chr3:130733041-130733062, chr3:30691866-30691886, chr11:115047027-115047051, chr1:149900980-149901006, chrX:101409249-101409275, chr8:79629733-79629757, chr11:125763605-125763628, chr5:67584507-67584529, chr3:164905643-164905664, chr5:58270452-58270474, chr2:211179760-211179781, chr1:237060940-237060965, chr3:123332870-123332896, chr18:319939-319960, chr2:64069272-64069297, chr12:13364421-13364441, chr4:83785669-83785697, chr5:88018364-88018386, chr5:88018383-88018406, chr21:30339200-30339221, chr17:1326749-1326773, chr5:161494985-161495007, chr15:37391747-37391769, chr6:43021971-43021993, chr7:94989250-94989277, chr2:99614590-99614613,

chr2:152236040-152236064, chr11:65268474-65268496, chr2:118854089-118854112, and chr18:649874-649899.

162. (Currently Amended) The method of claim 1, wherein the plurality of predetermined microsatellite loci comprises at least all of the human microsatellite loci ~~selected from the group consisting of~~ chr18:649874-649899, chr14:73959698-73959724, chr8:23712061-23712083, chr3:71008336-71008359, chr4:39501717-39501745, chr3:113377476-113377497, chr19:14104683-14104707, chr11:63149665-63149686, chr6:11714634-11714658, chr1:47325294-47325317, chr3:130733041-130733062, chr3:30691866-30691886, chr11:115047027-115047051, chr1:149900980-149901006, chrX:101409249-101409275, chr8:79629733-79629757, chr11:125763605-125763628, chr5:67584507-67584529, chr3:164905643-164905664, chr5:58270452-58270474, chr2:211179760-211179781, chr1:237060940-237060965, chr3:123332870-123332896, chr18:319939-319960, chr2:64069272-64069297, chr12:13364421-13364441, chr4:83785669-83785697, chr5:88018364-88018386, chr5:88018383-88018406, chr21:30339200-30339221, chr17:1326749-1326773, chr5:161494985-161495007, chr15:37391747-37391769, chr6:43021971-43021993, chr7:94989250-94989277, chr2:99614590-99614613, chr2:152236040-152236064, chr11:65268474-65268496, chr2:118854089-118854112, and chr18:649874-649899.

163. (Previously Presented) The method of claim 1, wherein the subject is a human.

164. (Previously Presented) The method of claim 1, the method further comprising:
sequencing the plurality of cell-free DNA fragments from the liquid biopsy sample to generate the plurality of cell-free nucleotide sequences.

165. (New) A method of determining a microsatellite instability (MSI) status of a test subject, the method comprising:

(A) sequencing a plurality of cell-free DNA fragments from a liquid biopsy sample from a test subject, to generate a set of raw sequence reads;

(B) aligning, at a first computer system having one or more processors, and memory storing one or more programs for execution by the one or more processors, each respective raw sequence read in the set of raw sequence reads to a reference genome for the test subject, thereby obtaining a corresponding set of aligned raw sequence reads for the respective DNA fragment, and collapsing the corresponding set of aligned raw sequence reads for the respective DNA fragment into a corresponding nucleotide sequence for the respective DNA fragment, thereby obtaining a plurality of aligned nucleotide sequences mapping to a microsatellite locus in a plurality of predetermined microsatellite loci in the reference genome for the species of the test subject, wherein the plurality of predetermined microsatellite loci comprises 30 or more loci, wherein a number of repeats within each microsatellite locus in the plurality of predetermined microsatellite loci in the germ line of the test subject is unknown, wherein the plurality of aligned nucleotide sequences comprises at least 15000 nucleotide sequences, and wherein the plurality of aligned nucleotide sequences has an average length of at least 50 nucleotides;

(B) determining, at a second computer system having one or more processors, and memory storing one or more programs for execution by the one or more processors, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, a corresponding density estimate of a number of repeat units in the respective microsatellite locus using a number of repeat units in each nucleotide sequence in a corresponding plurality of nucleotide sequences that map to the respective microsatellite locus obtained from biological samples of a cohort of at least 200 subjects, wherein the cohort consists of healthy subjects or subjects with stable microsatellite cancer, thereby determining at least 30 density estimates;

(C) converting, at the second computer system, each corresponding nucleotide sequence in the plurality of aligned nucleotide sequences to a likelihood score using (i) the corresponding density estimate of a number of repeat units in the respective microsatellite locus, which the corresponding nucleotide sequence maps to, from among the at least 30 density estimates and (ii) a number of repeat units in the corresponding nucleotide sequence, thereby obtaining a plurality of likelihood scores, each likelihood score in the plurality of likelihood scores associated with a corresponding microsatellite locus in the plurality of predetermined microsatellite loci;

(D) determining, at the second computer system, a respective value for a likelihood of microsatellite locus stability for each respective microsatellite locus in the plurality of

predetermined microsatellite loci by taking a measure of central tendency of those likelihood scores in the plurality of likelihood scores that are associated with the respective microsatellite locus;

(E) using, at the second computer system, one or more corresponding metric values for one or more metrics for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the one or more metrics including the likelihood of microsatellite locus stability of the respective microsatellite locus, to determine a proportion of the plurality of predetermined microsatellite loci that are unstable; and

(F) determining, at the second computer system, the MSI status of the test subject from the proportion of the plurality of predetermined microsatellite loci that are unstable.

Remarks/Arguments

Status of the Claims

Claims 1-13, 16, 19-25, 154, 155, and 159, 161-164 were previously pending in the application.

With this Response, claims 1, 25, and 162 are amended for informalities and/or clarity.

With this Response, claim 165 is added to recite a method for determining a microsatellite instability (MSI) status of a test subject that includes a sequencing step. Support for the newly added claims can be found throughout the application, for example at paragraphs [0002], [0041], [0063], [0065], [0073], [0108], [0203], [0220], [0267], [0285], [0331], [0352], [0368], [0369], [0579], and [0580] (as outlined in the previous response) and claims 1 and 2, as originally filed.

Accordingly, the claim amendments do not introduce any new matter. Applicant respectfully requests entry of the claim amendments.

Upon entry of the present amendment, claims 1-13, 16, 19-25, 154, 155, and 159, 161-165 will be pending for examination with claim 1 being independent.

The claim objection should be withdrawn

The Office Action objects to claim 25 for including an “and” before “plurality” in line 2. Applicant notes that the claim recited “the the” before plurality in line 2 and has canceled one recitation with this Response. Accordingly, Applicant respectfully requests the objection to claim 25 be withdrawn.

The rejection under 35 U.S.C. § 112(b) should be withdrawn

Claim 162 stands rejected as allegedly indefinite for reciting a plurality of loci that include all of an enumerated list and that all of the enumerated loci are selected from the list of enumerated loci. In an earnest attempt to expedite prosecution, and without acquiescing on the merits of the rejection, Applicant has amended claim 162 to remove the phrase “selected from

the group consisting of.” Accordingly, Applicant respectfully requests the rejection of claim 162 be withdrawn.

The rejection under 35 U.S.C. § 101 should be withdrawn

Claims 1-13, 16, 19-25, 154, 155, and 159, 161-164 stand rejected under 35 U.S.C. § 101 as allegedly being directed to an abstract idea without significantly more, and specifically to mental processes and/or mathematical concepts. To the extent that the rejection is asserted to apply to the amended claims, as well as newly presented claim 165, Applicant respectfully traverses the rejection for at least the following reasons.

The subject matter eligibility of a claimed method is examined according to the two-part *Alice* test.¹ This test requires an Examiner to:

- 1) determine whether the claim is “directed to” a judicial exception, *e.g.*, an abstract idea” and, if so,
- 2) “determine whether any element, or combination of elements, in the claim is sufficient to ensure that the claim amounts to significantly more than the judicial exception.”

Applicant analyzes the claims below under the *2019 Guidance*, which “supersedes all versions of the U.S.P.T.O.’s ‘Eligibility Quick Reference Sheet Identifying Abstract Ideas’ (first issued in July 2015 and updated most recently in July 2018),”² the October 2019 Patent Eligibility Guidance Update (the “Revised Guidance”), and the latest Manual of Patent Examining Procedures (MPEP 2106) for Patent Subject Matter Eligibility (Revision 10.2019).

¹ *Alice Corporation Pty. v. CLS Bank International*, 573 U.S. 208 (2014); *see also*, MPEP § 2106(I); *2014 Interim Guidance on Patent Subject Matter Eligibility*, 79 Fed. Reg. 74618 (December 16, 2014) (37 CFR Part 1) (hereinafter, the “*Interim Guidance*”).

² *2019 Revised Patent Subject Matter Eligibility Guidance*, Fed. Reg. 84:4 50 (2019) (hereinafter, the “*2019 Guidance*”).

The claims are patent eligible under the First Prong of Step 2A because they do not recite an abstract idea.

The claims do not recite limitations that can be practically performed in the human mind:

The Office Action contends that the claims recite judicial exceptions falling under the mental processes grouping. However, when properly assessed under the 2019 Guidance and Guidance Update, as outlined in Applicant's prior response filed February 20, 2024, claim 1 does not recite an abstract idea falling within the purview of this grouping. For at least this reason, the claims are patent eligible.

The 2019 Guidance Update states:

[C]laims do not recite a mental process when they do not contain limitations that can practically be performed in the human mind, for instance when the human mind is not equipped to perform the claim limitations. *Id.*, page 7, Section II(C)(i).

Applicant respectfully submits that claim 1 as amended contains limitations that cannot practically be performed in the human mind and thus cannot be directed to an abstract idea. The Office Action seems to misinterpret the complexity of the claimed method. For example, the Office Action alleges that "in the simplest embodiment of the claim, far fewer than 15,000 sequences may map to a locus, and only 30 loci need to be analyzed in simplest embodiment after inputting the mapped sequence data." Office Action at page 16, paragraph 36. Applicant disagrees and respectfully points out that the claim specifies the plurality of at least 15,000 nucleotide sequences have been mapped to a microsatellite locus in the plurality of 30 or more predetermined microsatellite loci. Thus, the claim expressly requires analysis of at least 15,000 sequences. For all of the reasons articulated in Applicant's response filed February 20, 2024, it would not be practical or possible for a human mind to performed the recited steps with respect to the analysis of at least 15,000 nucleotide sequences.

With respect to newly presented claim 165, the claim recites a step of mapping raw sequence reads against a reference genome for the species of the subject, which clearly cannot be performed mentally.

The claims do not recite mathematical concepts:

The Office Action at pages 5-6 contends that claim 1 recite a judicial exception falling under the category of mathematical concepts. Applicant respectfully traverses the contention because, regardless of whether the claims permissibly involve or are based on mathematical concepts, the claims do not recite mathematical concepts, as outlined in Applicant's prior response filed February 20, 2024.

The Office Action contends that steps (B), (C), (D), and (E) in claim 1 recite mathematical concepts. However, the only explanation given in the Office Action for why these particular steps recite mathematical concepts, rather than merely being based on or involving mathematical concepts, is that "the claims recite mathematical concepts that are expressed with words that operate on data to determine an MSI status." Office Action at page 15. This, however, is a conclusory statement that does not provide Applicant any basis for rebutting the analysis. Applicant respectfully request that the Examiner provide an explanation as to how this conclusion was reached.

Rather, Applicant contends that all of the identified steps are merely based on or involve a mathematical concept described in the specification, which according to MPEP § 2106.04(a)(2)(I) is insufficient for a finding of patent ineligibility "provided the mathematical concept itself is not recited in the claim."

For instance, the claim in Example 38 of the *U.S.P.T.O. Subject Matter Eligibility Examples* (the "PEG Training Examples") recites a method for providing a digital computer simulation of an analog mixer that includes steps of:

- generating a normally distributed first random value for each circuit element, using a pseudo random number generator, based on a respective initial value and manufacturing tolerance range; and
- simulating a first digital representation of the analog circuit based on the first random value and the location of each circuit element within the analog circuit.

As explained in the 2019 PEG Advanced Module, these steps are based upon mathematical relationships, formulations, or calculations. However, the 2019 PEG Advanced Module explains that because the mathematical relationships, formulas, or calculations are not **explicitly recited** in the claim, the claim **does not recite a mathematical concept**. See, 2019 PEG Advanced Module at slide 102; PEG Training Examples at Example 38.

By contrast, the 2019 Guidance Update lists three examples of claims that do recite mathematical concepts—PEG Training Examples 41, 43, and 45. In each of these examples, the claims recite a mathematical concept because a specific mathematical formulation or calculation is explicitly recited in the claim. For instance, the PEG Training Examples explains that the encoding step of Example 41 “recites a mathematical concept because the claim explicitly recites a mathematical formula $[C_A = M_A^e \pmod n]$ or calculation.” Similarly, the PEG Training Examples explains that the claim in Example 43 recites a mathematical concept because it recites calculating a ratio of C11 to C13 levels. Finally, the PEG Training Examples explains that the calculating step of Example 45 recites a mathematical concept because the claim recites using the Arrhenius equation.

Like Example 38 of the U.S.P.T.O. Training Materials, the steps of (i) determining a corresponding density estimate of a number of repeat units in the respective microsatellite loci (step B), (ii) converting each corresponding nucleotide sequence in the plurality of aligned nucleotide sequences to a likelihood score (step C), (iii) determining a respective value for a likelihood of microsatellite locus stability (step D), and determine a proportion of the plurality of predetermined microsatellite loci that are unstable (step E) of claim 1 may be based on or involve the use of an algorithm described in the specification, but the claim does not explicitly recite a particular algorithm. For instance, the claim in Example 38 of the U.S.P.T.O. Training Materials recites steps of (i) generating a normally distributed first random value and (ii) simulating a first digital representation of an analog circuit, both of which necessarily involve the use of an algorithm. However, the PEG Training Examples concludes that this claim does not recite a mathematical concept because it does not explicitly recite the underlying mathematical relationships, formulas, or calculations.

Thus, like Example 38, pending claim 1 does not recite a mathematical concept because it does not explicitly recite any underlying mathematical relationships, formulas, or calculations.

Thus, for at least the reasons above, the claims are patent eligible under the first prong of Step 2A of the *Alice* analysis because the claims cannot be mentally performed.

The claims are patent eligible under the Second Prong of Step 2A because they are not directed to an abstract idea.

Regardless of whether the amended claims recite an abstract idea, the claims are not directed to an abstract idea when properly viewed as a whole. For at least this reason, the claims are patent eligible.

“In Prong Two, examiners should evaluate whether the claim as a whole integrates the recited judicial exception into a practical application of the exception. A claim that integrates a judicial exception into a practical application will apply, rely on, or use the judicial exception in a manner that imposes a meaningful limit on the judicial exception, such that the claim is more than a drafting effort designed to monopolize the judicial exception.” *See* the 2019 Guidance. “It is critical that examiners **consider the claim as a whole** when evaluating whether the judicial exception is meaningfully limited by integration into a practical application of the exception.” *Id.*, emphasis added.

Section 2106.05(a) of the MPEP (emphasis added) states:

Thus, an examiner should evaluate whether a claim contains an improvement to the functioning of a computer **or to any other technology** or technical field at Step 2A Prong Two and Step 2B, as well as when considering whether the claim has such self-evident eligibility that it qualifies for the streamlined analysis.

Claim 1, as amended, represents an improvement in the field of clinical oncology. Specifically, the method recited in amended claim 1 facilitates determination of the microsatellite instability (MSI) status of a subject from a liquid biopsy assay, improving the diagnosis and treatment of cancer patients by both reducing the time and cost required to determine MSI status and by doing so in a less invasive way than conventional methods for determining MSI status. Specifically, as detailed below, prior to Applicant’s claimed method the standard of care for determining the MSI status of a cancer required testing of a solid tumor sample.

Applicant markets the claimed invention as part of the Tempus xF/xF+ Liquid Biopsy assay: <https://www.tempus.com/oncology/genomic-profiling/xf> accessed November 19, 2024,

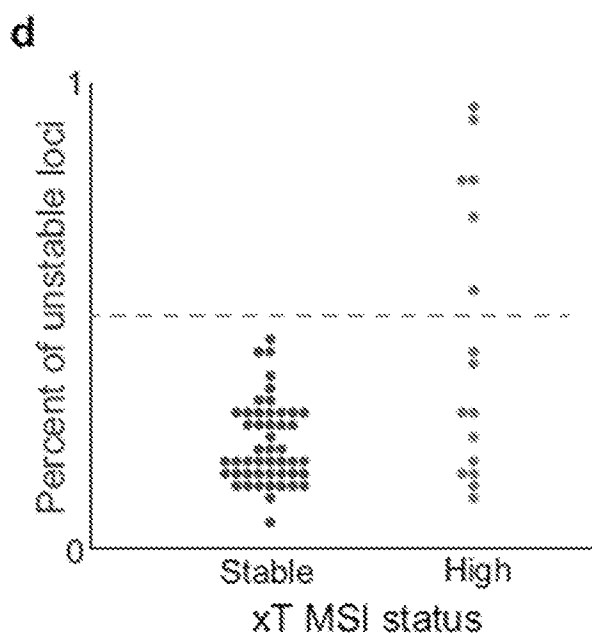
reference A3, in the Information Disclosure Statement filed on even date herewith, a portion of which is reproduced below:

xF+ PERFORMANCE SPECIFICATIONS

CHICAGO LAB

Variant Class	VAF	Sensitivity	Specificity	LOD
SNVs (Enhanced)	≥0.25%	>99.9%	>99.9%	0.25%
SNVs (Non Enhanced)	≥1%	>99.9%	>99.9%	1%
INDELs (Enhanced)	≥0.5%	98.00%	>99.9%	0.50%
INDELs (Non Enhanced)	≥2%	87.50%	>99.9%	2%
CNAs	≥1%	>99.9%	92.00%	1%
Rearrangements	≥1%	96.80%	>99.9%	1%
MSI-H Status	-	93.00%	>99.9%	-
BTMS	-	78.50%	>99.9%	-

The Tempus xF and xF+ assays are CAP/CLIA validated suites of molecular diagnostics that use data from cell-free DNA sequencing to provide diagnostic predictions for various cancer markers, including high microsatellite instability (MSI-H) status, with high sensitivity and specificity, as indicated in the xF+ Performance Specifications reproduced above. Consistent with the claimed invention, the MSI model employed within the xF and xF+ suites predict the probability that each microsatellite loci is unstable by evaluating normalized percent lower, mean lower, and mean log-likelihood metrics in k-nearest neighbors analysis (with k =100) and determine the MSI status of the test subject based on the probabilities from each loci, where >50% unstable loci considered MSI-high. *See*, Applicant's publication on the validation of the xF Liquid Biopsy assay at page 9, Finkle J.D., et al., "Validation of a liquid biopsy assay with molecular and clinical profiling of circulating tumor DNA," *Precision Oncology*, 5:63 (2021), in the Information Disclosure Statement filed on even date herewith. Finkle et al. used 65 samples previously classified using a solid tumor biopsy test or immunohistochemistry (*See*, Finkle et al. at page 4, left hand column) to validate the microsatellite instability model. Results of the validation are shown in Figure 1d of the paper, reproduced below:



As evidenced by Li et al., (“Microsatellite instability: a review of what the oncologist should know,” Cancer Cell Int., 20:16 (2020), in the Information Disclosure Statement filed on even date herewith), conventional methods for determining the microsatellite instability status of a cancer, as of the filing date of Applicant’s application, required solid tumor biopsy samples. See, Table 1 of Li et al., citing to Hempelmann et al., Arulananda et al., Cheah et al., and Waalkes et al., each of which is in the Information Disclosure Statement filed on even date herewith. Specifically, see, Hempelmann et al. at page 2, right column, Arulananda et al. at page 1589, right column, Cheah et al. at page 93, left column, and Waalkes et al. at page 3. Solid tumor biopsies require invasive removal of tissue from a solid tumor.

In contrast, the claimed invention allows for microsatellite instability status determination from a non-invasive, liquid biopsy sample. Advantageously, as outlined in Applicant’s specification, use of liquid biopsy procedures provide many advantageous over solid tumor biopsies:

[0016] Specifically, liquid biopsies offer several advantages over conventional solid tissue biopsy analysis. For instance, because bodily fluids can be collected in a minimally-invasive or non-invasive fashion, sample collection is simpler, faster, safer, and less expensive than solid tumor biopsies. Such methods require only small amounts of sample (e.g., 10 mL or less of whole blood per biopsy) and reduce the discomfort and risk of complications

experienced by patients during conventional tissue biopsies. In fact, liquid biological samples can be collected with limited or no assistance from medical professionals, and can be performed at almost any location. Further, *liquid biological samples can be collected from any patient, regardless of the location of their cancer, their overall health, and any previous biopsy collection.* This allows for analysis of the cancer genome of patients from which a solid tumor sample cannot be easily and/or safely obtained. In addition, because cell-free DNA in the bodily fluids arise from many different types of tissues in the patient, *the genomic alterations present in the pool of cell-free DNA are representative of various different clonal sub-populations of the cancerous tissue of the subject, facilitating a more comprehensive analysis of the cancerous genome of the subject than is possible from one or more sections of a single solid tumor sample.*

[0017] Liquid biopsies also enable serial genetic testing prior to cancer detection, during the early stages of cancer progression, throughout the course of treatment, and during remission, *e.g.*, to monitor for disease recurrence. The ability to conduct serial testing via non-invasive liquid biopsies throughout the course of disease could prove beneficial for many patients, *e.g.*, through monitoring patient response to therapies, the emergence of new actionable genomic alterations, and/or drug-resistance alterations. These types of information allow medical professionals to more quickly tailor and update therapeutic regimens, *e.g.*, facilitating more timely intervention in the case of disease progression. See, *e.g.*, Ilie and Hofman, Transl. Lung Cancer Res., 5(4):420-23 (2016).

Applicant's specification at paragraphs [0016] and [0017], emphasis added.

Accordingly, when viewed as a whole, the claimed method integrates any alleged judicial exception into a practical application that improves clinical oncology by reducing the time, cost, and invasiveness of testing for MSI status. Thus, for at least the reasons above, claim 1 is patent eligible under the second prong of Step 2A of the *Alice* analysis because the claim is not directed to an abstract idea.

Accordingly, claim 1 qualifies as eligible subject matter under 35 U.S.C. § 101. All other pending claims rejected under 35 U.S.C. § 101 depend from claim 1 and thus are patentable under 35 U.S.C. § 101 for at least the same reason as claim 1. Applicant therefore respectfully requests that the 35 U.S.C. § 101 rejection be withdrawn.

CONCLUSION

All the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn.

Applicant believes that a full and complete reply has been made to the outstanding Office Action, and as such, the present application is in condition for allowance. 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.

Except for issue fees payable under 37 CFR § 1.18, the Commissioner is hereby authorized by this paper to charge any necessary fees during the entire pendency of this application including fees due under 37 CFR §§ 1.16 and 1.17, which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310 (Order No.: 123138-5013-US).

Prompt and favorable consideration of this Amendment and Response is respectfully requested.

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS LLP

Dated: <u>November 21, 2024</u> Customer No.: 43850 Morgan, Lewis & Bockius LLP One Market, Spear Street Tower San Francisco, CA 94105 Telephone: (415) 442-1000 Facsimile: (415) 442-1001	By: <u>/ Andrew J. Antczak /</u> <u>Andrew J. Antczak, Reg. No. 80,781</u>
--	---



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 NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/945,588	07/31/2020	Ariane Lozac'hmeur	123138-5013-US	8972
43850	7590	05/21/2024		
Morgan, Lewis & Bockius LLP (SF) One Market, Spear Street Tower, Suite 2800 San Francisco, CA 94105			EXAMINER BAILEY, STEVEN WILLIAM	
			ART UNIT	PAPER NUMBER
			1672	
			NOTIFICATION DATE	DELIVERY MODE
			05/21/2024	ELECTRONIC

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

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

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

donald.mixon@morganlewis.com
sfipdocketing@morganlewis.com

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.
3. Applicant's submission filed on 20 February 2024 has been entered.

Status of the Claims

4. Claims 1-12, 16, 19-25, 154, 155, 159, and 161-164 are pending.
5. Claims 1-12, 16, 19-25, 154, 155, 159, and 161-164 are rejected.
6. Claim 25 is objected to.

Priority

7. Claims 1-12, 16, 19-25, 154, 155, 159, and 161-164 are given the benefit for priority to Provisional Application No. 62/881,845, filed 01 August 2019, Provisional Application No. 62/931,600, filed 06 November 2019, and Provisional Application No. 62/978,130, filed 18 February 2020.

Claim Interpretation

8. Claim 154 is interpreted as reciting a product-by-process limitation with the product being the data for enriched cell-free DNA fragments that comprises the plurality of predetermined microsatellite loci. The claim is further interpreted to not require the processing steps of producing the product.
9. Claim 1 at step (A) is interpreted as reciting a product-by-process limitation with the product being the data of a plurality of aligned nucleotide sequences that are mapped to a microsatellite locus in a plurality of predetermined microsatellite loci in a reference genome. The claim is further interpreted to not require the processing steps of producing the product.
10. Claim 1 at step (B) is interpreted as reciting a product-by-process limitation with the product being the data of respective microsatellite loci obtained from biological samples of a cohort of at least 200 subjects, wherein the cohort consists of healthy subjects or subjects with stable microsatellite cancer. The claim is further interpreted to not require the processing steps of producing the product.

Claim Objections

11. Claim 25 is objected to because of the following informalities: The word “and” in line two before the word “plurality” should be deleted.
12. Appropriate correction is required.

Claim Rejections - 35 USC § 112

13. The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.
14. 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.

15. Claim 162 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

16. Claim 162 is indefinite for reciting the limitation “the plurality of predetermined microsatellite loci comprises at least all of the human microsatellite loci selected from the group consisting of” because it is not clear how loci are to be selected from the group when the claim also recites “comprises all.” The claim is interpreted as limiting the plurality of at least 30 microsatellite loci to be selected from the group listed in the claim.

Claim Rejections - 35 USC § 101

17. The rejection of claims 1-12, 14-16, 19-25, 154, 155, and 159-164 under 35 U.S.C. 101 in the Office action mailed 20 September 2023 is maintained with modification in view of the amendment received 20 February 2024. The rejection of cancelled claims 14, 15, and 160 is withdrawn.

18. 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.

19. Claims 1-12, 16, 19-25, 154, 155, 159, and 161-164 are rejected under 35 U.S.C. 101 because the claimed invention is directed to an abstract idea without significantly more. The claims recite: (a) mathematical concepts, (e.g., mathematical relationships, formulas or equations, mathematical calculations); and (b) mental processes, i.e.,

concepts performed in the human mind, (e.g., observation, evaluation, judgement, opinion).

20. Following the flowchart in MPEP 2106:

Eligibility Step 1

21. Claims 1-12, 16, 19-25, 154, 155, 159, and 161-164 are directed to a method (process) of determining a microsatellite instability (MSI) status of a test subject.

Therefore, these claims are encompassed by the categories of statutory subject matter, and thus satisfy the subject matter eligibility requirements under Eligibility Step 1.

Eligibility Step 2A: Prong One

22. In determining whether a claim is directed to a judicial exception, examination is performed that analyzes whether the claim recites a judicial exception, i.e., whether a law of nature, natural phenomenon, or abstract idea is set forth or described in the claim.

23. Independent claim 1 recites a mental process at step (A) of considering data of a plurality of aligned nucleotide sequences comprising at least 15,000 nucleotide sequences and wherein the plurality of aligned nucleotide sequences has an average length of at least 50 nucleotides, and wherein the data of the plurality of aligned nucleotide sequences has been mapped to a microsatellite locus in a plurality of predetermined microsatellite loci in a reference genome for the species of the test subject, wherein the plurality of predetermined microsatellite loci comprises 30 or more loci and wherein a number of repeats within each microsatellite locus in the plurality of predetermined microsatellite loci in the germ line of the test subject is unknown; a mental process and a mathematical concept at step (B) of considering data for

determining, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, a corresponding density estimate of a number of repeat units in the respective microsatellite locus using a number of repeat units in each nucleotide sequence in a corresponding plurality of nucleotide sequences that map to the respective microsatellite locus obtained from biological samples of a cohort of at least 200 subjects, wherein the cohort consists of healthy subjects or subjects with stable microsatellite cancer, thereby determining at least 30 density estimates; a mental process and a mathematical concept at step (C) of considering data for converting each corresponding nucleotide sequence in the plurality of aligned nucleotide sequences to a likelihood score using (i) the corresponding density estimate of a number of repeat units in the respective microsatellite locus, which the corresponding nucleotide sequence maps to, from among the at least 30 density estimates and (ii) a number of repeat units in the corresponding nucleotide sequence, thereby obtaining a plurality of likelihood scores, each likelihood score in the plurality of likelihood scores associated with a corresponding microsatellite locus in the plurality of predetermined microsatellite loci; a mental process and a mathematical concept at step (D) of considering data for determining a respective value for a likelihood of microsatellite locus stability for each respective microsatellite locus in the plurality of predetermined microsatellite loci by taking a measure of central tendency of those likelihood scores in the plurality of likelihood scores that are associated with the respective microsatellite locus; a mental process and a mathematical concept at step (E) of considering data for using one or more corresponding metric values for one or more metrics for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the one or more

metrics including the likelihood of microsatellite locus stability of the respective microsatellite locus, to determine a proportion of the plurality of predetermined microsatellite loci that are unstable; and a mental process at step (F) of considering data for determining the MSI status of the test subject from the proportion of the plurality of predetermined microsatellite loci that are unstable.

24. Dependent claim 2 further recites a mental process of considering data for a corresponding set of raw sequence reads for the respective DNA fragment; a mathematical concept for aligning each respective raw sequence read in the set of raw sequence reads to the reference genome for the test subject, thereby obtaining a corresponding set of aligned raw sequence reads for the respective DNA fragment; a mental process and a mathematical concept of collapsing the corresponding set of aligned raw sequence reads for the respective DNA fragment into a corresponding nucleotide sequence for the respective DNA fragment that has been aligned to the human reference genome, thereby obtaining the plurality of aligned nucleotide sequences. Dependent claim 3 further recites a mental process of considering data wherein the plurality of aligned nucleotide sequences comprises at least 250,000 aligned nucleotide sequences. Dependent claim 4 further recites a mental process and a mathematical concept of considering data for determining that the one or more metrics further comprises a percentage score; a mental process and a mathematical concept of determining that the corresponding metric value for the percentage score is the percentage of aligned nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct

at the respective microsatellite locus. Dependent claim 5 further recites a mental process of considering data wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject. Dependent claim 6 further recites a mental process and a mathematical concept of considering data wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values, wherein each respective reference value in the plurality of reference values is determined at least in part based on a distribution of the number of repeat units at the respective microsatellite locus in a respective reference sample in a plurality of reference standards. Dependent claim 7 further recites a mental process and a mathematical concept of considering data wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus. Dependent claim 8 further recites a mental process and a mathematical concept of considering data wherein the one or more metrics further comprises a lower mean score; and a mental process and mathematical concept of considering data wherein the corresponding metric value for the lower mean score is determined at least in part by the mean number of repeat units in aligned nucleotide sequences, in the plurality of aligned nucleotides, mapping to the respective

microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus. Dependent claim 9 further recites a mental process and a mathematical concept of considering data wherein the mean number of repeat units is normalized by the reference number of repeat units representative of a stable construct at the respective microsatellite locus. Dependent claim 10 further recites a mental process and a mathematical concept of considering data wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject. Dependent claim 11 further recites a mental process and a mathematical concept of considering data wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values, wherein each respective reference value in the plurality of reference values is determined at least in part based on a distribution of the number of repeat units at the respective microsatellite locus in a respective reference sample in a plurality of reference samples. Dependent claim 12 further recites a mental process and a mathematical concept of considering data wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus. Dependent claim 16

further recites a mental process and a mathematical concept of considering data wherein the one or more corresponding metric values further comprises a corresponding standard deviation of the number of repeat units in the aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, mapping to the respective microsatellite locus. Dependent claim 19 further recites a mental process at step (E) of considering data of the corresponding metric value for each of the one or more metrics for each respective microsatellite locus in the plurality of microsatellite loci; and a mental process and a mathematical concept of considering a classifier that distinguishes between data of stable and unstable microsatellite loci. Dependent claim 20 further recites a mental process of considering data wherein the biological samples from the cohort include both (i) solid tumor samples from training subjects with stable microsatellite cancer and (ii) normal tissue samples. Dependent claim 21 further recites a mental process of considering data wherein the biological samples from the cohort further include (iii) solid tumor samples from training subjects with unstable microsatellite cancer. Dependent claim 22 further recites a mental process and a mathematical concept wherein the classifier comprises a k-nearest neighbors classifier. Dependent claim 23 further recites a mental process and a mathematical concept of considering data wherein the classifier assigns a stability status selected from unstable and stable to each respective microsatellite locus in the plurality of predetermined microsatellite loci, and the (F) determining classifies the subject as having a high level of microsatellite instability when at least a threshold proportion of microsatellite loci are assigned a status of unstable. Dependent claim 24 further recites a mental process and a mathematical concept of considering data wherein the threshold proportion of

microsatellite loci is at least 30% of the plurality of predetermined microsatellite loci.

Dependent claim 25 further recites a mental process and a mathematical concept of considering data wherein the threshold proportion of microsatellite loci is at least 50% of the plurality of predetermined microsatellite loci. Dependent claim 154 further recites a mental process of considering data wherein the plurality of cell-free DNA fragments from the liquid biopsy sample are enriched, relative to all cell-free DNA fragments in the liquid biopsy sample, for a set of cell-free DNA fragments that comprises the plurality of predetermined microsatellite loci. Dependent claim 155 further recites a mental process of considering data wherein the plurality of aligned sequence reads represents, on average, greater than 1000X sequence depth for each microsatellite locus in the plurality of predetermined microsatellite loci and the plurality of aligned nucleotide sequences comprises at least 30000 nucleotide sequences. Dependent claim 159 further recites a mental process of considering data from blood or blood plasma samples. Dependent claim 161 further recites a mental process of considering that the plurality of predetermined microsatellite loci comprises at least 10 of the microsatellite loci selected from a predefined group. Dependent claim 162 further recites a mental process of considering the plurality of predetermined microsatellite loci are selected from the group listed in the claim. Dependent claim 163 further recites a mental process of considering data from a human subject. Dependent claim 164 further recites a mental process of considering data of cell-free nucleotide sequences that are generated from sequencing cell-free DNA fragments.

25. The abstract ideas recited in the claims are evaluated under the broadest reasonable interpretation (BRI) and determined to be directed to the analysis of data

that in the simplest embodiments (sequence reads that are mapped to predetermined loci) are not too complex to be performed in the human mind with the aid of a pencil and paper. Additionally, the recited limitations that are identified as judicial exceptions from the mathematical concepts grouping of abstract ideas are abstract ideas regardless of whether or not the limitations are practical to perform in the human mind.

Eligibility Step 2A: Prong Two

26. In determining whether a claim is directed to a judicial exception, further examination is performed that analyzes if the claim recites additional elements that when examined as a whole integrates the judicial exception(s) into a practical application (MPEP 2106.04(d)). A claim that integrates a judicial exception into a practical application will apply, rely on, or use the judicial exception in a manner that imposes a meaningful limit on the judicial exception. The claimed additional elements are analyzed to determine if the abstract idea is integrated into a practical application (MPEP 2106.04(d)(I); MPEP 2106.05(a-h)). If the claim contains no additional elements beyond the abstract idea, the claim fails to integrate the abstract idea into a practical application (MPEP 2106.04(d)(III)).

27. The judicial exceptions noted above are not integrated into a practical application because the additional element of a computer system having one or more processors, and memory, in independent claim 1, does not improve the functioning of a generic computer, and therefore does not integrate the recited judicial exceptions into a practical application. The additional elements of sequencing DNA fragments from a liquid biopsy sample in claim 164; and obtaining sequence reads from DNA fragments in claim 2p[;kl; are data gathering steps used in the recited judicial exceptions, and

therefore do not integrate the recited judicial exceptions into a practical application. The additional element of obtaining data at steps (A) and (B) in claim 1 is an extra-solution activity that is part of the data gathering process used in the recited judicial exceptions, and therefore does not integrate the recited judicial exceptions into a practical application. The additional element of inputting data in claim 19 is an extra-solution activity that is part of the data gathering process used in the recited judicial exceptions, and therefore does not integrate the recited judicial exception into a practical application.

28. Claims 1-12, 16, 19-25, 154, 155, 159, and 161-164 do not recite additional elements which would integrate a judicial exception into a practical application.

Eligibility Step 2B

29. Because the claims recite an abstract idea, and do not integrate that abstract idea into a practical application, the claims are probed for a specific inventive concept. The judicial exception alone cannot provide that inventive concept or practical application (MPEP 2106.05). Identifying whether the additional elements beyond the abstract idea amount to such an inventive concept requires considering the additional elements individually and in combination to determine if they amount to significantly more than the judicial exception (MPEP 2106.05A i-vi).

30. The claims do not include additional elements that are sufficient to amount to significantly more than the judicial exception(s) because the additional elements of a computer system having one or more processors, and memory, in independent claim 1; obtaining data in claim 1; and inputting data in claim 19; are conventional (**see MPEP at**

2106.05(b) and 2106.05(d)(II) regarding conventionality of computer components and computer processes).

31. The additional elements of sequencing DNA fragments from a liquid biopsy sample in claim 164; and obtaining sequence reads from DNA fragments in claim 2; are conventional. Evidence for the conventionality is shown by Morganti et al. (Critical Reviews in Oncology, 2019 (Published January 2019), Vol. 133, pp. 171-182, as cited in the Office action mailed 20 September 2023). Morganti et al. reviews the complexity of genome sequencing and reporting, particularly focusing on next-generation sequencing (NGS) technologies and the implementation of precision medicine (Title; and Abstract). Morganti et al. shows that NGS technologies allow for the obtainment of extensive genetic information from liquid biopsies, and the obtainment of genetic material for sequencing from circulating tumor cells (CTCs) and circulating cell-free tumor DNA (ctDNA; page 172, column 2, para. 1; and page 177, column 2, Section 4.3). Morganti et al. further reviews NGS sequencing (page 173, Section 2.2) and NGS methods (page 174, Section 3), and further still, reviews advantages of NGS methodology with regard to microsatellite instability analyses (page 177, column 1, Section 4.2.2).

32. Furthermore, the additional elements evaluated in combination do not contribute an inventive concept, i.e., do not amount to significantly more than the judicial exception(s). The data gathering steps provide the data for the judicial exceptions, which are carried out by a general-purpose computer. Thus, there is not any non-routine step or element that has been clearly identified.

33. The Applicant's arguments received 20 February 2024 have been fully considered. The Applicant states on page 18 of the Remarks that the rejection under 35

U.S.C. § 101 should be withdrawn, further provides an overview of the subject matter eligibility analysis on pages 18-19. The Applicant further states on page 19 that the claims do not recite mathematical concepts, and states still further on page 20 that under the MPEP guidance, it is clear that Applicant's claim 1 does not recite mathematics, regardless of whether the claim involves or is based on any mathematical operations or algorithms. The Applicant further states that for instance, step (B) of claim 1 states what data is used for computing the density metric, but that the claim does not recite a particular method for computing the density metric, nor does the claim preclude others from computing density metrics for purposes other than determining a microsatellite instability (MSI) status of a test subject using cell-free DNA fragments from a liquid biopsy sample by counting repeats in microsatellites.

34. These arguments are not persuasive, because when determining whether a claim recites a mathematical concept (i.e., mathematical relationships, mathematical formulas or equations, and mathematical calculations), examiners should consider whether the claim recites a mathematical concept or merely limitations that are based on or involve a mathematical concept. A claim does not recite a mathematical concept (i.e., the claim limitations do not fall within the mathematical concept grouping), if it is only based on or involves a mathematical concept. Furthermore, it is important to note that a mathematical concept need not be expressed in mathematical symbols, because words used in a claim operating on data to solve a problem can serve the same purpose as a formula (MPEP 2106.04(a)(2)(I)). As noted in the rejection above at Eligibility Step 2A: Prong One, the claims recite mathematical concepts that are expressed with words that operate on data to determine an MSI status.

35. The Applicant states on page 21 of the Remarks that the claims do not recite mental processes because the amended claims do not contain limitations that can practically be performed in the human mind. The Applicant further states on pages 21-22 that step (A) of claim 1 requires obtaining at least 15,000 nucleotide sequences, and requires the retention of 1.5 million bytes of information, and that it would not be practical or possible for a human mind to memorize this amount of information, let alone assign each of these characters to a precise position in one of at least 15,000 sequences.

36. These arguments are not persuasive, because the step of obtaining data is identified as an additional element at Eligibility Step 2A: Prong Two, and there is no step of aligning sequences in claim 1, because that data is imported pre-aligned to a reference genome. With regard to claim 2, the step of aligning the sequence reads to a reference genome is identified as a mathematical concept (not a mental process) at Eligibility Step 2A: Prong One, and mathematical concepts are abstract ideas irrespective of whether or not a limitation recites a mental process. Furthermore, the recited mental processes do not require a human mind to memorize or store any particular amount of information, but only to perform in the mind with the aid of a pencil and paper. Still further, the simplest embodiment of the claim does not require the analysis of all 15,000 sequences at any particular locus, and only 30 loci need to be analyzed in the simplest embodiment after inputting the mapped sequence data.

37. The Applicant states on pages 22-24 of the Remarks that step (B) of claim 1 that a density estimate cannot be mentally performed. The Applicant further states that a

particular function (KernelDensity) that is not recited in the claim cannot be mentally performed, and that step (B) is not directed to a mathematical concept.

38. These arguments are not persuasive, because as noted in the response to arguments above, a mathematical concept is an abstract idea irrespective of whether or not a limitation also recites a mental process, and step (B) is identified at Eligibility Step 2A: Prong One in the rejection above as reciting a mathematical concept. Furthermore, the simplest embodiment of the claim is not too complex to perform a density estimate at a single locus, one locus at a time, for each respective locus in the plurality of predetermined loci.

39. The Applicant states on page 24 of the Remarks that it would not be practical or possible for a human mind to convert each of at least 15,000 nucleotide sequences into a separate likelihood score using the corresponding density estimate of the microsatellite loci that each such nucleotide sequence maps to as required by step (c) of claim 1.

40. This argument is not persuasive, because as noted in the response to arguments above, in the simplest embodiment of the claim, far fewer than 15,000 sequences may map to a locus, and only 30 loci need to be analyzed in the simplest embodiment after inputting the mapped sequence data. Therefore, the data analysis is not too complex to perform in the human mind with the aid of a pencil and paper. Furthermore, and as noted in the response to arguments above, a mathematical concept is an abstract idea irrespective of whether or not a limitation also recites a mental process, and step (C) is identified at Eligibility Step 2A: Prong One in the rejection above as reciting a mathematical concept.

41. The Applicant states on page 24 of the Remarks that it would not be practical or possible for a human mind to take a measure of central tendency (e.g., mean, average, mode, etc.) for each of at least 30 microsatellite loci using the likelihood scores, across the at least 30 microsatellite loci, of at least 15,000 nucleotide sequences as required by step (D) of claim 1, and thus neither claim 1 nor any dependent claim is directed to a mental process or any other abstract idea on this basis alone.

42. This argument is not persuasive, because as noted in the response to arguments above, in the simplest embodiment of the claim, far fewer than 15,000 sequences may map to a locus, and only 30 loci need to be analyzed in the simplest embodiment after inputting the mapped sequence data. Therefore, the data analysis at each of 30 loci is not too complex to perform in the human mind with the aid of a pencil and paper.

Furthermore, and as noted in the response to arguments above, a mathematical concept is an abstract idea irrespective of whether or not a limitation also recites a mental process, and step (D) is identified at Eligibility Step 2A: Prong One in the rejection above as reciting a mathematical concept.

43. The Applicant states on page 25 of the Remarks that regardless of whether the amended claims recite an abstract idea, the claims are not directed to an abstract idea when properly viewed as a whole, at least because the claims, as amended, integrate any alleged judicial exception into the practical application of an improvement in the technical field of determining a microsatellite instability status of a test subject from a liquid biopsy sample and the technical field of liquid biopsy assays by adding specific limitations and/or adding unconventional steps that confine the claims to the particular

useful application that provides accurate determination of the microsatellite instability status of a cancer.

44. These arguments are not persuasive, because as noted in the rejection above, the limitations that result in the determination of the MSI status of the test subject from the proportion of the plurality of predetermined microsatellite loci that are unstable comprise the recited judicial exceptions identified at Eligibility Step 2A: Prong One, and the judicial exceptions alone cannot provide a practical application (MPEP 2106.04(d)(III)) or inventive concept (MPEP 2106.05(I)). Because a judicial exception alone is not patent eligible subject matter, if there are no additional elements besides the judicial exception, that is insufficient to integrate the judicial exception into a practical application. As noted in the rejection above, claims 1-12, 16, 19-25, 154, 155, 159, and 161-164 do not recite any additional elements that would integrate a judicial exception into a practical application, e.g., an improvement in the functioning of a computer, or an improvement to any other technology or technical field (MPEP 2106.04(d)(1)). Furthermore, the claimed limitations for the determination of the MSI status of the test subject are a purported improvement to the abstract ideas (data analysis), and not an improvement to a technology or technical field.

45. The Applicant discusses claim limitations with regard to the Applicant's arguments for patentability of the claim under 35 U.S.C. 101 on pages 26-26, and states on page 30 of the Remarks that the instant claim 1 recites a specific and unconventional process that is not well-understood, nor routine, nor conventional activity in the field, and is a process that is confined by the claim to a particular useful application and enables accurate determination of the MSI status of a test subject from a liquid biopsy.

The Applicant further states that claim 1 recites a method that solves the technical problem(s) described in the specification, integrates the alleged abstract idea into an inventive concept that is significantly more than any abstract idea, and provides improvements to the technical field of determination of the MSI status of the test subject from a liquid biopsy sample.

46. These arguments are not persuasive, because the judicial exceptions noted above at Eligibility Step 2A: Prong One comprise the recited abstract ideas (data analysis limitations), which are not integrated into a practical application at Eligibility Step 2A: Prong Two because the claims do not recite additional elements that when examined as a whole, integrate the judicial exceptions into a practical application (MPEP 2106.04(d)). Furthermore, the claims do not recite additional elements that are sufficient to amount to significantly more than the judicial exceptions at Eligibility Step 2B because the additional elements of a computer system having one or more processors, and memory, in independent claim 1; obtaining data in claim 1; inputting data in claim 19; sequencing DNA fragments from a liquid biopsy sample in claim 164; and obtaining sequence reads from DNA fragments in claim 2; are conventional additional elements. Furthermore, the claimed method for determining the MSI status of the test subject is a purported improvement to the abstract ideas (data analysis), and not an improvement to a technology or technical field.

Conclusion

47. This Office action is a Non-Final action. A shortened statutory period for reply to this action is set to expire **THREE MONTHS** from the mailing date of this application.

48. Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN W. BAILEY whose telephone number is (571) 272-8170. The examiner can normally be reached Mon - Thurs 0730 - 1800.

49. 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>.

50. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry D. Riggs can be reached on (571) 270-3062. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

51. 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.

/S.W.B./
Examiner, Art Unit 1672
/JOHN S BRUSCA/
Primary Examiner, Art Unit 1672

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A method of determining a microsatellite instability (MSI) status of a test subject, the method comprising:

at a computer system having one or more processors, and memory storing one or more programs for execution by the one or more processors:

(A) obtaining, for each respective cell-free DNA fragment in a plurality of cell-free DNA fragments from a liquid biopsy sample from the test subject, a corresponding nucleotide sequence that has been mapped aligned to a microsatellite locus in a plurality of predetermined microsatellite loci in a reference genome for the species of the test subject, wherein the plurality of predetermined microsatellite loci comprises 30 or more loci and wherein a number of repeats within each microsatellite locus in the plurality of predetermined microsatellite loci in the germ line of the test subject is unknown, thereby obtaining a plurality of aligned nucleotide sequences, wherein the plurality of aligned nucleotide sequences comprises at least 15000 nucleotide sequences and wherein the plurality of aligned nucleotide sequences has an average length of at least 50 nucleotides;

(B) determining, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, a corresponding density estimate of a number of repeat units in the respective microsatellite locus using a number of repeat units in each nucleotide sequence in a corresponding plurality of nucleotide sequences that map to the respective microsatellite locus obtained from biological samples of a cohort of at least 200 subjects, wherein the cohort consists of healthy subjects or subjects with stable microsatellite cancer, thereby determining at least 30 density estimates;

(C) converting each corresponding nucleotide sequence in the plurality of aligned nucleotide sequences to a likelihood score using (i) the corresponding density estimate of a number of repeat units in the respective microsatellite locus, which the corresponding nucleotide sequence maps to, from among the at least 30 density estimates and (ii) a number of repeat units in the corresponding nucleotide sequence, thereby obtaining a plurality of likelihood scores, each

likelihood score in the plurality of likelihood scores associated with a corresponding microsatellite locus in the plurality of predetermined microsatellite loci;

(D) determining a respective value for a likelihood of microsatellite locus stability for each respective microsatellite locus in the plurality of predetermined microsatellite loci by taking a measure of central tendency of those likelihood scores in the plurality of likelihood scores that are associated with the respective microsatellite locus;

~~(B) using the plurality of aligned nucleotide sequences to determine, for each respective microsatellite locus in a plurality of predetermined microsatellite loci, wherein each respective microsatellite locus in the plurality of microsatellite loci has a nucleic acid sequence that includes a variable number of repeat units, a corresponding metric value for each of one or more metrics, wherein each respective metric in the one or more metrics is determined, at least in part, by a distribution of the number of repeat units in each aligned nucleotide sequence, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus, wherein~~

~~the one or more metrics comprises a likelihood score, and~~

~~the corresponding metric value for the likelihood score is a statistical measure of a distribution of probabilities that each respective aligned nucleotide sequence in a subset of the set of aligned nucleotide sequences encompassing the respective microsatellite locus is a member of a distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite locus, wherein the subset of aligned nucleotide sequences consists of the aligned nucleotide sequences encompassing the respective microsatellite locus that have a number of repeat units that falls within a threshold percentile of the smallest number of repeat units; and~~

(E) [(C)] using, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the one or more corresponding metric values for [(the)] one or more metrics for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the one or more metrics including the likelihood of microsatellite locus stability of the respective microsatellite locus, to determine a proportion of the plurality of predetermined microsatellite loci that are unstable; and

(F) corresponding reference metric values for the one or more metrics representative of a stable construct at the respective microsatellite locus, the reference metric values determined

~~across nucleotide sequences obtained from biological samples from a training cohort that includes (i) solid tumor samples from training subjects with stable microsatellite cancer or (ii) normal tissue samples, thereby~~ determining the MSI status of the test subject from the proportion of the plurality of predetermined microsatellite loci that are unstable.

2. (Currently Amended) The method of claim 1, wherein the obtaining (A) comprises, for each respective DNA fragment in the plurality of DNA fragments:

obtaining a corresponding set of raw sequence reads for the respective DNA fragment;
aligning each respective raw sequence read in the set of raw sequence reads to the reference genome for the test subject, thereby obtaining a corresponding set of aligned raw sequence reads for the respective DNA fragment; and

collapsing the corresponding set of aligned raw sequence reads for the respective DNA fragment into a corresponding nucleotide sequence for the respective DNA fragment that has been aligned to the human reference genome, thereby obtaining ~~[[a]]~~ the plurality of aligned nucleotide sequences.

3. (Previously Presented) The method of claim 1, wherein the plurality of aligned nucleotide sequences comprises at least 250,000 aligned nucleotide sequences.

4. (Currently Amended) The method of claim 1, wherein:

the one or more metrics further comprises a percentage score, and
the corresponding metric value for the percentage score is the percentage of aligned nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus.

5. (Original) The method of claim 4, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject.

6. (Original) The method of claim 4, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values, wherein each respective reference value in the plurality of reference values is determined at least in part based on a distribution of the number of repeat units at the respective microsatellite locus in a respective reference sample in a plurality of reference standards.

7. (Original) The method of claim 4, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus.

8. (Currently Amended) The method of claim 1, wherein:
the one or more metrics further comprises a lower mean score, and
the corresponding metric value for the lower mean score is determined at least in part by the mean number of repeat units in aligned nucleotide sequences, in the plurality of aligned nucleotides, ~~encompassing~~ mapping to the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus.

9. (Original) The method of claim 8, wherein the mean number of repeat units is normalized by the reference number of repeat units representative of a stable construct at the respective microsatellite locus.

10. (Previously Presented) The method of claim 8, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject.

11. (Previously Presented) The method of claim 8, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values, wherein each respective reference value in the plurality of reference values is determined at least in part based on a distribution of the number of repeat units at the respective microsatellite locus in a respective reference sample in a plurality of reference samples.

12. (Previously Presented) The method of claim 8, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus.

13-15. (Cancelled)

16. (Currently Amended) The method of claim 1, wherein the one or more corresponding metric values further comprises a corresponding standard deviation of the number of repeat units in the aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, ~~encompassing~~ mapping to the respective microsatellite locus.

17-18. (Cancelled)

19. (Currently Amended) The method of claim 1, wherein the ~~comparing C)~~ using E) comprises inputting, for each respective microsatellite locus in the plurality of microsatellite loci, the corresponding metric value for each of the one or more metrics to a classifier ~~trained to that~~ distinguishes between stable and unstable microsatellite loci, ~~wherein the classifier was trained using the reference metric values determined across the nucleotide sequences obtained from the biological samples from the training cohort that included (i) solid tumor samples from training subjects with stable microsatellite cancer or (ii) normal tissue samples.~~

20. (Currently Amended) The method of claim ~~[[19]]~~ 1, wherein the biological samples from the ~~training~~ cohort ~~included~~ include both (i) solid tumor samples from training subjects with stable microsatellite cancer and (ii) normal tissue samples.

21. (Currently Amended) The method of claim ~~[[19]]~~ 1, wherein the biological samples from the ~~training~~ cohort further ~~included~~ include (iii) solid tumor samples from training subjects with unstable microsatellite cancer.

22. (Currently Amended) The method of claim 19, wherein the classifier comprises a k-nearest neighbors classifier ~~algorithm~~.

23. (Currently Amended) The method of claim 19, wherein the classifier assigns a stability status selected from unstable and stable to each respective microsatellite locus in the plurality of predetermined microsatellite loci, and the (F) determining classifies the subject ~~is classified as~~ having a high level of microsatellite instability when at least a threshold ~~number~~ proportion of microsatellite loci are assigned a status of unstable.

24. (Currently Amended) The method of claim 23, wherein the threshold ~~number~~ proportion of microsatellite loci is at least 30% of the ~~total number of microsatellite loci in the~~ plurality of predetermined microsatellite loci.

25. (Currently Amended) The method of claim 23, wherein the threshold ~~number~~ proportion of microsatellite loci is at least 50% of the ~~total number of microsatellite loci in the~~ plurality of predetermined microsatellite loci.

Claims 26-153. (Canceled)

154. (Previously Presented) The method of claim 1, wherein the plurality of cell-free DNA fragments from the liquid biopsy sample are enriched, relative to all cell-free DNA fragments in the liquid biopsy sample, for a set of cell-free DNA fragments that comprises the plurality of predetermined microsatellite loci.

155. (Currently Amended) The method of claim 1, wherein the plurality of aligned sequence reads represents, on average, greater than 1000X sequence depth for each microsatellite locus in the plurality of predetermined microsatellite loci and the plurality of aligned nucleotide sequences comprises at least 30000 nucleotide sequences.

156-158.

159. (Previously Presented) The method of claim 1, wherein the liquid biopsy sample is a blood or blood plasma sample.

160. (Cancelled)

161. (Previously Presented) The method of claim 1, wherein the plurality of predetermined microsatellite loci comprises at least 10 of the human microsatellite loci selected from the group consisting of chr18:649874-649899, chr14:73959698-73959724, chr8:23712061-23712083, chr3:71008336-71008359, chr4:39501717-39501745, chr3:113377476-113377497, chr19:14104683-14104707, chr11:63149665-63149686, chr6:11714634-11714658, chr1:47325294-47325317, chr3:130733041-130733062, chr3:30691866-30691886, chr11:115047027-115047051, chr1:149900980-149901006, chrX:101409249-101409275, chr8:79629733-79629757, chr11:125763605-125763628, chr5:67584507-67584529, chr3:164905643-164905664, chr5:58270452-58270474, chr2:211179760-211179781, chr1:237060940-237060965, chr3:123332870-123332896, chr18:319939-319960, chr2:64069272-64069297, chr12:13364421-13364441, chr4:83785669-83785697, chr5:88018364-88018386, chr5:88018383-88018406, chr21:30339200-30339221, chr17:1326749-1326773, chr5:161494985-161495007, chr15:37391747-37391769, chr6:43021971-43021993, chr7:94989250-94989277, chr2:99614590-99614613, chr2:152236040-152236064, chr11:65268474-65268496, chr2:118854089-118854112, and chr18:649874-649899.

162. (Previously Presented) The method of claim 1, wherein the plurality of predetermined microsatellite loci comprises at least all of the human microsatellite loci selected from the group

consisting of chr18:649874-649899, chr14:73959698-73959724, chr8:23712061-23712083, chr3:71008336-71008359, chr4:39501717-39501745, chr3:113377476-113377497, chr19:14104683-14104707, chr11:63149665-63149686, chr6:11714634-11714658, chr1:47325294-47325317, chr3:130733041-130733062, chr3:30691866-30691886, chr11:115047027-115047051, chr1:149900980-149901006, chrX:101409249-101409275, chr8:79629733-79629757, chr11:125763605-125763628, chr5:67584507-67584529, chr3:164905643-164905664, chr5:58270452-58270474, chr2:211179760-211179781, chr1:237060940-237060965, chr3:123332870-123332896, chr18:319939-319960, chr2:64069272-64069297, chr12:13364421-13364441, chr4:83785669-83785697, chr5:88018364-88018386, chr5:88018383-88018406, chr21:30339200-30339221, chr17:1326749-1326773, chr5:161494985-161495007, chr15:37391747-37391769, chr6:43021971-43021993, chr7:94989250-94989277, chr2:99614590-99614613, chr2:152236040-152236064, chr11:65268474-65268496, chr2:118854089-118854112, and chr18:649874-649899.

163. (Previously Presented) The method of claim 1, wherein the subject is a human.

164. (Currently Amended) The method of claim 1, ~~wherein~~ the method further ~~comprises~~ comprising:

sequencing the plurality of cell-free DNA fragments from the liquid biopsy sample to generate the plurality of cell-free aligned nucleotide sequences.

Remarks/Arguments

Status of the Claims

1-12, 14-16, 19-25, 154, 155, and 159-164 were previously pending in the application.

With this Response, claim 1 is amended to recite with more particularity one embodiment of Applicant's invention. Example support for the amendments to claim 1 is found in the following Table.

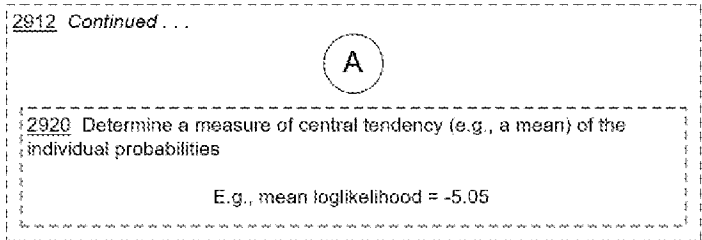
Claim 1	Example Support in Specification as Filed
(A) obtaining, for each respective <u>cell-free</u> DNA fragment in a plurality of <u>cell-free</u> DNA fragments from a liquid biopsy sample from the test subject,	[0002] The present disclosure relates generally to the use of cell-free DNA sequencing data to provide clinical support for personalized treatment of cancer. [0220] Liquid biopsy samples include cell free nucleic acids, including cell-free DNA (cfDNA).
a corresponding nucleotide sequence that has been <u>mapped aligned to a microsatellite locus in a plurality of predetermined microsatellite loci in</u> a reference genome for the species of the test subject,	[0285] In some embodiments, the read mapping process starts by building an index of either the reference genome or the reads, which is then used to retrieve the set of positions in the reference sequence where the reads are more likely to align.
<u>wherein the plurality of predetermined microsatellite loci comprises 30 or more loci</u>	[0331] For example, microsatellite instability status can be assessed by determining the number of repeating units present at a plurality of microsatellite loci, <i>e.g.</i> , 5, 10, 15, 20, 25, 30, 40, 50, 75, 100, 250, 500, 750, 1000, 2500, 5000, or more loci.
<u>and wherein a number of repeats within each microsatellite locus in the plurality of predetermined microsatellite loci in the germ line of the test subject is unknown</u>	In accordance with [0073] of the specification, since the germ line is unknown for the liquid biopsy assay sample, the number of repeats within each microsatellite locus in the plurality of predetermined microsatellite loci in the germ line of the test subject is also unknown: [0073] This is particularly true when performed in the context of a liquid biopsy assay, because liquid biological samples contain a complex mixture of short DNA fragments originating from many different germline (<i>e.g.</i> , healthy) and diseased (<i>e.g.</i> , cancerous)

Claim 1	Example Support in Specification as Filed
	tissues. Thus, the cellular origins of the sequence reads are unknown, and the sequence signals originating from cancerous cells, which may constitute multiple sub-clonal populations, must be computationally deconvoluted from signals originating from germline and hematopoietic origins, in order to provide relevant information about the subject's cancer. Thus, in addition to the computationally taxing processes required to align sequence reads to a human genome, there is a computation problem of determining whether a particular abnormal signal, <i>e.g.</i>, one or more sequence reads corresponding to a genomic alteration, (i) is not an artifact, and (ii) originated from a cancerous source in the subject. This is increasingly difficult during the early stages of cancer—when treatment is presumably most effective—when only small amounts of ctDNA are diluted by germline and hematopoietic DNA.
thereby obtaining a plurality of aligned nucleotide sequences, <u>wherein the plurality of aligned nucleotide sequences comprises at least 15000 nucleotide sequences</u>	Paragraph [0267] discloses using a depth of at least 500X. Paragraph [0108] defines depth of a locus as number of unique cell-free DNA fragments mapping to that locus. A depth of 500X multiplied by the minimum number of microsatellite loci already recited, 30, is 30 x 500, or at least 15000 nucleotide sequences: [00267] In some embodiments, panel-targeting sequencing is performed to an average on-target depth of at least 500x, at least 750x, at least 1000x, at least 2500x, at least 500x, at least 10,000x, or greater depth. [0108] As used herein, the term “read-depth,” “sequencing depth,” or “depth” can refer to a total number of unique nucleic acid fragments encompassing a particular locus or region of the genome of a subject that are sequenced in a particular sequencing reaction. Sequencing depth can be expressed as “Yx”, <i>e.g.</i>, 50x, 100x, <i>etc.</i>, where “Y” refers to the number of unique nucleic acid fragments encompassing a particular locus that are sequenced in a sequencing reaction.
<u>and wherein the plurality of aligned nucleotide sequences has an average length of at least 50 nucleotides;</u>	[00265] Next-generation sequencing produces millions of short reads (<i>e.g.</i>, sequence reads) for each biological sample. Accordingly, in some embodiments, the plurality of sequence reads obtained by next-generation

Claim 1	Example Support in Specification as Filed
	sequencing of cfDNA molecules are DNA sequence reads. In some embodiments, the sequence reads have an average length of at least fifty nucleotides. In other embodiments, the sequence reads have an average length of at least 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, or more nucleotides.
<u>(B) determining, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, a corresponding density estimate of a number of repeat units in the respective microsatellite locus using a number of repeat units in each nucleotide sequence in a corresponding plurality of nucleotide sequences that map to the respective microsatellite locus obtained from biological samples of a cohort of at least 200 subjects, wherein the cohort consists of healthy subjects or subjects with stable microsatellite cancer, thereby determining at least 30 density estimates;</u>	[0041] Figures 6A and 6B illustrate density estimates for reference distributions from a microsatellite locus with a single stable number of repeat units (6A) and a microsatellite locus with multiple stable numbers of repeat units (6B), in accordance with some embodiments of the present disclosure. [0063] Figure 28A illustrates a method for determining a mode-specific, e.g., mode = 16, 17, or 18, repeat unit density estimate for a microsatellite locus using a set of reference samples of microsatellite stable tissue, in accordance with some embodiments of the disclosure. [0065] Figure 28C illustrates mode-specific kernel density estimates for the distribution of repeat unit lengths from a set of reference samples of microsatellite stable tissues, determined as outlined in Figure 28A, in accordance with some embodiments of the disclosure. [00368] In some embodiments, the probability that a respective aligned nucleotide sequence is a member of a distribution encompassing a stable construct is determined using a density model of the distribution of the number of repeat units in a set of reference samples. For instance, in some embodiments, a density model is formed for the distribution of the number of repeat units at a particular microsatellite locus in one or more reference biological samples having stable microsatellite loci, e.g., one or more normal tissue samples and/or one or more solid tumor samples from microsatellite stable cancer (MSS). In some embodiments, the density estimate is a kernel density estimate (KDE). However, other methodologies for forming a density estimate are known in the field, and may be used in conjunction with the methods described herein.

Claim 1	Example Support in Specification as Filed
	[00369] In some embodiments, e.g., where the mode of a distribution of repeat units representative of a stable microsatellite locus varies within a population, the density model for the stable distribution is formed using reference samples having the same mode for the distribution of repeat units at the microsatellite locus as the mode of the distribution of repeat units at the microsatellite locus in the test sample. An example of forming mode-specific density estimates for a particular microsatellite locus is shown in Figure 28A. As illustrated, a plurality of reference samples having stable microsatellite loci are used, e.g., reference samples 1 through 5. For a particular microsatellite locus being evaluated, the mode (or other measure of central tendency) of the distribution of repeat unit lengths at the particular microsatellite locus is determined, e.g., 16, 17, or 18. Mode-specific density estimates are then formed from the pooled distributions of the repeat unit lengths from each reference sample having a particular mode. For instance, the repeat unit length distribution of reference sample 4 is used to create a density estimate for a mode of 16 repeat units; the repeat unit length distribution of reference sample 2 is used to create a density estimate for a mode of 17 repeat units; and the repeat unit length distributions of reference samples 1, 3, and 5 are used to create a density estimate for a mode of 18 repeat units. This process is repeated for each microsatellite locus, such that the density estimate for a first particular mode and microsatellite locus may be formed using a different subset of stable reference samples than the density estimate for a second particular mode and microsatellite locus. [0579] It is important to note that some loci have more than one stable number of repeat units in the population. For example, for a given locus A, patient 1 may have 14 repeat units in their germline DNA while patient 2 only has 12 repeat units. To account for this variability, a training set of 212 solid normal tissue samples and 133 solid tumor samples are used to generate, on a per locus basis, a sample-specific reference distribution and density estimate where only the reference samples that share the same mode of the

Claim 1	Example Support in Specification as Filed
	number of repeat units as the sample being analyzed are included the reference distribution and density estimate. In the aforementioned example, the locus for patient 1 would be compared to a reference distribution and density estimate made up of reference samples having a mode of 14 repeat units at that locus, while the locus for patient 2 would be compared to a reference distribution and density estimate made up of reference samples having a mode of 12 repeat units at that locus. For some loci, there is a single, stable number of repeat units in the population of reference samples (e.g., all samples have 12 repeat units at that locus). Examples of density estimates and reference distributions for a locus with a single stable number of repeat units in a population is shown in Figure 6A, while examples of a global density estimate, mode-specific density estimates, and a reference distribution for a locus with multiple stable numbers of repeat units in the population is shown in Figure 6B. [0580] Accordingly, for each locus in the set of 39 loci, the mode of the number of repeated units was determined. Sequencing data for reference distributions for each locus, which are each based on solid normal tissue samples and solid tumor samples from microsatellite stable cancers having a similar mode of the number of repeated units at the particular locus, were generated using a commercially available hybridization-based next generation sequencing methodology. Each reference distribution is used to model a density estimate of the number of repeat units in sequencing reads of a stable locus (using scikit-learn's KernelDensity function with a gaussian kernel and a bandwidth of 0.5). This density estimate gives an estimation of the probability of each sequencing read coming from a stable locus given the number of repeat units it contains. [0203] In some embodiments, a plurality of biological subjects is a clinical cohort, e.g., a group of participants in a clinical trial or study. In some embodiments, the plurality of subjects in the cohort comprises at least 10, at least 20, at least 30, at least 40,

Claim 1	Example Support in Specification as Filed
	at least 50, at least 100, at least 200 , at least 500, at least 1000, at least 2000, or at least 5000 subjects .
<u>(C) converting each corresponding nucleotide sequence in the plurality of aligned nucleotide sequences to a likelihood score using (i) the corresponding density estimate of a number of repeat units in the respective microsatellite locus, which the corresponding nucleotide sequence maps to, from among the at least 30 density estimates and (ii) a number of repeat units in the corresponding nucleotide sequence, thereby obtaining a plurality of likelihood scores, each likelihood score in the plurality of likelihood scores associated with a corresponding microsatellite locus in the plurality of predetermined microsatellite loci;</u>	[0580] Accordingly, for each locus in the set of 39 loci, the mode of the number of repeated units was determined. Sequencing data for reference distributions for each locus, which are each based on solid normal tissue samples and solid tumor samples from microsatellite stable cancers having a similar mode of the number of repeated units at the particular locus, were generated using a commercially available hybridization-based next generation sequencing methodology. Each reference distribution is used to model a density estimate of the number of repeat units in sequencing reads of a stable locus (using scikit-learn's KernelDensity function with a gaussian kernel and a bandwidth of 0.5). This density estimate gives an estimation of the probability of each sequencing read coming from a stable locus given the number of repeat units it contains.
<u>(D) determining a respective value for a likelihood of microsatellite locus stability for each respective microsatellite locus in the plurality of predetermined microsatellite loci by taking a measure of central tendency of those likelihood scores in the plurality of likelihood scores that are associated with the respective microsatellite locus;</u>	Block 2920 of Figure 29A: 
~~(B) using the plurality of aligned nucleotide sequences to determine, for each respective microsatellite locus in a plurality of predetermined microsatellite loci, wherein each respective microsatellite locus in the plurality of microsatellite loci has a nucleic acid sequence that includes a~~	Original clause B has been replaced by new clauses (B), (C), and (D) based on the support provided fore new clauses (B), (C), and (D) presented above. Moreover, the requirement for one or more metric values for one or more metrics for each microsatellite locus has been moved to clause (E) (formally clause (C))

Claim 1	Example Support in Specification as Filed
~~variable number of repeat units, a corresponding metric value for each of one or more metrics, wherein each respective metric in the one or more metrics is determined, at least in part, by a distribution of the number of repeat units in each aligned nucleotide sequence, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus, wherein~~	
~~the one or more metrics comprises a likelihood score, and the corresponding metric value for the likelihood score is a statistical measure of a distribution of probabilities that each respective aligned nucleotide sequence in a subset of the set of aligned nucleotide sequences encompassing the respective microsatellite locus is a member of a distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite locus, wherein the subset of aligned nucleotide sequences consists of the aligned nucleotide sequences encompassing the respective microsatellite locus that have a number of repeat units that falls within a threshold percentile of the smallest number of repeat units; and~~	
(E) ~~[(C)]~~ <u>using</u> , for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the <u>one or more</u> corresponding metric values for ~~[[the]]~~ one or more metrics <u>for each</u>	Original clause (B), now deleted, specified one or more corresponding metric values for one or more metrics for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the one or more metrics including the likelihood of microsatellite locus stability of the respective microsatellite locus

Claim 1	Example Support in Specification as Filed
<u>respective microsatellite locus in the plurality of predetermined microsatellite loci, the one or more metrics including the likelihood of microsatellite locus stability of the respective microsatellite locus.</u>	
to <u>determine a proportion of the plurality of predetermined microsatellite that are unstable; and</u> (F) ~~corresponding reference metric values for the one or more metrics representative of a stable construct at the respective microsatellite locus, the reference metric values determined across nucleotide sequences obtained from biological samples from a training cohort that includes (i) solid tumor samples from training subjects with stable microsatellite cancer or (ii) normal tissue samples, thereby determining the MSI status of the test subject from the proportion of the plurality of predetermined microsatellite loci that are unstable.~~	[0352] Then, the individual stability calls for each locus are used together to determine (462) the microsatellite stability status for the cancer of the subject. In some embodiments, the determination is made based on a threshold number of unstable microsatellite loci. For instance, in some embodiments, when at least 20% of the individual microsatellite loci are determined to be unstable, the cancer of the subject is classified as unstable. In other embodiments, when at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, or at least 70% of the individual microsatellite loci are determined to be unstable, the cancer of the subject is classified as unstable.

With this Response, claims 2, 4, 8, 16, 19-25, and 155 are amended to correct for clarity and to correct for antecedent basis. Support for the amendment is analogous to the support given for clause “at least 15000 nucleotide sequences” in the above Table.

With this Response, claims 14, and 15, and 160 are cancelled without prejudice.

Accordingly, the claim amendments do not introduce any new matter. Applicant respectfully requests entry of the claim amendments.

Upon entry of the present amendment, claims 1-13, 16, 19-25, 154, 155, and 159, 161-164 will be pending for examination with claim 1 being independent.

The rejection under 35 U.S.C. § 101 should be withdrawn

Claims 1-16, 19-25, 154, 155, and 159-163 stand rejected under 35 U.S.C. § 101 as allegedly being directed to an abstract idea without significantly more, and specifically to mental processes and/or mathematical concepts. To the extent that the rejection is asserted to apply to the amended claims, Applicant respectfully traverses the rejection for at least the following reasons. The subject matter eligibility of a claimed method is examined according to the two-part *Alice* test.¹ This test requires an Examiner to:

- 1) determine whether the claim is “directed to” a judicial exception, *e.g.*, an abstract idea” and, if so,
- 2) “determine whether any element, or combination of elements, in the claim is sufficient to ensure that the claim amounts to significantly more than the judicial exception.”

Applicant analyzes the claims below under the *2019 Guidance*, which “supersedes all versions of the U.S.P.T.O.’s ‘Eligibility Quick Reference Sheet Identifying Abstract Ideas’ (first issued in July 2015 and updated most recently in July 2018),”² the October 2019 Patent Eligibility Guidance Update (the “Revised Guidance”), and the latest Manual of Patent Examining Procedures (MPEP 2106) for Patent Subject Matter Eligibility (Revision 10.2019).

Step 1 of the 2019 Guidance requires considering whether the claimed subject matter falls within the four statutory categories of patentable subject matter identified by 35 U.S.C. § 101: Process, machine, manufacture, or composition of matter.

Step 2 of the 2019 Guidance integrates inquiries 1 and 2 of the *Alice* test as sub-steps 2A and 2B, respectively. In the first prong of Step 2A, the Examiner is required to evaluate whether the claim **recites** a judicial exception, *i.e.*, an abstract idea enumerated in the 2019 Guidance, a law of nature, or a natural phenomenon. If no judicial exception is recited, the claim is patent eligible. If an exception is recited in the claim, the analysis proceeds to the second prong of step

¹ *Alice Corporation Pty. v. CLS Bank International*, 573 U.S. 208 (2014); *see also*, MPEP § 2106(I); *2014 Interim Guidance on Patent Subject Matter Eligibility*, 79 Fed. Reg. 74618 (December 16, 2014) (37 CFR Part 1) (hereinafter, the “*Interim Guidance*”).

² *2019 Revised Patent Subject Matter Eligibility Guidance*, Fed. Reg. 84:4 50 (2019) (hereinafter, the “*2019 Guidance*”).

2A, to determine whether the claim is “directed to” the judicial exception recited in the claim. In the second prong, the Examiner is required to evaluate whether the claim recites additional elements that integrate the exception into a practical application of the exception. If the recited judicial exception is integrated into a practical application, the claim is patent eligible. If the exception recited in the claim is not integrated into a practical application, the analysis proceeds to Step 2B, to determine whether the claim contains “significantly more” than the judicial exception.

The claims are patent eligible under the First Prong of Step 2A because they do not recite an abstract idea.

The claims do not recite mathematical concepts:

The Office Action at pages 4-6 contends that claim 1 recite a judicial exception falling under the category of mathematical concepts. Applicant respectfully traverses the contention because, regardless of whether the claims permissibly involve or are based on mathematical concepts, the claims do not recite mathematical concepts.

As a preliminary matter, the standards for determining whether a claim recites a mathematical concept is not based on whether it merely encompasses a mathematical calculation or a mathematical procedure, as contended in the Office Action. MPEP 2106.04(a)(2) states:

When determining whether a claim recites a mathematical concept (*i.e.*, mathematical relationships, mathematical formulas or equations, and mathematical calculations), examiners should consider whether the claim **recites** a mathematical concept or merely limitations that are based on or involve a mathematical concept. ***A claim does not recite a mathematical concept (i.e., the claim limitations do not fall within the mathematical concept grouping), if it is only based on or involves a mathematical concept. See, e.g., Thales Visionix, Inc. v. United States, 850 F.3d 1343, 1348-49, 121 USPQ2d 1898, 1902-03 (Fed. Cir. 2017) (determining that the claims to a particular configuration of inertial sensors and a particular method of using the raw data from the sensors in order to more accurately calculate the position and orientation of an object on a moving platform did not merely recite “the abstract idea of using ‘mathematical equations for determining the relative position of a moving object to a moving reference frame’.”). For example, a limitation that is merely based on or involves a mathematical concept described in the specification may not be sufficient to fall***

into this grouping, provided the mathematical concept itself is not recited in the claim.

Under this MPEP guidance, it is clear that Applicant's claim 1 does not **recite** mathematics, regardless of whether the claim *involves* or is *based on* any mathematical operations or algorithms, since any mathematical calculations and/or mathematical relationships that may be involved in the claim limitations of determining, at a computer, a corresponding abundance of each respective microbial taxon in a plurality of microbial taxa, are not recited in the claim.

For example, even if the claim limitation

(B) determining, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, a corresponding density estimate of a number of repeat units in the respective microsatellite locus using a number of repeat units in each nucleotide sequence in a corresponding plurality of nucleotide sequences that map to the respective microsatellite locus obtained from biological samples of a cohort of at least 200 subjects, wherein the cohort consists of healthy subjects or subjects with stable microsatellite cancer, thereby determining at least 30 density estimates

of amended claim 1 may involve the use of a mathematical concept, any such mathematical concept is not recited in the claim. While the identified clause may *involve* mathematics, “a limitation that is merely based on or involves a mathematical concept described in the specification may not be sufficient to fall into this grouping, provided the mathematical concept itself is not recited in the claim.” *Id.* For instance, the claim states what data is used to compute a density estimate. The claim does not recite a particular method for computing the density metric. Nor does the claim preclude others from computing density metrics for purposes other than determining a microsatellite instability (MSI) status of a test subject using cell-free DNA fragments from a liquid biopsy sample by counting repeats in microsatellites.

Applicant respectfully submits that, while “all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas” (*Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289, 1293 (2012)), this is not sufficient to support a *prima facie* case of patent ineligibility under 35 U.S.C. § 101.

The claims do not recite mental processes:

The Office Action also contends at pages 4-6 that claim 1 recites a judicial exception falling under the mental processes grouping. Applicant respectfully traverses the contention because the amended claims do not contain limitations that can practically be performed in the human mind.

The 2019 Guidance Update states:

[C]laims do not recite a mental process when they do not contain limitations that can practically be performed in the human mind, for instance when the human mind is not equipped to perform the claim limitations. *Id.*, page 7, Section II(C)(i).

The courts consider a mental process (thinking) that “can be performed in the human mind, or by a human using a pen and paper” to be an abstract idea. *CyberSource Corp. v. Retail Decisions, Inc.*, 654 F. 3d 1366, 1372 99 USPQ2d 1690, 1695 (Fed. Cir. 2011). “Claims do not recite a mental process when they do not contain limitations that can practically be performed in the human mind.” MPEP 2106.04(a)(III)(A).

In particular, amended claim 1 recites the limitation:

(A) obtaining, for each respective cell-free DNA fragment in a plurality of cell-free DNA fragments from a liquid biopsy sample from the test subject, a corresponding nucleotide sequence that has been mapped to a microsatellite locus in a plurality of predetermined microsatellite loci in a reference genome for the species of the test subject, wherein the plurality of predetermined microsatellite loci comprises 30 or more loci and wherein a number of repeats within each microsatellite locus in the plurality of predetermined microsatellite loci in the germ line of the test subject is unknown, thereby obtaining a plurality of aligned nucleotide sequences, wherein the plurality of aligned nucleotide sequences comprises at least 15000 nucleotide sequences and wherein the plurality of aligned nucleotide sequences has an average length of at least 50 nucleotides;

Clause A cannot be mentally performed because it requires obtaining at least 15000 nucleotide sequences that have an average length of at least 50 nucleotides. Assuming that such nucleotides are represented in their most compact form of 1 letter per nucleotide, this clause requires obtaining 50 x 15000, or 750,000 characters. In computer science, 2 bytes are required

to store each character, and thus clause A requires the retention of 1.5 million bytes of information. Applicant respectfully submits it would not be practical or possible for a human mind to memorize 750,000 characters, or equivalently 1.5 million bytes of information, let alone assign each of these characters to a precise position in one of at least 15000 sequences. Thus, neither claim 1 nor any dependent claim is directed to a mental process or any other abstract idea on this basis alone.

Amended claim 1 further recites the limitation:

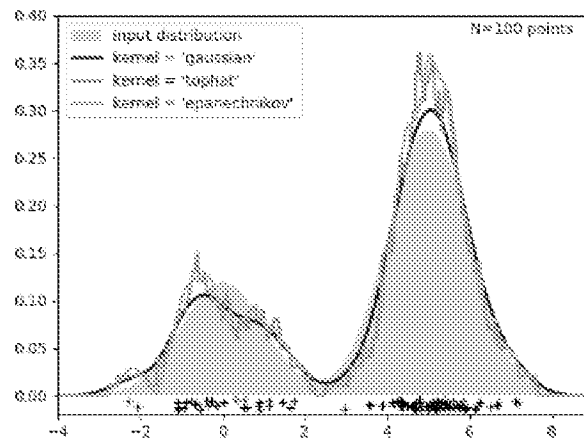
(B) determining, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, a corresponding density estimate of a number of repeat units in the respective microsatellite locus using a number of repeat units in each nucleotide sequence in a corresponding plurality of nucleotide sequences that map to the respective microsatellite locus obtained from biological samples of a cohort of at least 200 subjects, wherein the cohort consists of healthy subjects or subjects with stable microsatellite cancer, thereby determining at least 30 density estimates;

Clause B cannot be mentally performed because it requires determining, for each respective microsatellite in the 30 or more microsatellites, a corresponding density estimate of a number of repeat units in the respective microsatellite using a number of repeat units in each nucleotide sequence in a corresponding plurality of nucleotide sequences that map to the respective microsatellite locus obtained from biological samples of a cohort of at least 200 subjects. Clause B makes use of nucleotide sequences from at least 200 subjects that map to the 30 or more microsatellites. Thus, at the outset, clause B makes use of more information than can be retained in a human subject's mind. Moreover, the specification makes clear that a density estimate cannot be mentally performed. For example, paragraph [0580] of the specification as originally filed states that such a density estimate may be computed using scikit-learn's KernelDensity function with a gaussian kernel and a bandwidth of 0.5. A passage from scikit-learn describing KernelDensity at <https://scikit-learn.org/stable/modules/density.html#kernel-density> makes it clear that such a density function cannot be mentally performed:

2.8.2. Kernel Density Estimation

Kernel density estimation in scikit-learn is implemented in the `KernelDensity` estimator, which uses the Ball Tree or KD Tree for efficient queries (see Nearest Neighbors for a discussion of these). Though the above example uses a 1D data set for simplicity, kernel density estimation can be performed in any number of dimensions, though in practice the curse of dimensionality causes its performance to degrade in high dimensions.

In the following figure, 100 points are drawn from a bimodal distribution, and the kernel density estimates are shown for three choices of kernels:



It's clear how the kernel shape affects the smoothness of the resulting distribution. The scikit-learn kernel density estimator can be used as follows:

```
>>> from sklearn.neighbors import KernelDensity
>>> import numpy as np
>>> X = np.array([[1, -1], [-2, -1], [-3, -2], [1, 1], [4, 1], [3, 2]])
>>> kde = KernelDensity(kernel='gaussian', bandwidth=0.2).fit(X)
>>> kde.score_samples(X)
array([-0.41875698, -0.41875698, -0.41876871, -0.41875698, -0.41875698,
       -0.41876871])
```

Here we have used `kernel='gaussian'` as seen above. Mathematically, a kernel is a positive function $K(x; h)$ which is controlled by the bandwidth parameter h . Given this kernel form, the density estimate at a point y within a group of points $x_i; i = 1 \dots N$ is given by:

$$\rho_K(y) = \frac{1}{N} \sum_{i=1}^N K(y - x_i; h)$$

The bandwidth here acts as a smoothing parameter, controlling the tradeoff between bias and variance in the result. A large bandwidth leads to a very smooth (i.e. high-bias) density distribution. A small bandwidth leads to an unsmooth (i.e. high-variance) density distribution.

Applicant notes clause B of claim 1 does not recite scikit-learn's `KernelDensity` function, nor require that it be used to compute the recited density estimates. Applicant discusses scikit-

learn's KernelDensity function in the context of clause B to make the point that it is clear that clause B cannot be mentally performed. Moreover, as discussed above in Applicant's comments on the judicial exception of mathematical concepts, clause B is not directed to a mathematical concept either because, while clause B may *involve* the use of a mathematical concept, any such mathematical concept, such as computing the density estimate using scikit-learn's KernelDensity function, is not recited in the claim.

Amended claim 1 further recites the limitation:

(C) converting each corresponding nucleotide sequence in the plurality of aligned nucleotide sequences to a likelihood score using (i) the corresponding density estimate of a number of repeat units in the respective microsatellite locus, which the corresponding nucleotide sequence maps to, from among the at least 30 density estimates and (ii) a number of repeat units in the corresponding nucleotide sequence, thereby obtaining a plurality of likelihood scores, each likelihood score in the plurality of likelihood scores associated with a corresponding microsatellite locus in the plurality of predetermined microsatellite loci;

Applicant respectfully submits it would not be practical or possible for a human mind to convert each of at least 15,000 nucleotide sequences into a separate likelihood score using the corresponding density estimate of the microsatellite loci that each such nucleotide sequence maps to as required by clause C. Thus, neither claim 1 nor any dependent claim is directed to a mental process or any other abstract idea on this basis alone.

Amended claim 1 further recites the limitation:

(D) determining a respective value for a likelihood of microsatellite locus stability for each respective microsatellite locus in the plurality of predetermined microsatellite loci by taking a measure of central tendency of those likelihood scores in the plurality of likelihood scores that are associated with the respective microsatellite locus;

Applicant respectfully submits it would not be practical or possible for a human mind to take a measure of central tendency (*e.g.*, mean, average, mode, etc.) for each of at least 30 microsatellite loci using the likelihood scores, across the at least 30 microsatellite loci, of least 15,000 nucleotide sequences as required by clause D. Thus, neither claim 1 nor any dependent claim is directed to a mental process or any other abstract idea on this basis alone.

The claims are patent eligible under the Second Prong of Step 2A because any alleged abstract idea is integrated into a practical application.

Regardless of whether the amended claims *recite* an abstract idea – and Applicant respectfully contends that they do not – the claims are not *directed to* an abstract idea when properly viewed as a whole, at least because the claims, as amended, integrate any alleged judicial exception into the practical application of an improvement in the technical field of determining a microsatellite instability (MSI) status of a test subject (*e.g.*, human) from a liquid biopsy sample and the technical field of liquid biopsy assays by adding specific limitations and/or adding unconventional steps that confine the claims to the particular useful application that provides accurate determination of the microsatellite instability status of a cancer from a liquid biopsy sample.

As explained in the 2019 Guidance and the Revised Guidance, if the claim *as a whole* integrates a recited judicial exception into a practical application, based on considerations such as whether the claim improves a technology, effects a particular treatment, is implemented with a particular machine, *etc.*, the claim is eligible at Step 2A of the *Alice* analysis.

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. No further analysis is required. The claim is eligible at Step 2A.

Revised Guidance at page 11, emphasis added.

Applicant respectfully submits that the presently amended claims integrate any alleged abstract idea into a practical application by providing an improvement to the technical field of determining the microsatellite instability (MSI) status of a test subject (*e.g.*, human) from a liquid biopsy sample by adding specific limitations and/or adding unconventional steps that confine the claims to the particular useful application and providing accurate determination of the microsatellite instability status of a cancer from a liquid biopsy sample.

The claimed method includes a series of steps and specific limitations that result in the determination of the MSI status of a test subject (*e.g.*, human) from a liquid biopsy sample of the test subject. While the claimed method may involve judicial exceptions, the result of these

judicial exceptions is the determination of the MSI status of the test subject. This has nothing to do with the identified judicial exceptions. Moreover, the process that enables the determination of the MSI status of the test subject from a liquid biopsy sample is not an insignificant extra-solution activity because, as discussed below, conventional processes do not satisfactorily allow the determination of the MSI status of the test subject from a liquid biopsy sample. For discussion purposes, claim 1 is presented below with bolded passages recited in claim 1 because of their significance in Applicant's arguments for patentability of the claim under 35 U.S.C. § 101 provided in this response:

1. A method of determining a microsatellite instability (MSI) status of a test subject, the method comprising:
 - at a computer system having one or more processors, and memory storing one or more programs for execution by the one or more processors:
 - (A) obtaining, **for each respective cell-free DNA fragment in a plurality of cell-free DNA fragments from a liquid biopsy sample from the test subject**, a corresponding nucleotide sequence that has been mapped to a microsatellite locus in a plurality of predetermined microsatellite loci in a reference genome for the species of the test subject, wherein **the plurality of predetermined microsatellite loci comprises 30 or more loci** and wherein a number of repeats within each microsatellite locus in the plurality of predetermined microsatellite loci in the germ line of the test subject is unknown, thereby obtaining a plurality of aligned nucleotide sequences, **wherein the plurality of aligned nucleotide sequences comprises at least 15000 nucleotide sequences and wherein the plurality of aligned nucleotide sequences has an average length of at least 50 nucleotides**;
 - (B) determining, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, a corresponding density estimate of a number of repeat units in the respective microsatellite locus **using a number of repeat units in each nucleotide sequence in a corresponding plurality of nucleotide sequences that map to the respective microsatellite locus obtained from biological samples of a cohort of at least 200 subjects, wherein the cohort consists of healthy subjects or subjects with stable microsatellite cancer, thereby determining at least 30 density estimates**;
 - (C) converting each corresponding nucleotide sequence in the plurality of aligned nucleotide sequences to **a likelihood score using (i) the corresponding density estimate of a number of repeat units in the respective microsatellite locus, which the corresponding nucleotide sequence maps to, from among the at least 30 density estimates and (ii) a number of repeat units in the corresponding nucleotide sequence**, thereby obtaining a plurality of likelihood scores, each likelihood score in the plurality of likelihood scores associated with a corresponding microsatellite locus in the plurality of predetermined microsatellite

loci;

(D) determining a respective value for a likelihood of microsatellite locus stability for each respective microsatellite locus in the plurality of predetermined microsatellite loci **by taking a measure of central tendency of those likelihood scores in the plurality of likelihood scores that are associated with the respective microsatellite locus;**

(E) using one or more corresponding metric values for one or more metrics for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the one or more metrics including the likelihood of microsatellite locus stability of the respective microsatellite locus, to determine a proportion of the plurality of predetermined microsatellite loci that are unstable; and

(F) determining the MSI status of the test subject from the proportion of the plurality of predetermined microsatellite loci that are unstable.

(claim 1, as amended, emphasis added)

As can be seen, claim 1 is directed to determining the MSI status of a test subject using a plurality of mapped cell-free nucleotide sequences from a liquid biopsy sample of the test subject despite the fact that detecting and/or validating cancer-specific genomic alterations of a liquid biopsy sample is significantly challenging and problematic. Thus, the claimed method is a practical application that addresses a technical problem in the field of determining the MSI status from a liquid biopsy sample and therefore is an advancement in the technical field of liquid biopsy assays for personalized cancer treatment.

The specification explains the challenges and technical problems addressed by claim 1. For instance, paragraphs [0017]-[0020] of the specification state:

[0017] Nevertheless, while liquid biopsies are promising tools for improving outcomes using precision oncology, there are significant challenges specific to the use of cell-free DNA for evaluation of a subject's cancer genome. For instance, there is a highly variable signal-to-noise ratio from one liquid biological sample to the next. This occurs because cfDNA originates from a variety of different cells in a subject, both healthy and diseased. Depending on the stage and type of cancer in any particular subject, the fraction of cfDNA fragments originating from cancerous cells (the "tumor fraction" or "ctDNA fraction" of the sample/subject) can range from almost 0% to well over 50%. Other factors, including tumor type and mutation profile, can also impact the amount of DNA released from cancerous tissues. For instance, cfDNA clearance through the liver and kidneys is affected by a variety of factors, including renal dysfunction or other tissue damaging factors (*e.g.*, chemotherapy, surgery, and/or radiotherapy).

[0018] This, in turn, leads to problems detecting and/or validating cancer-specific genomic alterations in a liquid sample. This is particularly true during early stages of the disease—when cancer therapies have much higher success rates—because the tumor fraction in the patient is lowest at this point. Thus, early stage cancer patients can have ctDNA fractions below the limit of detection (LOD) for one or more informative genomic alterations, limiting clinical utility because of the risk of false negatives and/or providing an incomplete picture of the cancer genome of the patient. Further, because cancers, and even individual tumors, can be clonally diverse, actionable genomic alterations that arise in only a subset of clonal populations are diluted below the overall tumor fraction of the sample, further frustrating attempts to tailor combination therapies to the various actionable mutations in the patient’s cancer genome. Consequently, most studies using liquid biopsy samples to date have focused on late stage patients for assay validation and research.

[0019] Another challenge associated with liquid biopsies is the accurate determination of tumor fraction in a sample. This difficulty arises from at least the heterogeneity of cancers and the increased frequency of large chromosomal duplications and deletions found in cancers. As a result, the frequency of genomic alterations from cancerous tissues varies from locus to locus based on at least (i) their prevalence in different subclonal populations of the subject’s cancer, and (ii) their location within the genome, relative to large chromosomal copy number variations. The difficulty in accurately determining the tumor fraction of liquid biological samples affects accurate measurement of various cancer features shown to have diagnostic value for the analysis of solid tumor biopsies. These include allelic ratios, copy number variations, overall mutational burden, frequency of abnormal methylation patterns, *etc.*, all of which are correlated with the percentage of DNA fragments that arise from cancerous tissue, as opposed to healthy tissue.

[0020] Altogether, these factors result in highly variable concentrations of ctDNA—from patient to patient and possibly from locus to locus—that confound accurate measurement of disease indicators and actionable genomic alterations. Further, the quantity and quality of cfDNA obtained from liquid biopsy samples are highly dependent on the particular methodology for collecting the samples, storing the samples, sequencing the samples, and standardizing the sequencing data.

In paragraphs [0021] and [0069], the specification points out the current status of liquid biopsy assays. The specification states in paragraph [0021] that few studies have corroborated results with orthogonal methods, or between particular testing platforms, *e.g.*, different NGS technologies and/or targeted panel sequencing versus whole genome/exome sequencing, and

liquid biopsy-based studies are limited by comparison to non-comprehensive tissue testing algorithms including Sanger sequencing, small NGS hotspot panels, polymerase chain reaction (PCR), and fluorescent in situ hybridization (FISH). The specification states in paragraph [0069] that *conventional liquid biopsy assays do not provide accurate determination of the microsatellite stability status of a cancer.*

In paragraphs [0071]-[0073], the specification explains the technical problem(s) encountered when using a liquid biopsy sample for determining the MSI status:

[0071] The identification of actionable genomic alterations in a patient's cancer genome is a ***difficult and computationally demanding problem***. For instance, the determination of various prognostic metrics useful for precision oncology, such as variant allelic ratio, copy number variation, tumor mutational burden, microsatellite instability status, *etc.*, requires analysis of hundreds of millions to billions, of sequenced nucleic acid bases. An example of a typical bioinformatics pipeline established for this purpose includes at least five stages of analysis: assessment of the quality of raw next generation sequencing data, generation of collapsed nucleic acid fragment sequences and alignment of such sequences to a reference genome, detection of structural variants in the aligned sequence data, annotation of identified variants, and visualization of the data. See, Wadapurkar and Vyas, Informatics in Medicine Unlocked, 11:75-82 (2018), the content of which is hereby incorporated by reference, in its entirety, for all purposes. Each one of these procedures is computationally taxing in its own right.

[0072] For instance, the overall temporal and spatial computation complexity of simple global and local pairwise sequence alignment algorithms are quadratic in nature (*e.g.*, second order problems), that increase rapidly as a function of the size of the nucleic acid sequences (n and m) being compared. Specifically, the temporal and spatial complexities of these sequence alignment algorithms can be estimated as $O(mn)$, where O is the upper bound on the asymptotic growth rate of the algorithm, n is the number of bases in the first nucleic acid sequence, and m is the number of bases in the second nucleic acid sequence. See, Baichoo and Ouzounis, BioSystems, 156–157:72-85 (2017), the content of which is hereby incorporated by reference, in its entirety, for all purposes. Given that the human genome contains more than 3 billion bases, these alignment algorithms are extremely computationally taxing, especially when used to analyze next generation sequencing (NGS) data, which can generate more than 3 billion sequence reads per reaction.

[0073] *This is particularly true when performed in the context of a liquid biopsy assay, because liquid biological samples contain a complex mixture of short DNA fragments originating from many different germline (*e.g.*, healthy) and diseased (*e.g.*, cancerous) tissues.* Thus, the cellular origins of the sequence

reads are unknown, and the sequence signals originating from cancerous cells, which may constitute multiple sub-clonal populations, must be computationally deconvoluted from signals originating from germline and hematopoietic origins, in order to provide relevant information about the subject's cancer. ***Thus, in addition to the computationally taxing processes required to align sequence reads to a human genome, there is a computation problem of determining whether a particular abnormal signal, e.g., one or more sequence reads corresponding to a genomic alteration, (i) is not an artifact, and (ii) originated from a cancerous source in the subject.*** This is increasingly difficult during the early stages of cancer—when treatment is presumably most effective—when only small amounts of ctDNA are diluted by germline and hematopoietic DNA. (emphasis added)

Claim 1 addresses the above-described technical problem(s) and thus enables the practical application of determining the MSI status of a test subject from a liquid biopsy sample of a test subject by converting each of over 15,000 cell-free nucleotide sequences obtained from a liquid biopsy sample into at least 15,000 likelihood scores. Each such likelihood score is a probability that the microsatellite that the corresponding nucleotide sequence maps to is stable (or conversely unstable). Claim 1 then uses these individual likelihood scores to determine the proportion of at least 30 microsatellites that are unstable and, from this proportion, the microsatellite instability status of the subject.

This specific and unconventional process is not well-understood, nor routine, nor conventional activity in the field. Instead, it is specific and unconventional. This specific and unconventional process is confined by the claim to a particular useful application and enables accurate determination of the MSI status of a test subject from a liquid biopsy. For instance, as disclosed in paragraphs [0070] and [0074] of the specification, this specific and unconventional claimed process allows for accurate prediction of the overall microsatellite stability of a cancer. It improves the computational elucidation of actionable genomic alterations from a liquid biopsy sample of a cancer patient and improves upon the accuracy of microsatellite stability determination from a liquid biopsy assay.

Thus, claim 1 recites a method that solves the technical problem(s) described in the specification, integrates the alleged abstract idea into an inventive concept that is significantly more than any abstract idea, and provides improvements to the technical field of determination

of the MSI status of the test subject from a liquid biopsy sample. Accordingly, claim 1 qualifies as eligible subject matter under 35 U.S.C. § 101.

All other pending claims rejected under 35 U.S.C. § 101 depend from claim 1 and thus are patentable under 35 U.S.C. § 101 for at least the same reason as claim 1. Applicant therefore respectfully requests that the 35 U.S.C. § 101 rejection be withdrawn.

CONCLUSION

All the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn.

Applicant believes that a full and complete reply has been made to the outstanding Office Action, and as such, the present application is in condition for allowance. 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.

Except for issue fees payable under 37 CFR § 1.18, the Commissioner is hereby authorized by this paper to charge any necessary fees during the entire pendency of this application including fees due under 37 CFR §§ 1.16 and 1.17, which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310 (Order No.: 123138-5013-US).

Prompt and favorable consideration of this Amendment and Response is respectfully requested.

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS LLP

Dated: February 20, 2024

By: /Brett Lovejoy/

Customer No.: 43850

Brett A. Lovejoy, Reg. No. 42,813

Morgan, Lewis & Bockius LLP

One Market, Spear Street Tower

San Francisco, CA 94105

Telephone: (415) 442-1000

Facsimile: (415) 442-1001



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 NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/945,588	07/31/2020	Ariane Lozac'hmeur	123138-5013-US	8972
43850	7590	12/21/2023	EXAMINER	
Morgan, Lewis & Bockius LLP (SF)			BAILEY, STEVEN WILLIAM	
One Market, Spear Street Tower, Suite 2800			ART UNIT	PAPER NUMBER
San Francisco, CA 94105			1672	
			NOTIFICATION DATE	DELIVERY MODE
			12/21/2023	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):

donald.mixon@morganlewis.com
sfipdocketing@morganlewis.com

<i>Applicant-Initiated Interview Summary</i>	Application No. 16/945,588	Applicant(s) Lozac'hmeur et al.		
	Examiner STEVEN W BAILEY	Art Unit 1672	AIA (First Inventor to File) Status Yes	Page 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	Title	Type
STEVEN W BAILEY	Examiner	Video Conference
JOHN S. BRUSCA	Primary Examiner	
ANDREW ANTCAZAK	Attorney	

Date of Interview: 14 December 2023

Issues Discussed:

35 U.S.C. 101

The Applicant discussed the rejection under 35 U.S.C. 101 in the Office action mailed 20 September 2023, in particular the mathematical concept and mental process judicial exceptions identified at Eligibility Step 2A: Prong One. The Applicant and Examiner discussed potential amendments that may overcome the rejection, including potential practical applications, however agreement was not reached.

/STEVEN W. BAILEY/ Examiner, Art Unit 1672	/JOHN S BRUSCA/ 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.

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.



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 NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/945,588	07/31/2020	Ariane Lozac'hmeur	123138-5013-US	8972
43850	7590	09/20/2023		
Morgan, Lewis & Bockius LLP (SF) One Market, Spear Street Tower, Suite 2800 San Francisco, CA 94105			EXAMINER BAILEY, STEVEN WILLIAM	
			ART UNIT	PAPER NUMBER
			1672	
			NOTIFICATION DATE	DELIVERY MODE
			09/20/2023	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):

donald.mixon@morganlewis.com
sfipdocketing@morganlewis.com

Office Action Summary	Application No. 16/945,588	Applicant(s) Lozac'hmeur et al.	
	Examiner STEVEN W BAILEY	Art Unit 1672	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 03 July 2023.

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

2a) ☒ This action is **FINAL**.

2b) ☐ This action is non-final.

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

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

Disposition of Claims*

5) ☒ Claim(s) 1-12,14-16,19-25,154-155 and 159-164 is/are pending in the application.

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

6) ☐ Claim(s) ____ is/are allowed.

7) ☒ Claim(s) 1-12,14-16,19-25,154-155 and 159-164 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)

3) ☐ Interview Summary (PTO-413)

Paper No(s)/Mail Date ____.

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)

4) ☐ Other: ____.

Paper No(s)/Mail Date 06 September 2023; 27 March 2023.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Status of the Claims

2. Claims 1-12, 14-16, 19-25, 154, 155, and 159-164 are pending.

Claims 1-12, 14-16, 19-25, 154, 155, and 159-164 are rejected.

Priority

3. Claims 1-12, 14-16, 19-25, 154, 155, and 159-164 are given the benefit for priority to Provisional Application No. 62/881,845, filed 01 August 2019, Provisional Application No. 62/931,600, filed 06 November 2019, and Provisional Application No. 62/978,130, filed 18 February 2020.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on 06 September 2023 and 27 March 2023 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Specification

5. The substitute Specification was received on 03 July 2023. This Specification is accepted.

Nucleotide and/or Amino Acid Sequence Disclosures

6. The Sequence Listing (Text File) was received on 03 July 2023. This Sequence Listing is accepted.

7. The Sequence Listing in Computer Readable Format (CRF) was received on 08 July 2023. This Sequence Listing is accepted.

Claim Interpretation

8. Claim 154 is interpreted as reciting a product-by-process limitation with the product being the data for enriched cell-free DNA fragments that comprises the plurality of predetermined microsatellite loci. The claim is further interpreted to not require the processing steps of producing the product.

9. Claim 1 at step (A) is interpreted to be limited to obtaining data of a corresponding nucleotide sequence that has been aligned to a reference genome, and inputting that data into a computer program for analysis.

Claim Rejections - 35 USC § 112

10. The rejection of claims 161 and 162 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, in the Office Action mailed 03 January 2023 is withdrawn in view of the amendments received 03 July 2023.

Claim Rejections - 35 USC § 101

11. The rejection of claims 1-16, 19-25, 154, 155, and 159-163 under 35 U.S.C. 101 in the Office Action mailed 03 January 2023 is maintained with modification in view of the amendments received 03 July 2023. The rejection of cancelled claim 13 is withdrawn. The newly added claim 164 is rejected.

12. 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.

13. Claims 1-12, 14-16, 19-25, 154, 155, and 159-164 are rejected under 35 U.S.C. 101 because the claimed invention is directed to an abstract idea without significantly more. The claims recite: (a) mathematical concepts, (e.g., mathematical relationships, formulas or equations, mathematical calculations); and (b) mental processes, i.e., concepts performed in the human mind, (e.g., observation, evaluation, judgement, opinion).

Following the flowchart in MPEP 2106:

Eligibility Step 1

14. Claims 1-12, 14-16, 19-25, 154, 155, and 159-164 are directed to a method (process) of determining a microsatellite instability (MSI) status of a test subject.

Therefore, these claims are encompassed by the categories of statutory subject matter, and thus satisfy the subject matter eligibility requirements under Eligibility Step 1.

Eligibility Step 2A: Prong One

15. In determining whether a claim is directed to a judicial exception, examination is performed that analyzes whether the claim recites a judicial exception, i.e., whether a law of nature, natural phenomenon, or abstract idea is set forth or described in the claim.

16. Independent claim 1 recites a mental process of considering the selection of a corresponding nucleotide sequence that has been aligned to a reference genome for the species of the test subject, thereby obtaining a plurality of aligned nucleotide sequences; a mental process and a mathematical concept of using the plurality of aligned nucleotide sequences to determine, for each respective microsatellite locus in a plurality of predetermined microsatellite loci, wherein each respective microsatellite

locus in the plurality of microsatellite loci has a nucleic acid sequence that includes a variable number of repeat units, a corresponding metric value for each of one or more metrics; a mental process and a mathematical concept of considering wherein each respective metric in the one or more metrics is determined, at least in part, by a distribution of the number of repeat units in each aligned nucleotide sequence, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus; a mental process and a mathematical concept of considering the one or more metrics comprises a likelihood score; a mental process and a mathematical concept of considering the corresponding metric value for the likelihood score is a statistical measure of a distribution of probabilities that each respective aligned nucleotide sequence in a subset of the set of aligned nucleotide sequences encompassing the respective microsatellite locus is a member of a distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite locus; a mental process and a mathematical concept of considering the subset of aligned nucleotide sequences consists of the aligned nucleotide sequences encompassing the respective microsatellite locus that have a number of repeat units that falls within a threshold percentile of the smallest number of repeat units; a mental process and a mathematical concept of comparing, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the corresponding metric values for the one or more metrics to corresponding reference metric values for the one or more metrics representative of a stable construct at the respective microsatellite locus; and a mental process of considering the reference metric values determined across nucleotide sequences obtained from biological samples from a training cohort that includes (i) solid

tumor samples from training subjects with stable microsatellite cancer or (ii) normal tissue samples, thereby determining the MSI status of the test subject.

17. Dependent claim 2 further recites a mental process of considering a corresponding set of raw sequence reads for the respective DNA fragment; a mental process of considering a corresponding set of aligned raw sequence reads for the respective DNA fragment; a mental process of collapsing the corresponding set of aligned raw sequence reads for the respective DNA fragment into a corresponding nucleotide sequence for the respective DNA fragment that has been aligned to the human reference genome, thereby obtaining a plurality of aligned nucleotide sequences. Dependent claim 3 further recites a mental process of considering whether the plurality of aligned nucleotide sequences comprises at least 250,000 aligned nucleotide sequences. Dependent claim 4 further recites a mental process and a mathematical concept of determining that the one or more metrics comprises a percentage score; a mental process and a mathematical concept of determining that the corresponding metric value for the percentage score is the percentage of aligned nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus. Dependent claim 5 further recites a mental process of considering that for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject. Dependent claim 6 further recites a mental process and a mathematical

concept of determining that the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values; and a mental process of considering whether each respective reference value in the plurality of reference values is determined at least in part based on a distribution of the number of repeat units at the respective microsatellite locus in a respective reference sample in a plurality of reference standards. Dependent claim 7 further recites a mental process and a mathematical concept of determining that the reference number of repeat units representative of a stable construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus. Dependent claim 8 further recites a mental process and a mathematical concept of determining that the one or more metrics comprises a lower mean score; and a mental process and mathematical concept of determining that the corresponding metric value for the lower mean score is determined at least in part by the mean number of repeat units in aligned nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus. Dependent claim 9 further recites a mental process and a mathematical concept of determining that the mean number of repeat units is normalized by the reference number of repeat units representative of a stable construct at the respective microsatellite locus. Dependent claim 10 further recites a mental process of considering that for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units

representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject. Dependent claim 11 further recites a mental process and a mathematical concept of determining that the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values; and a mental process of considering whether each respective reference value in the plurality of reference values is determined at least in part based on a distribution of the number of repeat units at the respective microsatellite locus in a respective reference sample in a plurality of reference samples. Dependent claim 12 further recites a mental process and a mathematical concept of determining that the reference number of repeat units representative of a stable construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus. Dependent claim 14 further recites a mental process and a mathematical concept of determining that the statistical measure is a mean of the distribution of probabilities that each aligned nucleotide sequence in the subset of aligned nucleotide sequences encompassing the respective microsatellite locus is a member of the distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite locus. Dependent claim 15 further recites a mental process and a mathematical concept of determining that the distribution of probabilities is a plurality of p-values, wherein each respective p-value in the plurality of p-values is a probability value that a respective aligned nucleotide sequence in the subset of aligned nucleotide sequences is a member of the distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite

locus. Dependent claim 16 further recites a mental process and a mathematical concept of determining that one or more corresponding metric values comprises a corresponding standard deviation of the number of repeat units in the aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus. Dependent claim 19 further recites a mental process of organizing metric value data according to classification; a mental process and a mathematical concept of training a classification model using the reference metric values determined across the nucleotide sequences obtained from the biological samples from the training cohort that included (i) solid tumor samples from training subjects with stable microsatellite cancer or (ii) normal tissue samples; and a mental process of distinguishing between stable and unstable microsatellite loci. Dependent claim 20 further recites a mental process of considering that the biological samples from the training cohort included both (i) solid tumor samples from training subjects with stable microsatellite cancer and (ii) normal tissue samples. Dependent claim 21 further recites a mental process of considering that the biological samples from the training cohort further included (iii) solid tumor samples from training subjects with unstable microsatellite cancer. Dependent claim 22 further recites a mental process of determining that the classifier comprises a k-nearest neighbors algorithm. Dependent claim 23 further recites a mental process and a mathematical concept of the classifier assigning a stability status selected from unstable and stable to each respective microsatellite locus in the plurality of predetermined microsatellite loci, and the subject is classified as having a high level of microsatellite instability when at least a threshold number of microsatellite loci are assigned a status of unstable. Dependent claim 24

further recites a mental process and a mathematical concept of determining that the threshold number of microsatellite loci is at least 30% of the total number of microsatellite loci in the plurality of microsatellite loci. Dependent claim 25 further recites a mental process and a mathematical concept of determining that the threshold number of microsatellite loci is at least 50% of the total number of microsatellite loci in the plurality of microsatellite loci. Dependent claim 154 further recites a mental process of considering sequence data. Dependent claim 155 further recites a mental process of considering and analyzing sequence reads that represent, on average, greater than 1000X sequence depth for each microsatellite locus in the plurality of predetermined microsatellite loci. Dependent claim 159 further recites a mental process of considering data from blood or blood plasma samples. Dependent claim 160 further recites a mental process of considering that the plurality of predetermined microsatellite loci comprises at least 25 microsatellite loci. Dependent claim 161 further recites a mental process of considering that the plurality of predetermined microsatellite loci comprises at least 10 of the microsatellite loci selected from a predefined group. Dependent claim 162 further recites a mental process of considering that the plurality of predetermined microsatellite loci comprises at least all of the microsatellite loci listed in a predetermined group. Dependent claim 163 further recites a mental process of considering data from a human subject.

Eligibility Step 2A: Prong Two

18. In determining whether a claim is directed to a judicial exception, further examination is performed that analyzes if the claim recites additional elements that when examined as a whole integrates the judicial exception(s) into a practical

application (MPEP 2106.04(d)). A claim that integrates a judicial exception into a practical application will apply, rely on, or use the judicial exception in a manner that imposes a meaningful limit on the judicial exception. The claimed additional elements are analyzed to determine if the abstract idea is integrated into a practical application (MPEP 2106.04(d).I; MPEP 2106.05(a-h)). If the claim contains no additional elements beyond the abstract idea, the claim fails to integrate the abstract idea into a practical application (MPEP 2106.04(d).III).

19. The judicial exceptions noted above are not integrated into a practical application because the additional element of a computer system in independent claim 1 does not improve the functioning of a generic computer, and therefore does not integrate the recited judicial exceptions into a practical application. Furthermore, the additional element of using a computer system in independent claim 1 is part of the data gathering process used in the recited abstract ideas, and therefore does not integrate the recited judicial exceptions into a practical application. The additional element in claim 164 of sequencing the plurality of DNA fragments from the liquid biopsy sample, and the additional element of obtaining a corresponding set of raw sequence reads in claim 2 are data gathering steps that do not integrate the recited judicial exceptions into a practical application. The additional element in claim 2 of aligning a nucleotide sequence to a reference genome is too complex to be practical, and does not recite a mental process grouping of abstract ideas. However, the additional element of aligning a nucleotide sequence to a reference genome is a data gathering step used in the recited abstract idea, and therefore does not integrate the recited judicial exception into a practical application. The additional element in claim 1 of obtaining data of a plurality

of aligned nucleotide sequences, and the additional element in claim 19 of inputting metric values into a classifier, are a data inputting step that is part of the data gathering process, and therefore do not integrate the recited judicial exception into a practical application.

20. Data gathering steps are not an abstract idea, but rather they are extra-solution activity, as they collect the data needed to carry out the abstract idea. Data gathering does not impose any meaningful limitation on the abstract idea, or how the abstract idea is performed. Data gathering steps are not sufficient to integrate an abstract idea into a practical application.

21. Claims 1-12, 14-16, 19-25, 154, 155, and 159-164 do not recite additional elements which would integrate a judicial exception into a practical application.

Eligibility Step 2B

22. Because the claims recite an abstract idea, and do not integrate that abstract idea into a practical application, the claims are probed for a specific inventive concept. The judicial exception alone cannot provide that inventive concept or practical application (MPEP 2106.05). Identifying whether the additional elements beyond the abstract idea amount to such an inventive concept requires considering the additional elements individually and in combination to determine if they amount to significantly more than the judicial exception (MPEP 2106.05A i-vi).

23. The claims do not include additional elements that are sufficient to amount to significantly more than the judicial exception(s) because the additional element of a computer system in claim 1; genomic sequencing the plurality of DNA fragments from

the liquid biopsy sample and sequence alignment in claim 2; and data inputting in claims 1 and 19, are conventional.

24. Regarding conventionality of computer components and computer processes, the MPEP states at 2106.05(b):

2106.05(b) Particular Machine [R-10.2019]

When determining whether a claim integrates a judicial exception, into a practical application in Step 2A Prong Two and whether a claim recites significantly more than a judicial exception in Step 2B, examiners should consider whether the judicial exception is applied with, or by use of, a particular machine. "The machine-or-transformation test is a useful and important clue, and investigative tool" for determining whether a claim is patent eligible under *Bilski v. Kappos*, 561 U.S. 593, 604, 95 USPQ2d 1001, 1007 (2010).

It is noted that while the application of a judicial exception by or with a particular machine is an important clue, it is not a stand-alone test for eligibility. *Id.*

All claims must be evaluated for eligibility using the two-part test from *Alice/Mayo*. If a claim passes the *Alice/Mayo* test (*i.e.*, is not directed to an exception at Step 2A, or amounts to significantly more than any recited exception in Step 2B), then the claim is eligible even if it fails the machine-or-transformation test ("M-or-T test"). *Bilski v. Kappos*, 561 U.S. 593, 604, 95 USPQ2d 1001, 1007 (2010) (explaining that a claim may be eligible even if it does not satisfy the M-or-T test); *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 837 F.3d 1299, 1315, 120 USPQ2d 1091, 1102 (Fed. Cir. 2016) ("[T]here is nothing that requires a method 'be tied to a machine or transform an article' to be patentable"). And if a claim fails the *Alice/Mayo* test (*i.e.*, is directed to an exception at Step 2A and does not amount to significantly more than the exception in Step 2B), then the claim is ineligible even if it passes the M-or-T test. *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1256, 113 USPQ2d 1097, 1104 (Fed. Cir. 2014) ("[I]n *Mayo*, the Supreme Court emphasized that satisfying the machine-or-transformation test, by itself, is not sufficient to render a claim patent-eligible, as not all transformations or machine implementations infuse an otherwise ineligible claim with an 'inventive concept.'").

Examiners may find it helpful to evaluate other considerations such as the mere instructions to apply an exception consideration (see **MPEP § 2106.05(f)**), the insignificant extra-solution activity consideration (see **MPEP § 2106.05(g)**), and the field of use and technological environment consideration (see **MPEP § 2106.05(h)**), when making a determination of whether an element (or combination of elements) is a particular machine. For information on the definition of the term "machine," see **MPEP § 2106.03**.

When determining whether a machine recited in a claim provides significantly more, the following factors are relevant.

I. THE PARTICULARITY OR GENERALITY OF THE ELEMENTS OF THE MACHINE OR APPARATUS

The particularity or generality of the elements of the machine or apparatus, *i.e.*, the degree to which the machine in the claim can be specifically identified (not any and all machines). One example of applying a judicial exception with a particular machine is *Mackay Radio & Tel. Co. v. Radio Corp. of America*, 306 U.S. 86, 40 USPQ 199 (1939). In this case, a mathematical formula was employed to use standing wave phenomena in an antenna system. The claim recited the particular type of antenna and included details as to the shape of the antenna and the conductors, particularly the length and angle at which they were arranged. 306 U.S. at 95-96; 40 USPQ at 203. Another example is *Eibel Process*, in which gravity (a law of nature or natural phenomenon) was applied by a Fourdrinier machine (which was understood in the art to have a specific structure comprising a headbox, a paper-making wire, and a series of rolls) arranged in

a particular way to optimize the speed of the machine while maintaining quality of the formed paper web. *Eibel Process Co. v. Minn. & Ont. Paper Co.*, 261 U.S. 45, 64-65 (1923).

It is important to note that a general purpose computer that applies a judicial exception, such as an abstract idea, by use of conventional computer functions does not qualify as a particular machine. *Ultramercial, Inc. v. Hulu, LLC*, 772 F.3d 709, 716-17, 112 USPQ2d 1750, 1755-56 (Fed. Cir. 2014). See also *TLI Communications LLC v. AV Automotive LLC*, 823 F.3d 607, 613, 118 USPQ2d 1744, 1748 (Fed. Cir. 2016) (mere recitation of concrete or tangible components is not an inventive concept); *Eon Corp. IP Holdings LLC v. AT&T Mobility LLC*, 785 F.3d 616, 623, 114 USPQ2d 1711, 1715 (Fed. Cir. 2015) (noting that *Alappat*'s rationale that an otherwise ineligible algorithm or software could be made patent-eligible by merely adding a generic computer to the claim was superseded by the Supreme Court's *Bilski* and *Alice Corp.* decisions). If applicant amends a claim to add a generic computer or generic computer components and asserts that the claim recites significantly more because the generic computer is 'specially programmed' (as in *Alappat*, now considered superseded) or is a 'particular machine' (as in *Bilski*), the examiner should look at whether the added elements integrate the exception into a practical application or provide significantly more than the judicial exception. Merely adding a generic computer, generic computer components, or a programmed computer to perform generic computer functions does not automatically overcome an eligibility rejection. *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 573 U.S. 208, 223-24, 110 USPQ2d 1976, 1983-84 (2014). See *In re Alappat*, 33 F.3d 1526, 1545 (Fed. Cir. 1994); *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008)

II. WHETHER THE MACHINE OR APPARATUS IMPLEMENTS THE STEPS OF THE METHOD

Integral use of a machine to achieve performance of a method may integrate the recited judicial exception into a practical application or provide significantly more, in contrast to where the machine is merely an object on which the method operates, which does not integrate the exception into a practical application or provide significantly more. See *CyberSource v. Retail Decisions*, 654 F.3d 1366, 1370, 99 USPQ2d 1690, 1694 (Fed. Cir. 2011) ("We are not persuaded by the appellant's argument that the claimed method is tied to a particular machine because it 'would not be necessary or possible without the Internet.' . . . Regardless of whether "the Internet" can be viewed as a machine, it is clear that the Internet cannot perform the fraud detection steps of the claimed method"). For example, as described in **MPEP § 2106.05(f)**, additional elements that invoke computers or other machinery merely as a tool to perform an existing process will generally not amount to significantly more than a judicial exception. See, e.g., *Versata Development Group v. SAP America*, 793 F.3d 1306, 1335, 115 USPQ2d 1681, 1702 (Fed. Cir. 2015) (explaining that in order for a machine to add significantly more, it must "play a significant part in permitting the claimed method to be performed, rather than function solely as an obvious mechanism for permitting a solution to be achieved more quickly").

III. WHETHER ITS INVOLVEMENT IS EXTRA-SOLUTION ACTIVITY OR A FIELD-OF-USE

Whether its involvement is extra-solution activity or a field-of-use, *i.e.*, the extent to which (or how) the machine or apparatus imposes meaningful limits on the claim. Use of a machine that contributes only nominally or insignificantly to the execution of the claimed method (e.g., in a data gathering step or in a field-of-use limitation) would not integrate a judicial exception or provide significantly more. See *Bilski*, 561 U.S. at 610, 95 USPQ2d at 1009 (citing *Parker v. Flook*, 437 U.S. 584, 590, 198 USPQ 193, 197 (1978)), and *CyberSource v. Retail Decisions*, 654 F.3d 1366, 1370, 99 USPQ2d 1690 (Fed. Cir. 2011) (citations omitted) ("[N]othing in claim 3 requires an infringer to use the Internet to obtain that data. The Internet is merely described as the source of the data. We have held that mere '[data-gathering] step[s]' cannot make an otherwise nonstatutory claim statutory." 654 F.3d at 1375, 99 USPQ2d at 1694 (citation omitted)). See **MPEP § 2106.05(g) & (h)** for more information on insignificant extra-solution activity and field of use, respectively.

The MPEP further discusses conventional computer processes at 2106.05(d)II:

II. ELEMENTS THAT THE COURTS HAVE RECOGNIZED AS WELL-UNDERSTOOD, ROUTINE, CONVENTIONAL ACTIVITY IN PARTICULAR FIELDS

Because examiners should rely on what the courts have recognized, or those of ordinary skill in the art would recognize, as elements that describe well-understood, routine activities, the following section provides examples of elements that have been recognized by the courts as well-understood, routine, conventional activity in particular fields. It should be noted, however, that many of these examples failed to satisfy other considerations (*e.g.*, because they were recited at a high level of generality and thus were mere instructions to apply an exception, or were insignificant extra-solution activity). Thus, examiners should carefully analyze additional elements in a claim with respect to all relevant Step 2B considerations, including this consideration, before making a conclusion as to whether they amount to an inventive concept.

The courts have recognized the following computer functions as well-understood, routine, and conventional functions when they are claimed in a merely generic manner (*e.g.*, at a high level of generality) or as insignificant extra-solution activity.

- i. Receiving or transmitting data over a network, *e.g.*, using the Internet to gather data, *Symantec*, 838 F.3d at 1321, 120 USPQ2d at 1362 (utilizing an intermediary computer to forward information); *TLI Communications LLC v. AV Auto. LLC*, 823 F.3d 607, 610, 118 USPQ2d 1744, 1745 (Fed. Cir. 2016) (using a telephone for image transmission); *OIP Techs., Inc., v. Amazon.com, Inc.*, 788 F.3d 1359, 1363, 115 USPQ2d 1090, 1093 (Fed. Cir. 2015) (sending messages over a network); *buySAFE, Inc. v. Google, Inc.*, 765 F.3d 1350, 1355, 112 USPQ2d 1093, 1096 (Fed. Cir. 2014) (computer receives and sends information over a network); but see *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1258, 113 USPQ2d 1097, 1106 (Fed. Cir. 2014) ("Unlike the claims in *Ultramercial*, the claims at issue here specify **how** interactions with the Internet are manipulated to yield a desired result--a result that overrides the routine and conventional sequence of events ordinarily triggered by the click of a hyperlink." (emphasis added));
- ii. Performing repetitive calculations, *Flook*, 437 U.S. at 594, 198 USPQ2d at 199 (recomputing or readjusting alarm limit values); *Bancorp Services v. Sun Life*, 687 F.3d 1266, 1278, 103 USPQ2d 1425, 1433 (Fed. Cir. 2012) ("The computer required by some of *Bancorp's* claims is employed only for its most basic function, the performance of repetitive calculations, and as such does not impose meaningful limits on the scope of those claims.");
- iii. Electronic recordkeeping, *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 573 U.S. 208, 225, 110 USPQ2d 1984 (2014) (creating and maintaining "shadow accounts"); *Ultramercial*, 772 F.3d at 716, 112 USPQ2d at 1755 (updating an activity log);
- iv. Storing and retrieving information in memory, *Versata Dev. Group, Inc. v. SAP Am., Inc.*, 793 F.3d 1306, 1334, 115 USPQ2d 1681, 1701 (Fed. Cir. 2015); *OIP Techs.*, 788 F.3d at 1363, 115 USPQ2d at 1092-93;
- v. Electronically scanning or extracting data from a physical document, *Content Extraction and Transmission, LLC v. Wells Fargo Bank*, 776 F.3d 1343, 1348, 113 USPQ2d 1354, 1358 (Fed. Cir. 2014) (optical character recognition); and
- vi. A Web browser's back and forward button functionality, *Internet Patent Corp. v. Active Network, Inc.*, 790 F.3d 1343, 1348, 115 USPQ2d 1414, 1418 (Fed. Cir. 2015).

This listing is not meant to imply that all computer functions are well-understood, routine, conventional activities, or that a claim reciting a generic computer component performing a generic computer function is necessarily ineligible. See *e.g.* *Amdocs (Israel), Ltd. v. Openet Telecom, Inc.*, 841 F.3d 1288, 1316, 120 USPQ2d 1527, 1549 (Fed. Cir. 2016), *BASCOM Global Internet Servs. v. AT&T Mobility LLC*, 827 F.3d 1341, 1348, 119 USPQ2d 1236, 1241 (Fed. Cir. 2016). Courts have held computer-implemented processes not to be significantly more than an abstract idea (and thus ineligible) where the claim as a whole amounts to nothing more than generic computer functions merely used to implement an abstract

idea, such as an idea that could be done by a human analog (i.e., by hand or by merely thinking). On the other hand, courts have held computer-implemented processes to be significantly more than an abstract idea (and thus eligible), where generic computer components are able in combination to perform functions that are not merely generic. *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1257-59, 113 USPQ2d 1097, 1105-07 (Fed. Cir. 2014).

25. The additional elements of genomic sequencing the plurality of DNA fragments from the liquid biopsy sample and sequence alignment in claim 2 are conventional.

Evidence for the conventionality is shown by Morganti et al. (Critical Reviews in Oncology, 2019 (Published January 2019), Vol. 133, pp. 171-182). Morganti et al. reviews the complexity of genome sequencing and reporting, particularly focusing on next-generation sequencing (NGS) technologies and the implementation of precision medicine (Title; and Abstract). Morganti et al. shows that NGS technologies allow for the obtainment of extensive genetic information from liquid biopsies, and the obtainment of genetic material for sequencing from circulating tumor cells (CTCs) and circulating cell-free tumor DNA (ctDNA; page 172, column 2, para, 1; and page 177, column 2, Section 4.3). Morganti et al. further reviews NGS sequencing (page 173, Section 2.2) and NGS methods (page 174, Section 3), and further still, reviews advantages of NGS methodology with regard to microsatellite instability analyses (page 177, column 1, Section 4.2.2).

26. Furthermore, the additional elements evaluated in combination do not contribute an inventive concept, i.e., do not amount to significantly more than the judicial exception(s). The data gathering steps provide the data for the judicial exceptions, which are carried out by a general-purpose computer. Thus, there is not any non-routine step or element that has been clearly identified.

27. The Applicant's Remarks/Arguments received 03 July 2023 have been fully considered. The Applicant states that the claims of the present invention are not

directed to an abstract idea and are thus patent eligible under 35 U.S.C. § 101 because (i) they integrate any alleged abstract idea into the practical application of determining a microsatellite instability (MSI) status of a test subject (e.g., human) from a liquid biopsy sample and (ii) they improve the technical field of liquid biopsy assay by adding specific limitations and/or adding unconventional steps that confine the claims to the particular useful application and provide accurate determination of the microsatellite instability status of a cancer from a liquid biopsy sample. This argument is not persuasive because the judicial exceptions noted above at Eligibility Step 2A: Prong One comprise the recited data analysis limitations, which are not integrated into a practical application at Eligibility Step 2A: Prong Two because the claims do not recite additional elements that when examined as a whole, integrate the judicial exceptions into a practical application (MPEP 2106.04(d)). Furthermore, the claims do not recite additional elements that are sufficient to amount to significantly more than the judicial exceptions at Eligibility Step 2B because the additional element of a computer system in claim 1; genomic sequencing the plurality of DNA fragments from the liquid biopsy sample and sequence alignment in claim 2; and data inputting in claims 1 and 19, are conventional additional elements. Furthermore, the added specific limitations for determination of the microsatellite instability status of a cancer from a liquid biopsy sample as noted above are a purported improvement to the abstract ideas, and not an improvement to a technology field.

28. The Applicant further states that the claimed method includes a series of steps and specific limitations that result in the determination of the MSI status of a test subject (e.g., human) from a liquid biopsy sample of the test subject and that while the claimed

method may involve judicial exceptions, the result of these judicial exceptions is the determination of the MSI status of the test subject, which has nothing to do with the identified judicial exceptions. The Applicant further states that moreover, the process that enables the determination of the MSI status of the test subject from liquid biopsy sample is not an insignificant extra-solution activity because conventional processes do not satisfactorily allow the determination of the MSI status of the test subject from a liquid biopsy sample. This argument is not persuasive because the limitations that result in the determination of the MSI status comprise the judicial exceptions, and the judicial exceptions alone cannot provide the practical application or inventive concept (MPEP 2106.05). Identifying whether the additional elements beyond the abstract ideas integrate the judicial exceptions into a practical application requires further examination to be performed that analyzes if the claim recites additional elements that when examined as a whole integrates the judicial exception(s) into a practical application (MPEP 2106.04(d)). A claim that integrates a judicial exception into a practical application will apply, rely on, or use the judicial exception in a manner that imposes a meaningful limit on the judicial exception. The claimed additional elements are analyzed to determine if the abstract idea is integrated into a practical application (MPEP 2106.04(d).I; MPEP 2106.05(a-h)). If the claim contains no additional elements beyond the abstract idea, the claim fails to integrate the abstract idea into a practical application (MPEP 2106.04(d).III). Claims 1-12, 14-16, 19-25, 154, 155, and 159-164 do not recite additional elements which would integrate a judicial exception into a practical application, as noted above at section 19. Identifying whether the additional elements beyond the abstract ideas amount to an inventive concept requires considering the

additional elements individually and in combination to determine if they amount to significantly more than the judicial exceptions (MPEP 2106.05A i-vi). However, the claims do not include additional elements that are sufficient to amount to significantly more than the judicial exceptions because the additional element of a computer system in claim 1; genomic sequencing the plurality of DNA fragments from the liquid biopsy sample and sequence alignment in claim 2; and data inputting in claims 1 and 19, are conventional.

29. The Applicant's Remarks/Arguments at page 16 of 25 presents claim 1 with bolded passages because of their significance in the Applicant's arguments for patentability of the claim under 35 U.S.C. § 101, and Applicant states that as can be seen, claim 1 is directed to determining the MSI status of a test subject using a plurality of aligned nucleotide sequences from a liquid biopsy sample of the test subject despite the fact that detecting and/or validating cancer-specific genomic alterations of a liquid biopsy sample is significantly challenging and problematic. The Applicant further states that the claimed method is a practical application that addresses a technical problem in the field of determining the MSI status from a liquid biopsy sample and therefore is an advancement in the technical field of liquid biopsy assays for personalized cancer treatment. This argument is not persuasive because the bolded passage at step (A) is a conventional additional element that is a part of the data gathering process, as shown at Eligibility Step 2A: Prong Two and at Eligibility Step 2B, as noted above. Furthermore, the bolded passage at step (B) comprises judicial exceptions identified at Eligibility Step 2A: Prong One that are not integrated into a practical application at Eligibility Step 2A:

Prong Two, as noted above. Further still, the bolded passage at step (C) is the data output that is generated by the judicial exceptions.

30. The Applicant points to sections of the Specification discussing the state of the art, and states at page 20 of 25 that claim 1 addresses the technical problems in the art as stated in the Specification, and thus enables the practical application of determining the MSI status of a test subject from a liquid biopsy sample of the test subject by using one or more novel metrics of microsatellite stability for determination of the stability of each of a plurality of microsatellite loci in a cancer. The Applicant further states that the one or more novel metrics include a specific and unconventional likelihood score and its corresponding metric value, which is a statistical measure of a distribution of probabilities that each respective aligned nucleotide sequence in a subset of the set of aligned nucleotide sequences encompassing the respective microsatellite locus is a member of a distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite locus, wherein the subset of aligned nucleotide sequences consists of the aligned nucleotide sequences encompassing the respective microsatellite locus that have a number of repeat units that falls within a threshold percentile of the smallest number of repeat units. The Applicant states further still, that this specific and unconventional likelihood score and determination of its corresponding metric values are not well-understood, nor routine, nor conventional activity in the field, and instead they are specific and unconventional, and that this specific and unconventional likelihood score and determination of its corresponding metric value confine the claim to a particular useful application and enables accurate determination of the MSI status of a test subject from a liquid biopsy sample in a computationally lucid

and efficient manner. This argument is not persuasive because the one or more novel metrics that include a likelihood score and its corresponding metric value are judicial exceptions identified at Eligibility Step 2A: Prong One that are not integrated into a practical application at Eligibility Step 2A: Prong Two, as noted above. Furthermore, as noted above, the claims do not include additional elements that are sufficient to amount to significantly more than the judicial exceptions because the additional element of a computer system in claim 1; genomic sequencing the plurality of DNA fragments from the liquid biopsy sample and sequence alignment in claim 2; and data inputting in claims 1 and 19, are conventional. Further still, the determination of the MSI status is the data output that is generated by the judicial exceptions, which is a purported improvement to the abstract ideas, and not an improvement to a technology field.

Claim Rejections - 35 USC § 103

31. The rejection of claims 1, 2, 4-6, 8-11, 14-16, 19-21, 23, 24, and 154, 155, and 159 under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al. in view of Hinrichsen et al. in view of Huang et al. in the Office Action mailed 03 January 2023 is withdrawn in view of the amendments received 03 July 2023.

32. The rejection of claim 3 under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al. in view of Hinrichsen et al. in view of Huang et al. as applied to claims 1, 2, 4-6, 8-11, 14-16, 19-21, 23, 24, and 154, 155, and 159 above, and further in view of Cheng et al. in the Office Action mailed 03 January 2023 is withdrawn in view of the amendments received 03 July 2023.

33. The rejection of claims 7 and 12 under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al. in view of Hinrichsen et al. in view of Huang et al. in view

of Cheng et al. as applied to claims 1-6, 8-11, 14-16, 19-21, 23, 24, and 154, 155, and 159 above, and further in view of Zahir et al. in the Office Action mailed 03 January 2023 is withdrawn in view of the amendments received 03 July 2023.

34. The rejection of claim 13 under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al. in view of Hinrichsen et al. in view of Huang et al. in view of Cheng et al. in view of Zahir et al. as applied to claims 1-12, 14-16, 19-21, 23, 24, and 154, 155, and 159 above, and further in view of Saunders et al. in the Office Action mailed 03 January 2023 is withdrawn in view of the amendments received 03 July 2023.

35. The rejection of claim 22 under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al. in view of Hinrichsen et al. in view of Huang et al. in view of Cheng et al. in view of Zahir et al. in view of Saunders et al. as applied to claims 1-16, 19-21, 23, 24, and 154, 155, and 159 above, and further in view of Hong et al. in the Office Action mailed 03 January 2023 is withdrawn in view of the amendments received 03 July 2023.

36. The rejection of claim 25 under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al. in view of Hinrichsen et al. in view of Huang et al. in view of Cheng et al. in view of Zahir et al. in view of Saunders et al. in view of Hong et al. as applied to claims 1-16, 19-24, and 154, 155, and 159 above, and further in view of Salipante et al. in the Office Action mailed 03 January 2023 is withdrawn in view of the amendments received 03 July 2023.

37. The rejection of claims 160-163 under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al. in view of Hinrichsen et al. in view of Huang et al. in view of Cheng et al. in view of Zahir et al. in view of Saunders et al. in view of Hong et al. in

view of Salipante et al. as applied to claims 1-16, 19-25, and 154, 155, and 159 above, and further in view of Cotes-Ciriano et al. in the Office Action mailed 03 January 2023 is withdrawn in view of the amendments received 03 July 2023.

38. The Applicant's Remarks/Arguments received 03 July 2023 have been fully considered. The Applicant states that the cited references do not disclose the specific and unconventional likelihood score and its corresponding metric value of the claimed invention. Specifically, the Applicant states that the cited references do not disclose the computing of any likelihood as a statistical measure of a distribution of probabilities that each respective aligned nucleotide sequence in a subset of the set of aligned nucleotide sequences encompassing the respective microsatellite locus is a member of a distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite locus, wherein the subset of aligned nucleotide sequences consists of the aligned nucleotide sequences encompassing the respective microsatellite locus that have a number of repeat units that falls within a threshold percentile of the smallest number of repeat units, as required by amended claim 1. This argument is persuasive.

Conclusion

39. 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).

40. 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.

41. Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN W. BAILEY whose telephone number is (571) 272-8170. The examiner can normally be reached Mon - Thurs 0730 - 1800.

42. 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>.

43. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry D. Riggs can be reached on (571) 270-3062. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

44. 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

Application/Control Number: 16/945,588
Art Unit: 1672

Page 25

(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.

/JOHN S BRUSCA/
Primary Examiner, Art Unit 1672

/S.W.B./
Examiner, Art Unit 1672

Remarks/Arguments

Status of the Claims

Claims 1-16, 19-25, 154, 155, and 159-163 were previously pending in the application.

With this Response, claim 1 is amended to incorporate the subject matter of claim 13, and claim 13 is cancelled without prejudice or disclaimer.

With this Response, claims 14 and 15 each are amended to update the dependency in light of the amendment to claim 1 and cancellation of claim 13.

With this Response, claims 161 and 162 each are amended to recite the microsatellite loci of Table 2 as suggested by the Examiner on page 6 of the Office Action.

With this Response, claim 164 is added. Support for the subject matter is found in the application as originally filed, for instance, in at least paragraphs [0264]-[0269].

The claim amendments do not introduce any new matters. Accordingly, Applicant respectfully requests entry of the claim amendments.

Upon entry of the present amendment, claims 1-16, 19-25, 154, 155, and 159-164 will be pending for examination with claim 1 being independent.

Amendments to the Specification

With this Response, Applicant submits a substitute specification. The substitute specification includes addition of SEQ ID NO identifiers, in accordance with 37 C.F.R. §§ 1.821-1.825. The substitute specification also removes reference to sequences and figures not filed in the application.

In accordance with 37 CFR §§ 1.121(b)(3) and 1.125, the substitute specification contains no new matter.

With this Response, Applicant submits a sequence listing, in accordance with 37 C.F.R. §§ 1.821-1.825.

Accordingly, Applicant respectfully requests entry of the substitute specification and Sequence Listing.

Requirements for Patent Applications Containing Nucleotide and/or Amino Acid Sequence Disclosures

With this Response, Applicant submits a sequence listing as an ASCII text file, named 123138-5013-US_Sequence_Listing_ST25, containing SEQ ID NOs: 1-4. The sequence listing in computer readable form was prepared through the use of the software program “PatentIn, version 3.5” in accordance with 37 C.F.R. §§ 1.821-1.825.

According to the Legal Framework for EFS-Web (September 2008), if a sequence listing text file submitted via EFS-Web complies with the requirements of 37 C.F.R. § 1.824(a)(2)-(6) and (b), the text file will serve as both the paper copy required by 37 C.F.R. § 1.821(c) and the CRF required by 37 C.F.R. § 1.821(e). Therefor a paper copy of the referenced sequence listing is not included with this application.

The Office Action indicates that a Sequence Listing as a PDF or as physical sheets of paper were filed in the application. Applicant respectfully disagrees. However, to the extent the Office Action is referring to the listing of the sequences in Figure 18 of the Drawings, Applicant acknowledges that the content of the CFR of the sequence listing is identical to the “Sequence Listing” part of the disclosure, submitted as a PDF file or on physical sheets of paper, as required by 37 CFR 1.821(e)(1)(ii) or 1.821(e)(2)(ii).

Response to Office Action

The Office Action dated January 3, 2023:

- Rejects claims 161 and 162 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as allegedly 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;

- Rejects claims 1-16, 19-25, 154, 155, and 159-163 under 35 U.S.C. 101 because the claimed invention is directed to an abstract idea without significantly more;
- It is stated 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;
- Rejects claims 1, 2, 4-6, 8-11, 14-16, 19-21, 23, 24, and 154, 155, and 159 under 35 U.S.C. 103 as allegedly being unpatentable over Wang et al. (Nature Genetics. 2014. Vol. 46(6), pp. 573-582) in view of Lu et al. (PLoS ONE. 2013. Vol. 8(5): e63056, pp. 1-10), Hinrichsen et al. (Journal of Laboratory Medicine. 2016. Vol. 40(5), pp. 313-322), and Huang et al. (Scientific Reports. 2015. Vol. 5(13321), pp. 1-10);
- Rejects claim 3 under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., and Huang et al. as applied to claims 1, 2, 4-6, 8-11, 14-16, 19-21, 23, 24, and 154, 155, and 159 above, and further in view of Cheng et al. (Clinical Biochemistry. 2017. Vol. 50, pp. 496-501);
- Rejects claims 7 and 12 under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., and Cheng et al. as applied to claims 1-6, 8-11, 14-16, 19-21, 23, 24, and 154, 155, and 159 above, and further in view of Zahir et al. (Journal of Ayub Medical College Abbottabad. 2014. Vol. 26(1), pp. 95-97);
- Rejects claim 13 under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., and Zahir et al. as applied to claims 1-12, 14-16, 19-21, 23, 24, and 154, 155, and 159 above, and further in view of Saunders et al. (Bioinformatics. 2012. Vol. 28(14), pp. 1811-1817);
- Rejects claim 22 under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et al., and Saunders et al. as applied to claims 1-16, 19-21, 23, 24, and 154, 155, and 159 above, and further in view of Hong et al. (Clinical & Experimental Metastasis. 2010. Vol. 27, pp. 83-90);

- Rejects claim 25 under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et al., Saunders et al., and Hong et al. as applied to claims 1-16, 19-24, and 154, 155, and 159 above, and further in view of Salipante et al. (Clinical Chemistry. 2014. Vol. 60(9), pp. 1192-1199);
- Rejects claims 160-163 under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et al., Saunders et al., Hong et al., and Salipante et al. as applied to claims 1-16, 19-25, and 154, 155, and 159 above, and further in view of Cotes-Ciriano et al. (Nature Communications. 2017. Vol. 8(15180), 1-12).

Claim interpretation

The Office Action interprets claim 154 as a product-by-process claim with the product being the data for enriched cell-free DNA fragments. The claim is further interpreted to not require the processing steps of producing the product.

Applicant agrees that the claim does not require the processing steps associated with enrichment of cell-free DNA fragments from the liquid biopsy sample. However, Applicant respectfully disagrees that the claim is a product-by-process, as the claim is still directed to a method of determining a microsatellite instability (MSI) status of a test subject. Claim 154 further defines the source of the plurality of DNA fragments recited in step (A) of claim 1.

The rejection of claims 161 and 162 under 35 U.S.C. § 112(b) should be withdrawn

Claims 161 and 162 stand rejected as allegedly 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.

With this Response, claims 161 and 162 each are amended to explicitly recite the content of Table 2 as suggested by the Examiner on page 6 of the Office Action.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection.

The rejection under 35 U.S.C. § 101 should be withdrawn

Claims 1-16, 19-25, 154, 155, and 159-163 stand rejected as allegedly being directed to an abstract idea without significantly more, and specifically to mental processes and/or mathematical concepts.

To the extent that the rejection is asserted to apply to the amended claims, Applicant respectfully traverses the rejection for at least the following reasons.

MPEP § 2106.05 states: “claims that integrate [abstract ideas, natural phenomenon, and laws of nature] into ***an inventive concept*** are thereby transformed into patent-eligible inventions.” MPEP § 2106.04(a)(I)(II) also states: “[s]ome claims reciting an abstract idea are not directed to the abstract idea because they also recite additional elements (***such as an improvement***) demonstrating that the claims as a whole clearly do not seek to tie up the abstract idea”.

Similarly, the 2019 Guidance states: “[i]n Prong Two, examiners should evaluate whether the claim as a whole integrates the recited judicial exception into a practical application of the exception. A claim that integrates a judicial exception into a practical application will apply, rely on, or use the judicial exception in a manner that imposes a meaningful limit on the judicial exception, such that the claim is more than a drafting effort designed to monopolize the judicial exception.” Moreover, the 2019 Guidance Update states at page 11: “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. No further analysis is required. The claim is eligible at Step 2A.”

The claims of the present invention **are not directed to** an abstract idea and are thus patent eligible under 35 U.S.C. § 101 because (i) they integrate any alleged abstract idea into the practical application of determining a microsatellite instability (MSI) status of a test subject (*e.g.*,

human) from a liquid biopsy sample and (ii) they improve the technical field of liquid biopsy assay by adding specific limitations and/or adding unconventional steps that confine the claims to the particular useful application and provide accurate determination of the microsatellite instability status of a cancer from a liquid biopsy sample.

The claimed method includes a series of steps and specific limitations that result in the determination of the MSI status of a test subject (*e.g.*, human) from a liquid biopsy sample of the test subject. While the claimed method may involve judicial exceptions, the result of these judicial exceptions is the determination of the MSI status of the test subject. This has nothing to do with the identified judicial exceptions. Moreover, the process that enables the determination of the MSI status of the test subject from a liquid biopsy sample is not an insignificant extra-solution activity because, as discussed below, conventional processes do not satisfactorily allow the determination of the MSI status of the test subject from a liquid biopsy sample. For discussion purposes, claim 1 is presented below with bolded passages recited in claim 1 because of their significance in Applicant's arguments for patentability of the claim under 35 U.S.C. § 101 provided in this response:

1. A method of determining a microsatellite instability (MSI) status of a test subject, the method comprising:
 - at a computer system having one or more processors, and memory storing one or more programs for execution by the one or more processors:
 - (A) obtaining, ***for each respective DNA fragment in a plurality of DNA fragments from a liquid biopsy sample from the test subject***, a corresponding nucleotide sequence that has been aligned to a reference genome for the species of the test subject, thereby obtaining a plurality of aligned nucleotide sequences;
 - (B) using the plurality of aligned nucleotide sequences to determine, for each respective microsatellite locus in a plurality of predetermined microsatellite loci, wherein each respective microsatellite locus in the plurality of microsatellite loci has a nucleic acid sequence that includes a variable number of repeat units, a corresponding metric value for each of one or more metrics, wherein each respective metric in the one or more metrics is determined, at least in part, by a distribution of the number of repeat units in each aligned nucleotide sequence, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus,
the one or more metrics comprises a likelihood score, and

the corresponding metric value for the likelihood score is a statistical measure of a distribution of probabilities that each respective aligned nucleotide sequence in a subset of the set of aligned nucleotide sequences encompassing the respective microsatellite locus is a member of a distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite locus, wherein the subset of aligned nucleotide sequences consists of the aligned nucleotide sequences encompassing the respective microsatellite locus that have a number of repeat units that falls within a threshold percentile of the smallest number of repeat units; and

(C) comparing, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the corresponding metric values for the one or more metrics to corresponding reference metric values for the one or more metrics representative of a stable construct at the respective microsatellite locus, the reference metric values determined across nucleotide sequences obtained from biological samples from a training cohort that includes (i) solid tumor samples from training subjects with stable microsatellite cancer or (ii) normal tissue samples, ***thereby determining the MSI status of the test subject.***

(claim 1, emphasis added)

As can be seen, claim 1 is directed to determining the MSI status of a test subject using a plurality of aligned nucleotide sequences from a liquid biopsy sample of the test subject despite the fact that detecting and/or validating cancer-specific genomic alterations of a liquid biopsy sample is significantly challenging and problematic. Thus, the claimed method is a practical application that addresses a technical problem in the field of determining the MSI status from a liquid biopsy sample and therefore is an advancement in the technical field of liquid biopsy assays for personalized cancer treatment.

The specification explains the challenges and technical problems addressed by claim 1. For instance, paragraphs [0017]-[0020] of the specification state:

[0017] Nevertheless, while liquid biopsies are promising tools for improving outcomes using precision oncology, there are significant challenges specific to the use of cell-free DNA for evaluation of a subject's cancer genome. For instance, there is a highly variable signal-to-noise ratio from one liquid biological sample to the next. This occurs because cfDNA originates from a variety of different cells in a subject, both healthy and

diseased. Depending on the stage and type of cancer in any particular subject, the fraction of cfDNA fragments originating from cancerous cells (the “tumor fraction” or “ctDNA fraction” of the sample/subject) can range from almost 0% to well over 50%. Other factors, including tumor type and mutation profile, can also impact the amount of DNA released from cancerous tissues. For instance, cfDNA clearance through the liver and kidneys is affected by a variety of factors, including renal dysfunction or other tissue damaging factors (*e.g.*, chemotherapy, surgery, and/or radiotherapy).

[0018] This, in turn, leads to problems detecting and/or validating cancer-specific genomic alterations in a liquid sample. This is particularly true during early stages of the disease—when cancer therapies have much higher success rates—because the tumor fraction in the patient is lowest at this point. Thus, early stage cancer patients can have ctDNA fractions below the limit of detection (LOD) for one or more informative genomic alterations, limiting clinical utility because of the risk of false negatives and/or providing an incomplete picture of the cancer genome of the patient. Further, because cancers, and even individual tumors, can be clonally diverse, actionable genomic alterations that arise in only a subset of clonal populations are diluted below the overall tumor fraction of the sample, further frustrating attempts to tailor combination therapies to the various actionable mutations in the patient’s cancer genome. Consequently, most studies using liquid biopsy samples to date have focused on late stage patients for assay validation and research.

[0019] Another challenge associated with liquid biopsies is the accurate determination of tumor fraction in a sample. This difficulty arises from at least the heterogeneity of cancers and the increased frequency of large chromosomal duplications and deletions found in cancers. As a result, the frequency of genomic alterations from cancerous tissues varies from locus to locus based on at least (i) their prevalence in different subclonal populations of the subject’s cancer, and (ii) their location within the genome, relative to large chromosomal copy number variations. The difficulty in accurately determining the tumor fraction of liquid biological samples affects accurate measurement of various cancer features shown to have diagnostic value for the analysis of solid tumor biopsies. These include allelic ratios, copy number variations, overall mutational burden, frequency of abnormal methylation patterns, *etc.*, all of which are correlated with the percentage of DNA fragments that arise from cancerous tissue, as opposed to healthy tissue.

[0020] Altogether, these factors result in highly variable concentrations of ctDNA—from patient to patient and possibly from locus to locus—that confound accurate measurement of disease indicators and actionable genomic alterations. Further, the quantity and quality of cfDNA obtained from liquid biopsy samples are highly dependent on the particular methodology for collecting the samples, storing the samples, sequencing the samples, and standardizing the sequencing data.

In paragraphs [0021] and [0069], the specification points out the current status of liquid biopsy assays. The specification states in paragraph [0021] that few studies have corroborated results with orthogonal methods, or between particular testing platforms, *e.g.*, different NGS technologies and/or targeted panel sequencing versus whole genome/exome sequencing, and liquid biopsy-based studies are limited by comparison to non-comprehensive tissue testing algorithms including Sanger sequencing, small NGS hotspot panels, polymerase chain reaction (PCR), and fluorescent in situ hybridization (FISH). The specification states in paragraph [0069] that *conventional liquid biopsy assays do not provide accurate determination of the microsatellite stability status of a cancer.*

In paragraphs [0071]-[0073], the specification explains the technical problem(s) encountered when using a liquid biopsy sample for determining the MSI status:

[0071] The identification of actionable genomic alterations in a patient's cancer genome is a ***difficult and computationally demanding problem***. For instance, the determination of various prognostic metrics useful for precision oncology, such as variant allelic ratio, copy number variation, tumor mutational burden, microsatellite instability status, *etc.*, requires analysis of hundreds of millions to billions, of sequenced nucleic acid bases. An example of a typical bioinformatics pipeline established for this purpose includes at least five stages of analysis: assessment of the quality of raw next generation sequencing data, generation of collapsed nucleic acid fragment sequences and alignment of such sequences to a reference genome, detection of structural variants in the aligned sequence data, annotation of identified variants, and visualization of the data. See, Wadapurkar and Vyas, Informatics in Medicine Unlocked, 11:75-82 (2018), the content of which is hereby incorporated by reference, in its entirety, for all purposes. Each one of these procedures is computationally taxing in its own right.

[0072] For instance, the overall temporal and spatial computation complexity of simple global and local pairwise sequence alignment algorithms are quadratic in nature (e.g., second order problems), that increase rapidly as a function of the size of the nucleic acid sequences (n and m) being compared. Specifically, the temporal and spatial complexities of these sequence alignment algorithms can be estimated as $O(mn)$, where O is the upper bound on the asymptotic growth rate of the algorithm, n is the number of bases in the first nucleic acid sequence, and m is the number of bases in the second nucleic acid sequence. See, Baichoo and Ouzounis, *BioSystems*, 156–157:72-85 (2017), the content of which is hereby incorporated by reference, in its entirety, for all purposes. Given that the human genome contains more than 3 billion bases, these alignment algorithms are extremely computationally taxing, especially when used to analyze next generation sequencing (NGS) data, which can generate more than 3 billion sequence reads per reaction.

[0073] *This is particularly true when performed in the context of a liquid biopsy assay, because liquid biological samples contain a complex mixture of short DNA fragments originating from many different germline (e.g., healthy) and diseased (e.g., cancerous) tissues.* Thus, the cellular origins of the sequence reads are unknown, and the sequence signals originating from cancerous cells, which may constitute multiple sub-clonal populations, must be computationally deconvoluted from signals originating from germline and hematopoietic origins, in order to provide relevant information about the subject's cancer. *Thus, in addition to the computationally taxing processes required to align sequence reads to a human genome, there is a computation problem of determining whether a particular abnormal signal, e.g., one or more sequence reads corresponding to a genomic alteration, (i) is not an artifact, and (ii) originated from a cancerous source in the subject.* This is increasingly difficult during the early stages of cancer—when treatment is presumably most effective—when only small amounts of ctDNA are diluted by germline and hematopoietic DNA.

(emphasis added)

Claim 1 addresses the above-described technical problem(s) and thus enables the practical application of determining the MSI status of a test subject from a liquid biopsy sample of the test subject by using one or more novel metrics of microsatellite stability for determination of the stability of each of a plurality of microsatellite loci in a cancer. The one or more novel metrics include a specific and unconventional likelihood score and its corresponding metric

value, which is “a statistical measure of a distribution of probabilities that each respective aligned nucleotide sequence in a subset of the set of aligned nucleotide sequences encompassing the respective microsatellite locus is a member of a distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite locus, wherein the subset of aligned nucleotide sequences consists of the aligned nucleotide sequences encompassing the respective microsatellite locus that have a number of repeat units that falls within a threshold percentile of the smallest number of repeat units.”

This specific and unconventional likelihood score and determination of its corresponding metric value are not well-understood, nor routine, nor conventional activity in the field. Instead, they are specific and unconventional. This specific and unconventional likelihood score and determination of its corresponding metric value confine the claim to a particular useful application and enables accurate determination of the MSI status of a test subject from a liquid biopsy sample in a computationally lucid and efficient manner. For instance, as disclosed in paragraphs [0070] and [0074] of the specification, this specific and unconventional likelihood score and determination of its corresponding metric value, together with other novel metrics of microsatellite stability, allows for accurate prediction of the overall microsatellite stability of a cancer. It improves the computational elucidation of actionable genomic alterations from a liquid biopsy sample of a cancer patient, improves upon the accuracy of microsatellite stability determination from a liquid biopsy assay, which is inherently a computational problem, and improves precision oncology methodologies for assigning and/or administering personalized treatment because of the improved accuracy of microsatellite stability classification. The claimed method enables accurate determination of the MSI status of a test subject from a liquid biopsy sample in a computationally lucid and efficient manner, where the conventional liquid biopsy assays have not been considered or failed, *e.g.*, in instances where the sequence reads from the liquid biopsy sample require proper alignment and determination of whether a particular abnormal signal is an artifact or originated from a cancerous source in the subject.

Thus, claim 1 recites a method that solves the technical problem(s) described in the specification, integrates the alleged abstract idea into an inventive concept that is significantly more than any abstract idea, and provides improvements to the technical field of liquid biopsy

assays. Accordingly, claim 1 qualifies as eligible subject matter under 35 U.S.C. § 101. Claims 2-16, 19-25, 154, 155, and 159-163 depend from claim 1 and thus are patentable under 35 U.S.C. § 101 for at least the same reason as claim 1.

Applicant therefore respectfully requests that the 35 U.S.C. § 101 rejection of claims 1-16, 19-25, 154, 155, and 159-163 be withdrawn.

The rejection under 35 U.S.C. § 103 should be withdrawn

Claims 1, 2, 4-6, 8-11, 14-16, 19-21, 23, 24, and 154, 155, and 159 stand rejected as allegedly being unpatentable over Wang et al. (Nature Genetics. 2014. Vol. 46(6), pp. 573-582) in view of Lu et al. (PLoS ONE. 2013. Vol. 8(5): e63056, pp. 1-10), Hinrichsen et al. (Journal of Laboratory Medicine. 2016. Vol. 40(5), pp. 313-322), and Huang et al. (Scientific Reports. 2015. Vol. 5(13321), pp. 1-10).

Claim 3 stands rejected as allegedly being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., and Huang et al. as applied to claims 1, 2, 4-6, 8-11, 14-16, 19-21, 23, 24, and 154, 155, and 159 above, and further in view of Cheng et al. (Clinical Biochemistry. 2017. Vol. 50, pp. 496-501).

Claims 7 and 12 stand rejected as allegedly being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., and Cheng et al. as applied to claims 1-6, 8-11, 14-16, 19-21, 23, 24, and 154, 155, and 159 above, and further in view of Zahir et al. (Journal of Ayub Medical College Abbottabad. 2014. Vol. 26(1), pp. 95-97).

Claim 13 stands rejected as allegedly being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., and Zahir et al. as applied to claims 1-12, 14-16, 19-21, 23, 24, and 154, 155, and 159 above, and further in view of Saunders et al. (Bioinformatics. 2012. Vol. 28(14), pp. 1811-1817).

Claim 22 stands rejected as allegedly being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et al., and Saunders et al. as applied to claims 1-16, 19-21, 23, 24, and 154, 155, and 159 above, and further in view of Hong et al. (Clinical & Experimental Metastasis. 2010. Vol. 27, pp. 83-90).

Claim 25 stands rejected as allegedly being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et al., Saunders et al., and Hong et al. as applied to claims 1-16, 19-24, and 154, 155, and 159 above, and further in view of Salipante et al. (Clinical Chemistry. 2014. Vol. 60(9), pp. 1192-1199).

Claims 160-163 stand rejected as allegedly being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et al., Saunders et al., Hong et al., and Salipante et al. as applied to claims 1-16, 19-25, and 154, 155, and 159 above, and further in view of Cotes-Ciriano et al. (Nature Communications. 2017. Vol. 8(15180), 1-12).

Solely to further prosecution of this application and without conceding to the propriety of this rejection, Applicant has amended claim 1 to incorporate the subject matter of previously presented claim 13, *i.e.*, to recite that the one or more metrics comprises a likelihood score. On pages 31-32, the Office Action alleges that Saunders discloses a likelihood score as a statistical measure of a distribution of probabilities at Section 2.3 on page 1813. Applicant respectfully disagrees.

Saunders does not teach or suggest the specific and unconventional likelihood score and its corresponding metric value as required by amended claim 1. Instead, the cited section of Saunders discloses a somatic variant calling model that approximates a posterior probability on the joint tumor and normal allele frequencies. The joint likelihood is computed from independent sample-specific allele frequency likelihoods, which Saunders describes in Supplementary Methods. In Supplementary Methods, Saunders discloses that the sample SNV likelihood is computed from the set of base calls aligned to each site following the tier-specific read filtration and realignment steps and the indel likelihood is computed from the set of reads intersecting the indel. Neither Section 2.3 nor Supplementary Methods of Saunders discloses computing of any likelihood as a statistical measure of a distribution of probabilities that each respective aligned nucleotide sequence in a subset of the set of aligned nucleotide sequences encompassing the respective microsatellite locus is ***a member of a distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite locus***, wherein the subset of aligned nucleotide sequences ***consists of*** the aligned nucleotide sequences encompassing the respective microsatellite locus ***that have a number of repeat units that falls***

within a threshold percentile of the smallest number of repeat units, as required by amended claim 1. Thus, while the cited section of Saunders discloses computation of likelihoods, none of them can be equated to the specific and unconventional likelihood score and its corresponding metric value of the claimed invention. Indeed, throughout its entirety, Saunders does not teach or suggest the specific and unconventional likelihood score and its corresponding metric value of the claimed invention.

The remaining cited references are not cited for, and in fact do not disclose, the specific and unconventional likelihood score and its corresponding metric value of the claimed invention.

Since the cited references individually do not disclose or suggest the features noted above, the combination of these references necessarily cannot provide these features of the claimed invention. Accordingly, claim 1 and its dependent claims 2-12, 14-16, 19-25, 154, 155, and 159-163 are patentable over the art of record.

The rejection to claim 13 is moot in view of the cancellation thereto.

Applicant therefore respectfully requests reconsideration and withdrawal of the rejection.

Other matter

New claim 164 depends from claim 1 and is thus patentable for at least the same reasons as claim 1.

CONCLUSION

All the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn.

Applicant believes that a full and complete reply has been made to the outstanding Office Action, and as such, the present application is in condition for allowance. 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.

Except for issue fees payable under 37 CFR § 1.18, the Commissioner is hereby authorized by this paper to charge any necessary fees during the entire pendency of this application including fees due under 37 CFR §§ 1.16 and 1.17, which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310 (Order No.: 123138-5013-US).

Prompt and favorable consideration of this Amendment and Response is respectfully requested.

Respectfully submitted,
MORGAN, LEWIS & BOCKIUS LLP

Dated: <u>July 3, 2023</u> Customer No.: 12139 Morgan, Lewis & Bockius LLP One Market, Spear Street Tower San Francisco, CA 94105 Telephone: (415) 442-1000 Facsimile: (415) 442-1001	By: <u>/Andrew J. Antczak/</u> Andrew J. Antczak, Ph.D. Reg. No. 70,871 <i>for</i> Brett A. Lovejoy, Ph. D., Reg. No. 42,813
---	---



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 NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/945,588	07/31/2020	Ariane Lozac'hmeur	123138-5013-US	8972
43850	7590	01/03/2023	EXAMINER	
Morgan, Lewis & Bockius LLP (SF)			BAILEY, STEVEN WILLIAM	
One Market, Spear Street Tower, Suite 2800			ART UNIT	PAPER NUMBER
San Francisco, CA 94105			1671	
			NOTIFICATION DATE	DELIVERY MODE
			01/03/2023	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):

donald.mixon@morganlewis.com
sfipdocketing@morganlewis.com

Continuation of Attachment(s) 2) Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date: 11/10/2021, 09/07/2021, 08/04/2021, 06/30/2021, 02/09/2021, 09/17/2020

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Status of the Claims

2. Claims 1-16, 19-25, 154, 155, and 159-163 are pending.

Claims 1-16, 19-25, 154, 155, and 159-163 are rejected.

Priority

3. Claims 1-16, 19-25, 154, 155, and 159-163 are given the benefit for priority to Provisional Application No. 62/,881,845, filed 01 August 2019, Provisional Application No. 62/931,600, filed 06 November 2019, and Provisional Application No. 62/978,130, filed 18 February 2020.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on 10 November 2021, 07 September 2021, 04 August 2021, 30 June 2021, 09 February 2021, and 17 September 2020 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Drawings

5. The drawings were received on 31 July 2020. These drawings are accepted.

Nucleotide and/or Amino Acid Sequence Disclosures

6. **REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

Items 1) and 2) provide general guidance related to requirements for sequence disclosures.

- 1) 37 CFR 1.821(c) requires that patent applications which contain disclosures of nucleotide and/or amino acid sequences that fall within the definitions of 37 CFR 1.821(a) must contain a "Sequence Listing," as a separate part of the disclosure, which presents the nucleotide and/or amino acid sequences and associated information using the symbols and format in accordance with the requirements of 37 CFR 1.821 - 1.825. This "Sequence Listing" part of the disclosure may be submitted:
 - a) In accordance with 37 CFR 1.821(c)(1) via the USPTO's electronic filing system (see Section I.1 of the Legal Framework for EFS-Web or Patent Center (<https://www.uspto.gov/patents-application-process/filing-online/legal-framework-efs-web>), hereinafter "Legal Framework") as an ASCII text file, together with an incorporation-by-reference of the material in the ASCII text file in a separate paragraph of the specification as required by 37 CFR 1.823(b)(1) identifying:
 - i) the name of the ASCII text file;
 - ii) the date of creation; and
 - iii) the size of the ASCII text file in bytes;
 - b) In accordance with 37 CFR 1.821(c)(1) on read-only optical disc(s) as permitted by 37 CFR 1.52(e)(1)(ii), labeled according to 37 CFR 1.52(e)(5), with an incorporation-by-reference of the material in the ASCII text file according to 37 CFR 1.52(e)(8) and 37 CFR 1.823(b)(1) in a separate paragraph of the specification identifying:
 - i) the name of the ASCII text file;
 - ii) the date of creation; and
 - iii) the size of the ASCII text file in bytes;

- c) In accordance with 37 CFR 1.821(c)(2) via EFS-Web or Patent Center as a PDF file (not recommended); or
 - d) In accordance with 37 CFR 1.821(c)(3) on physical sheets of paper (not recommended).
- 2) When a "Sequence Listing" has been submitted as a PDF file as in 1(c) above (37 CFR 1.821(c)(2)) or on physical sheets of paper as in 1(d) above (37 CFR 1.821(c)(3)), 37 CFR 1.821(e)(1) requires a computer readable form (CRF) of the "Sequence Listing" in accordance with the requirements of 37 CFR 1.824.
- a) If the "Sequence Listing" required by 37 CFR 1.821(c) is filed via EFS-Web or Patent Center as a PDF, then 37 CFR 1.821(e)(1)(ii) or 1.821(e)(2)(ii) requires submission of a statement that the "Sequence Listing" content of the PDF copy and the CRF copy (the ASCII text file copy) are identical.
 - b) If the "Sequence Listing" required by 37 CFR 1.821(c) is filed on paper or read-only optical disc, then 37 CFR 1.821(e)(1)(ii) or 1.821(e)(2)(ii) requires submission of a statement that the "Sequence Listing" content of the paper or read-only optical disc copy and the CRF are identical.

Specific deficiencies and the required response to this Office Action are as follows:

Refer to Figure 18 in the Drawings, which depicts sequences with associated sequence identification numbers.

7. **Specific deficiency** - This application contains a "Sequence Listing as a PDF file (37 CFR 1.821(c)(2)) or as physical sheets of paper (37 CFR 1.821(c)(3)), but fails to comply with the requirements of 37 CFR 1.821 - 1.825 because a copy of the

"Sequence Listing" in computer readable form (CRF) has not been submitted as required by 37 CFR 1.821(e)(1)(i) or 1.821(e)(2)(i) as indicated in item 2) above.

Required response - Applicant must provide:

- A new CRF of the "Sequence Listing" in accordance with 37 CFR 1.821(e)(1)(i) or 1.821(e)(2)(i) and
- A statement that the content of the CRF is identical of the "Sequence Listing" part of the disclosure, submitted as a PDF file (37 CFR 1.821(c)(2)) or on physical sheets of paper (37 CFR 1.821(c)(3)), as required by 37 CFR 1.821(e)(1)(ii) or 1.821(e)(2)(ii).

Claim Interpretation

8. Claim 154 is interpreted as a product-by-process claim with the product being the data for enriched cell-free DNA fragments. The claim is further interpreted to not require the processing steps of producing the product.

Claim Rejections - 35 USC § 112

9. 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.

10. Claims 161 and 162 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.

Claims 161 and 162 are indefinite for recitation of a limitation of a figure or table at line 3. Where possible, claims are to be complete in themselves (MPEP 2173.05(s)).

This rejection may be overcome by adding the contents of Table 2 to the claims.

Claim Rejections - 35 USC § 101

11. 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.

12. Claims 1-16, 19-25, 154, 155, and 159-163 are rejected under 35 U.S.C. 101 because the claimed invention is directed to an abstract idea without significantly more.

The claims recite: (a) mathematical concepts, (e.g., mathematical relationships, formulas or equations, mathematical calculations); and (b) mental processes, i.e., concepts performed in the human mind, (e.g., observation, evaluation, judgement, opinion).

Following the flowchart in MPEP 2106:

Eligibility Step 1

The claims are directed to methods and products which are encompassed by the categories of statutory subject matter. Thus, the claims satisfy the subject matter eligibility requirements under step 1.

Eligibility Step 2A: Prong one

In determining whether a claim is directed to a judicial exception, examination is performed that analyzes whether the claim recites a judicial exception, i.e., whether a law of nature, natural phenomenon, or abstract idea is set forth or described in the claim.

Independent claim 1 recites a mental process of selecting a plurality of nucleotide sequences that have been aligned to a reference genome for the species of the test subject; a mental process and a mathematical concept of determining a metric value based in part on a distribution of the number of repeat units in each aligned nucleotide sequence encompassing the respective microsatellite locus; a mental concept of comparing the corresponding metric values for each respective microsatellite locus to corresponding reference metric values representative of a stable construct at the respective microsatellite locus; a mental process and a mathematical concept of determining reference metric values determined across nucleotide sequences obtained from biological samples from a training cohort that includes (i) solid tumor samples from training subjects with stable microsatellite cancer or (ii) normal tissue samples, thereby determining the MSI status of the test subject.

Dependent claim 2 further recites a mental process of selecting a corresponding set of raw sequence reads for the respective DNA fragment; a mental process of collapsing the corresponding set of aligned raw sequence reads for the respective DNA fragment into a corresponding nucleotide sequence for the respective DNA fragment that has been aligned to the human reference genome, thereby obtaining a plurality of aligned nucleotide sequences. Dependent claim 3 further recites a mental process of considering whether the plurality of aligned nucleotide sequences comprises at least 250,000 aligned nucleotide sequences. Dependent claim 4 further recites a mental process of determining that the one or more metrics comprises a percentage score; a mental process and a mathematical concept of determining that the corresponding metric value for the percentage score is the percentage of aligned nucleotide

sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus. Dependent claim 5 further recites a mental process of considering that for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject. Dependent claim 6 further recites a mental process and a mathematical concept of determining that the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values; and a mental process of considering whether each respective reference value in the plurality of reference values is determined at least in part based on a distribution of the number of repeat units at the respective microsatellite locus in a respective reference sample in a plurality of reference standards. Dependent claim 7 further recites a mental process and a mathematical concept of determining that the reference number of repeat units representative of a stable construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus. Dependent claim 8 further recites a mental process and a mathematical concept of determining that the one or more metrics comprises a lower mean score; and a mental process and mathematical concept of determining that the corresponding metric value for the lower mean score is determined at least in part by the mean number of repeat units in aligned nucleotide sequences, in the plurality of aligned nucleotides,

encompassing the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus. Dependent claim 9 further recites a mental process and a mathematical concept of determining that the mean number of repeat units is normalized by the reference number of repeat units representative of a stable construct at the respective microsatellite locus. Dependent claim 10 further recites a mental process of considering that for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject. Dependent claim 11 further recites a mental process and a mathematical concept of determining that the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values; and a mental process of considering whether each respective reference value in the plurality of reference values is determined at least in part based on a distribution of the number of repeat units at the respective microsatellite locus in a respective reference sample in a plurality of reference samples. Dependent claim 12 further recites a mental process and a mathematical concept of determining that the reference number of repeat units representative of a stable construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus. Dependent claim 13 further recites a mental process and a mathematical concept of determining that the one or more metrics comprises a likelihood score; a mental process and a mathematical concept of determining that the

corresponding metric value for the likelihood score is a statistical measure of a distribution of probabilities that each respective aligned nucleotide sequence in a subset of the set of aligned nucleotide sequences encompassing the respective microsatellite locus is a member of a distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite locus; and a mental process and a mathematical concept of determining that the subset of aligned nucleotide sequences consists of the aligned nucleotide sequences encompassing the respective microsatellite locus that have a number of repeat units that falls within a threshold percentile of the smallest number of repeat units. Dependent claim 14 further recites a mental process and a mathematical concept of determining that the statistical measure is a mean of the distribution of probabilities that each aligned nucleotide sequence in the subset of aligned nucleotide sequences encompassing the respective microsatellite locus is a member of the distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite locus. Dependent claim 15 further recites a mental process and a mathematical concept of determining that the distribution of probabilities is a plurality of p-values, wherein each respective p-value in the plurality of p-values is a probability value that a respective aligned nucleotide sequence in the subset of aligned nucleotide sequences is a member of the distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite locus. Dependent claim 16 further recites a mental process and a mathematical concept of determining that one or more corresponding metric values comprises a corresponding standard deviation of the number of repeat units in the aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, encompassing the

respective microsatellite locus. Dependent claim 19 further recites a mental process of organizing metric value data according to classification; and a mental process of comparing between stable and unstable microsatellite loci. Dependent claim 20 further recites a mental process of considering that the biological samples from the training cohort included both (i) solid tumor samples from training subjects with stable microsatellite cancer and (ii) normal tissue samples. Dependent claim 21 further recites a mental process of considering that the biological samples from the training cohort further included (iii) solid tumor samples from training subjects with unstable microsatellite cancer. Dependent claim 22 further recites a mental process of determining that the classifier comprises a k-nearest neighbors algorithm. Dependent claim 23 further recites a mental process and a mathematical concept of the classifier assigning a stability status selected from unstable and stable to each respective microsatellite locus in the plurality of predetermined microsatellite loci, and the subject is classified as having a high level of microsatellite instability when at least a threshold number of microsatellite loci are assigned a status of unstable. Dependent claim 24 further recites a mental process and a mathematical concept of determining that the threshold number of microsatellite loci is at least 30% of the total number of microsatellite loci in the plurality of microsatellite loci. Dependent claim 25 further recites a mental process and a mathematical concept of determining that the threshold number of microsatellite loci is at least 50% of the total number of microsatellite loci in the plurality of microsatellite loci. Dependent claim 154 further recites a mental process of considering sequence data. Dependent claim 155 further recites a mental process of considering and analyzing sequence reads that represent, on average, greater than

1000X sequence depth for each microsatellite locus in the plurality of predetermined microsatellite loci. Dependent claim 159 further recites a mental process of considering data from blood or blood plasma samples. Dependent claim 160 further recites a mental process of considering that the plurality of predetermined microsatellite loci comprises at least 25 microsatellite loci. Dependent claim 161 further recites a mental process of considering that the plurality of predetermined microsatellite loci comprises at least 10 of the microsatellite loci listed in Table 2. Dependent claim 162 further recites a mental process of considering that the plurality of predetermined microsatellite loci comprises at least all of the microsatellite loci listed in Table 2. Dependent claim 163 further recites a mental process of considering data from a human subject.

Eligibility Step 2A: Prong two

In determining whether a claim is directed to a judicial exception, further examination is performed that analyzes if the claim recites additional elements that when examined as a whole integrates the judicial exception(s) into a practical application (MPEP 2106.04(d)). A claim that integrates a judicial exception into a practical application will apply, rely on, or use the judicial exception in a manner that imposes a meaningful limit on the judicial exception. The claimed additional elements are analyzed to determine if the abstract idea is integrated into a practical application (MPEP 2106.04(d).I; MPEP 2106.05(a-h)). If the claim contains no additional elements beyond the abstract idea, the claim fails to integrate the abstract idea into a practical application (MPEP 2106.04(d).III).

The judicial exceptions noted above are not integrated into a practical application because the additional element of a computer in independent claim 1 does not improve

the functioning of a generic computer and therefore does not integrate the recited judicial exceptions into a practical application. Data gathering steps are not an abstract idea, but rather they are extra-solution activity, as they collect the data needed to carry out the abstract idea. Data gathering does not impose any meaningful limitation on the abstract idea, or how the abstract idea is performed. Data gathering steps are not sufficient to integrate an abstract idea into a practical application.

Eligibility Step 2B

Because the claims recite an abstract idea, and do not integrate that abstract idea into a practical application, the claims are probed for a specific inventive concept. The judicial exception alone cannot provide that inventive concept or practical application (MPEP 2106.05). Identifying whether the additional elements beyond the abstract idea amount to such an inventive concept requires considering the additional elements individually and in combination to determine if they amount to significantly more than the judicial exception (MPEP 2106.05A i-vi).

The claims do not include additional elements that are sufficient to amount to significantly more than the judicial exception(s) because the additional element of a computer in claim 1 is conventional.

Regarding conventionality of computer components and computer processes, the MPEP states at 2106.05(b):

2106.05(b) Particular Machine [R-10.2019]

When determining whether a claim integrates a judicial exception, into a practical application in Step 2A Prong Two and whether a claim recites significantly more than a judicial exception in Step 2B, examiners should consider whether the judicial exception is applied with, or by use of, a particular machine. "The machine-or-transformation test is a useful and important clue, and investigative tool" for determining whether a claim is patent eligible under § 101. *Bilski v. Kappos*, 561 U.S. 593, 604, 95 USPQ2d 1001, 1007 (2010).

It is noted that while the application of a judicial exception by or with a particular machine is an important clue, it is not a stand-alone test for eligibility. *Id.*

All claims must be evaluated for eligibility using the two-part test from *Alice/Mayo*. If a claim passes the *Alice/Mayo* test (*i.e.*, is not directed to an exception at Step 2A, or amounts to significantly more than any recited exception in Step 2B), then the claim is eligible even if it fails the machine-or-transformation test ("M-or-T test"). *Bilski v. Kappos*, 561 U.S. 593, 604, 95 USPQ2d 1001, 1007 (2010) (explaining that a claim may be eligible even if it does not satisfy the M-or-T test); *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 837 F.3d 1299, 1315, 120 USPQ2d 1091, 1102 (Fed. Cir. 2016) ("[T]here is nothing that requires a method 'be tied to a machine or transform an article' to be patentable"). And if a claim fails the *Alice/Mayo* test (*i.e.*, is directed to an exception at Step 2A and does not amount to significantly more than the exception in Step 2B), then the claim is ineligible even if it passes the M-or-T test. *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1256, 113 USPQ2d 1097, 1104 (Fed. Cir. 2014) ("[I]n *Mayo*, the Supreme Court emphasized that satisfying the machine-or-transformation test, by itself, is not sufficient to render a claim patent-eligible, as not all transformations or machine implementations infuse an otherwise ineligible claim with an 'inventive concept.'").

Examiners may find it helpful to evaluate other considerations such as the mere instructions to apply an exception consideration (see **MPEP § 2106.05(f)**), the insignificant extra-solution activity consideration (see **MPEP § 2106.05(g)**), and the field of use and technological environment consideration (see **MPEP § 2106.05(h)**), when making a determination of whether an element (or combination of elements) is a particular machine. For information on the definition of the term "machine," see **MPEP § 2106.03**.

When determining whether a machine recited in a claim provides significantly more, the following factors are relevant.

I. THE PARTICULARITY OR GENERALITY OF THE ELEMENTS OF THE MACHINE OR APPARATUS

The particularity or generality of the elements of the machine or apparatus, *i.e.*, the degree to which the machine in the claim can be specifically identified (not any and all machines). One example of applying a judicial exception with a particular machine is *Mackay Radio & Tel. Co. v. Radio Corp. of America*, 306 U.S. 86, 40 USPQ 199 (1939). In this case, a mathematical formula was employed to use standing wave phenomena in an antenna system. The claim recited the particular type of antenna and included details as to the shape of the antenna and the conductors, particularly the length and angle at which they were arranged. 306 U.S. at 95-96; 40 USPQ at 203. Another example is *Eibel Process*, in which gravity (a law of nature or natural phenomenon) was applied by a Fourdrinier machine (which was understood in the art to have a specific structure comprising a headbox, a paper-making wire, and a series of rolls) arranged in a particular way to optimize the speed of the machine while maintaining quality of the formed paper web. *Eibel Process Co. v. Minn. & Ont. Paper Co.*, 261 U.S. 45, 64-65 (1923).

It is important to note that a general purpose computer that applies a judicial exception, such as an abstract idea, by use of conventional computer functions does not qualify as a particular machine. *Ultramercial, Inc. v. Hulu, LLC*, 772 F.3d 709, 716-17, 112 USPQ2d 1750, 1755-56 (Fed. Cir. 2014). See also *TLI Communications LLC v. AV Automotive LLC*, 823 F.3d 607, 613, 118 USPQ2d 1744, 1748 (Fed. Cir. 2016) (mere recitation of concrete or tangible components is not an inventive concept); *Eon Corp. IP Holdings LLC v. AT&T Mobility LLC*, 785 F.3d 616, 623, 114 USPQ2d 1711, 1715 (Fed. Cir. 2015) (noting that *Alappat's* rationale that an otherwise ineligible algorithm or software could be made patent-eligible by merely adding a generic computer to the claim was superseded by the Supreme Court's *Bilski* and *Alice Corp.* decisions). If applicant amends a claim to add a generic computer or generic computer components and asserts that the claim recites significantly more because the generic computer is 'specially programmed' (as in *Alappat*, now considered superseded) or is a 'particular machine' (as in *Bilski*), the examiner should look at whether the added elements integrate the exception into a practical application or provide significantly more than the judicial exception. Merely adding a generic computer, generic computer components, or a programmed computer to perform generic computer functions does not automatically overcome an eligibility rejection. *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 573 U.S. 208, 223-24, 110 USPQ2d 1976, 1983-84 (2014). See *In re Alappat*, 33 F.3d 1526, 1545 (Fed. Cir. 1994); *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008).

II. WHETHER THE MACHINE OR APPARATUS IMPLEMENTS THE STEPS OF THE METHOD

Integral use of a machine to achieve performance of a method may integrate the recited judicial exception into a practical application or provide significantly more, in contrast to where the machine is merely an object on which the method operates, which does not integrate the exception into a practical application or provide significantly more. See *CyberSource v. Retail Decisions*, 654 F.3d 1366, 1370, 99 USPQ2d 1690, 1694 (Fed. Cir. 2011) ("We are not persuaded by the appellant's argument that the claimed method is tied to a particular machine because it 'would not be necessary or possible without the Internet.' . . . Regardless of whether "the Internet" can be viewed as a machine, it is clear that the Internet cannot perform the fraud detection steps of the claimed method"). For example, as described in **MPEP § 2106.05(f)**, additional elements that invoke computers or other machinery merely as a tool to perform an existing process will generally not amount to significantly more than a judicial exception. See, e.g., *Versata Development Group v. SAP America*, 793 F.3d 1306, 1335, 115 USPQ2d 1681, 1702 (Fed. Cir. 2015) (explaining that in order for a machine to add significantly more, it must "play a significant part in permitting the claimed method to be performed, rather than function solely as an obvious mechanism for permitting a solution to be achieved more quickly").

III. WHETHER ITS INVOLVEMENT IS EXTRA-SOLUTION ACTIVITY OR A FIELD-OF-USE

Whether its involvement is extra-solution activity or a field-of-use, *i.e.*, the extent to which (or how) the machine or apparatus imposes meaningful limits on the claim. Use of a machine that contributes only nominally or insignificantly to the execution of the claimed method (e.g., in a data gathering step or in a field-of-use limitation) would not integrate a judicial exception or provide significantly more. See *Bilski*, 561 U.S. at 610, 95 USPQ2d at 1009 (citing *Parker v. Flook*, 437 U.S. 584, 590, 198 USPQ 193, 197 (1978)), and *CyberSource v. Retail Decisions*, 654 F.3d 1366, 1370, 99 USPQ2d 1690 (Fed. Cir. 2011) (citations omitted) ("[N]othing in claim 3 requires an infringer to use the Internet to obtain that data. The Internet is merely described as the source of the data. We have held that mere '[data-gathering] step[s]' cannot make an otherwise nonstatutory claim statutory." 654 F.3d at 1375, 99 USPQ2d at 1694 (citation omitted)). See **MPEP § 2106.05(g) & (h)** for more information on insignificant extra-solution activity and field of use, respectively.

The MPEP further discusses conventional computer processes at 2106.05(d)II:

II. ELEMENTS THAT THE COURTS HAVE RECOGNIZED AS WELL-UNDERSTOOD, ROUTINE, CONVENTIONAL ACTIVITY IN PARTICULAR FIELDS

Because examiners should rely on what the courts have recognized, or those of ordinary skill in the art would recognize, as elements that describe well-understood, routine activities, the following section provides examples of elements that have been recognized by the courts as well-understood, routine, conventional activity in particular fields. It should be noted, however, that many of these examples failed to satisfy other considerations (e.g., because they were recited at a high level of generality and thus were mere instructions to apply an exception, or were insignificant extra-solution activity). Thus, examiners should carefully analyze additional elements in a claim with respect to all relevant Step 2B considerations, including this consideration, before making a conclusion as to whether they amount to an inventive concept.

The courts have recognized the following computer functions as well-understood, routine, and conventional functions when they are claimed in a merely generic manner (e.g., at a high level of generality) or as insignificant extra-solution activity.

- i. Receiving or transmitting data over a network, e.g., using the Internet to gather data, *Symantec*, 838 F.3d at 1321, 120 USPQ2d at 1362 (utilizing an intermediary computer to forward information); *TLI Communications LLC v. AV Auto. LLC*, 823 F.3d 607, 610, 118 USPQ2d 1744, 1745 (Fed. Cir. 2016) (using a telephone for image transmission); *OIP Techs., Inc., v. Amazon.com, Inc.*, 788 F.3d 1359, 1363, 115 USPQ2d 1090, 1093 (Fed. Cir. 2015) (sending messages over a network); *buySAFE, Inc. v. Google, Inc.*, 765 F.3d 1350, 1355, 112 USPQ2d 1093, 1096 (Fed. Cir. 2014) (computer receives and sends information over a network); but see *DDR Holdings, LLC v.*

Hotels.com, L.P., 773 F.3d 1245, 1258, 113 USPQ2d 1097, 1106 (Fed. Cir. 2014) ("Unlike the claims in *Ultramercial*, the claims at issue here specify **how** interactions with the Internet are manipulated to yield a desired result--a result that overrides the routine and conventional sequence of events ordinarily triggered by the click of a hyperlink." (emphasis added));

ii. Performing repetitive calculations, *Flook*, 437 U.S. at 594, 198 USPQ2d at 199 (recomputing or readjusting alarm limit values); *Bancorp Services v. Sun Life*, 687 F.3d 1266, 1278, 103 USPQ2d 1425, 1433 (Fed. Cir. 2012) ("The computer required by some of *Bancorp*'s claims is employed only for its most basic function, the performance of repetitive calculations, and as such does not impose meaningful limits on the scope of those claims.");

iii. Electronic recordkeeping, *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 573 U.S. 208, 225, 110 USPQ2d 1984 (2014) (creating and maintaining "shadow accounts"); *Ultramercial*, 772 F.3d at 716, 112 USPQ2d at 1755 (updating an activity log);

iv. Storing and retrieving information in memory, *Versata Dev. Group, Inc. v. SAP Am., Inc.*, 793 F.3d 1306, 1334, 115 USPQ2d 1681, 1701 (Fed. Cir. 2015); *OIP Techs.*, 788 F.3d at 1363, 115 USPQ2d at 1092-93;

v. Electronically scanning or extracting data from a physical document, *Content Extraction and Transmission, LLC v. Wells Fargo Bank*, 776 F.3d 1343, 1348, 113 USPQ2d 1354, 1358 (Fed. Cir. 2014) (optical character recognition); and

vi. A Web browser's back and forward button functionality, *Internet Patent Corp. v. Active Network, Inc.*, 790 F.3d 1343, 1348, 115 USPQ2d 1414, 1418 (Fed. Cir. 2015).

This listing is not meant to imply that all computer functions are well-understood, routine, conventional activities, or that a claim reciting a generic computer component performing a generic computer function is necessarily ineligible. See e.g. *Amdocs (Israel), Ltd. v. Openet Telecom, Inc.*, 841 F.3d 1288, 1316, 120 USPQ2d 1527, 1549 (Fed. Cir. 2016), *BASCOM Global Internet Servs. v. AT&T Mobility LLC*, 827 F.3d 1341, 1348, 119 USPQ2d 1236, 1241 (Fed. Cir. 2016). Courts have held computer-implemented processes not to be significantly more than an abstract idea (and thus ineligible) where the claim as a whole amounts to nothing more than generic computer functions merely used to implement an abstract idea, such as an idea that could be done by a human analog (i.e., by hand or by merely thinking). On the other hand, courts have held computer-implemented processes to be significantly more than an abstract idea (and thus eligible), where generic computer components are able in combination to perform functions that are not merely generic. *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1257-59, 113 USPQ2d 1097, 1105-07 (Fed. Cir. 2014).

Furthermore, the additional elements evaluated in combination do not contribute an inventive concept, i.e., do not amount to significantly more than the judicial exception(s). The data gathering steps provide the data for the judicial exceptions,

which are carried out by a general-purpose computer. Thus, there is not any non-routine step or element that has been clearly identified.

Claim Rejections - 35 USC § 103

13. 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.

14. 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.

15. 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.

16. Claims 1, 2, 4-6, 8-11, 14-16, 19-21, 23, 24, and 154, 155, and 159 are rejected under 35 U.S.C. 103 as being unpatentable over Wang et al. (Nature Genetics. 2014.

Vol. 46(6), pp. 573-582) in view of Lu et al. (PLoS ONE. 2013. Vol. 8(5): e63056, pp. 1-10), Hinrichsen et al. (Journal of Laboratory Medicine. 2016. Vol. 40(5), pp. 313-322), and Huang et al. (Scientific Reports. 2015. Vol. 5(13321), pp. 1-10).

Independent claim 1 recites a method of determining a microsatellite instability (MSI) status of a test subject, the method comprising: at a computer system having one or more processors, and memory storing one or more programs for execution by the one or more processors: (A) obtaining, for each respective DNA fragment in a plurality of DNA fragments from a liquid biopsy sample from the test subject, a corresponding nucleotide sequence that has been aligned to a reference genome for the species of the test subject, thereby obtaining a plurality of aligned nucleotide sequences; (B) using the plurality of aligned nucleotide sequences to determine, for each respective microsatellite locus in a plurality of predetermined microsatellite loci, wherein each respective microsatellite locus in the plurality of microsatellite loci has a nucleic acid sequence that includes a variable number of repeat units, a corresponding metric value for each of one or more metrics, wherein each respective metric in the one or more metrics is determined, at least in part, by a distribution of the number of repeat units in each aligned nucleotide sequence, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus; and (C) comparing, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the corresponding metric values for the one or more metrics to corresponding reference metric values for the one or more metrics representative of a stable construct at the respective microsatellite locus, the reference metric values determined across nucleotide sequences obtained from biological samples from a training cohort that

includes (i) solid tumor samples from training subjects with stable microsatellite cancer or (ii) normal tissue samples, thereby determining the MSI status of the test subject.

Dependent claim 2 further recites the method of claim 1, wherein the obtaining (A) comprises, for each respective DNA fragment in the plurality of DNA fragments: obtaining a corresponding set of raw sequence reads for the respective DNA fragment; aligning each respective raw sequence read in the set of raw sequence reads to the reference genome for the test subject, thereby obtaining a corresponding set of aligned raw sequence reads for the respective DNA fragment; and collapsing the corresponding set of aligned raw sequence reads for the respective DNA fragment into a corresponding nucleotide sequence for the respective DNA fragment that has been aligned to the human reference genome, thereby obtaining a plurality of aligned nucleotide sequences. Dependent claim 4 further recites the method of claim 1, wherein: the one or more metrics comprises a percentage score, and the corresponding metric value for the percentage score is the percentage of aligned nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus. Dependent claim 5 further recites the method of claim 4, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject. Dependent claim 6 further recites the method of claim 4, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference

number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values, wherein each respective reference value in the plurality of reference values is determined at least in part based on a distribution of the number of repeat units at the respective microsatellite locus in a respective reference sample in a plurality of reference standards. Dependent claim 8 further recites the method of claim 1, wherein: the one or more metrics comprises a lower mean score, and the corresponding metric value for the lower mean score is determined at least in part by the mean number of repeat units in aligned nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus. Dependent claim 9 further recites the method of claim 8, wherein the mean number of repeat units is normalized by the reference number of repeat units representative of a stable construct at the respective microsatellite locus. Dependent claim 10 further recites the method of claim 8, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject. Dependent claim 11 further recites the method of claim 8, wherein, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values, wherein each respective reference value in the plurality of reference values is determined at least in part based on a distribution of the number of repeat units at the respective

microsatellite locus in a respective reference sample in a plurality of reference samples.

Dependent claim 14 further recites the method of claim 13, wherein the statistical measure is a mean of the distribution of probabilities that each aligned nucleotide sequence in the subset of aligned nucleotide sequences encompassing the respective microsatellite locus is a member of the distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite locus. Dependent claim 15 further recites the method of claim 13, wherein the distribution of probabilities is a plurality of p-values, wherein each respective p-value in the plurality of p-values is a probability value that a respective aligned nucleotide sequence in the subset of aligned nucleotide sequences is a member of the distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite locus. Dependent claim 16 further recites the method of claim 1, wherein the one or more corresponding metric values comprises a corresponding standard deviation of the number of repeat units in the aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus. Dependent claim 19 further recites the method of claim 1, wherein the comparing C) comprises inputting, for each respective microsatellite locus in the plurality of microsatellite loci, the corresponding metric value for each of the one or more metrics to a classifier trained to distinguish between stable and unstable microsatellite loci, wherein the classifier was trained using the reference metric values determined across the nucleotide sequences obtained from the biological samples from the training cohort that included (i) solid tumor samples from training subjects with stable microsatellite cancer or (ii) normal tissue samples. Dependent claim 20 further recites the method of claim 19, wherein the biological

samples from the training cohort included both (i) solid tumor samples from training subjects with stable microsatellite cancer and (ii) normal tissue samples. Dependent claim 21 further recites the method of claim 19, wherein the biological samples from the training cohort further included (iii) solid tumor samples from training subjects with unstable microsatellite cancer. Dependent claim 23 further recites the method of claim 19, wherein the classifier assigns a stability status selected from unstable and stable to each respective microsatellite locus in the plurality of predetermined microsatellite loci, and the subject is classified as having a high level of microsatellite instability when at least a threshold number of microsatellite loci are assigned a status of unstable. Dependent claim 24 further recites the method of claim 23, wherein the threshold number of microsatellite loci is at least 30% of the total number of microsatellite loci in the plurality of microsatellite loci. Dependent claim 154 further recites the method of claim 1, wherein the plurality of cell-free DNA fragments from the liquid biopsy sample are enriched, relative to all cell-free DNA fragments in the liquid biopsy sample, for a set of cell-free DNA fragments that comprises the plurality of predetermined microsatellite loci. Dependent claim 155 further recites the method of claim 1, wherein the plurality of aligned sequence reads represents, on average, greater than 1000X sequence depth for each microsatellite locus in the plurality of predetermined microsatellite loci. Dependent claim 159 further recites the method of claim 1, wherein the liquid biopsy sample is a blood or blood plasma sample.

Wang et al. shows a method of determining a microsatellite instability (MSI) status of a test subject (page 580, column 2, para. 3), the method comprising at a computer system having one or more processors, and memory storing one or more

programs for execution by the one or more processors (Supplementary Note: page 6, para. 1): (A) obtaining, for each respective DNA fragment in a plurality of DNA fragments a corresponding nucleotide sequence that has been aligned to a reference genome for the species of the test subject, thereby obtaining a plurality of aligned nucleotide sequences (page 573, column 2, para. 1); (B) using the plurality of aligned nucleotide sequences to determine, for each respective microsatellite locus in a plurality of predetermined microsatellite loci, wherein each respective microsatellite locus in the plurality of microsatellite loci has a nucleic acid sequence that includes a variable number of repeat units (page 573, column 2, para. 1), a corresponding metric value for each of one or more metrics, wherein each respective metric in the one or more metrics is determined, at least in part, by a distribution of the number of repeat units in each aligned nucleotide sequence, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus (page 573, column 2, para. 1); and (C) comparing, for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the corresponding metric values for the one or more metrics to corresponding reference metric values for the one or more metrics representative of a stable construct at the respective microsatellite locus (page 573, column 2, para. 1); obtaining a corresponding set of raw sequence reads for the respective DNA fragment (page 573, column 2, para. 1); aligning each respective raw sequence read in the set of raw sequence reads to the reference genome for the test subject, thereby obtaining a corresponding set of aligned raw sequence reads for the respective DNA fragment (page 573, column 2, para. 1); and collapsing the corresponding set of aligned raw sequence reads for the respective DNA fragment into a corresponding nucleotide

sequence for the respective DNA fragment that has been aligned to the human reference genome, thereby obtaining a plurality of aligned nucleotide sequences (page 573, column 2, para. 1); the one or more metrics comprises a percentage score, and the corresponding metric value for the percentage score is the percentage of aligned nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus (Supplementary Figures 17-19); for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject (page 573, column 2, para. 1); for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values, wherein each respective reference value in the plurality of reference values is determined at least in part based on a distribution of the number of repeat units at the respective microsatellite locus in a respective reference sample in a plurality of reference standards (page 574, column 2, para. 2; and Supplementary Figure 7); the one or more metrics comprises a lower mean score, and the corresponding metric value for the lower mean score is determined at least in part by the mean number of repeat units in aligned nucleotide sequences, in the plurality of aligned nucleotides, encompassing the respective microsatellite locus that have a number of repeat units that is less than a reference number of repeat units representative of a stable construct at the respective microsatellite locus (page 573,

column 2, para. 1); the mean number of repeat units is normalized by the reference number of repeat units representative of a stable construct at the respective microsatellite locus (page 584, column 2, para. 4); for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a number of repeat units present in a reference genome for the species of the subject (page 573, column 2, para. 1); for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is a measure of central tendency of a plurality of reference values (page 573, column 2, para. 1); the subset of aligned nucleotide sequences consists of the aligned nucleotide sequences encompassing the respective microsatellite locus that have a number of repeat units that falls within a threshold percentile of the smallest number of repeat units (page 1815, column 2, para. 2); the statistical measure is a mean of the distribution of probabilities that each aligned nucleotide sequence in the subset of aligned nucleotide sequences encompassing the respective microsatellite locus is a member of the distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite locus (page 573, column 2, para. 2; and Supplementary Figure 3); the distribution of probabilities is a plurality of p-values, wherein each respective p-value in the plurality of p-values is a probability value that a respective aligned nucleotide sequence in the subset of aligned nucleotide sequences is a member of the distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite locus (page 573, column 2, para. 2; and Supplementary Figure 3);

Wang et al. does not show obtaining DNA fragments from a liquid biopsy sample from the test subject; the reference metric values determined across nucleotide sequences obtained from biological samples from a training cohort that includes (i) solid tumor samples from training subjects with stable microsatellite cancer or (ii) normal tissue samples; the one or more corresponding metric values comprises a corresponding standard deviation of the number of repeat units in the aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus; inputting, for each respective microsatellite locus in the plurality of microsatellite loci, the corresponding metric value for each of the one or more metrics to a classifier trained to distinguish between stable and unstable microsatellite loci; the classifier was trained using the reference metric values determined across the nucleotide sequences obtained from the biological samples from the training cohort that included (i) solid tumor samples from training subjects with stable microsatellite cancer or (ii) normal tissue samples; the biological samples from the training cohort further included (iii) solid tumor samples from training subjects with unstable microsatellite cancer; the classifier assigns a stability status selected from unstable and stable to each respective microsatellite locus in the plurality of predetermined microsatellite loci and the subject is classified as having a high level of microsatellite instability when at least a threshold number of microsatellite loci are assigned a status of unstable; the threshold number of microsatellite loci is at least 30% of the total number of microsatellite loci in the plurality of microsatellite loci; the plurality of aligned sequence reads represents, on average, greater than 1000X sequence depth

for each microsatellite locus in the plurality of predetermined microsatellite loci; or the liquid biopsy sample is a blood or blood plasma sample.

Lu et al. shows reference metric values determined across nucleotide sequences obtained from paired cancer tumor and normal samples from patients diagnosed with MSI tumors and patients diagnosed with MSS tumors (page 2, column 1, para. 2).

Hinrichsen et al. shows obtaining DNA fragments from a blood-based liquid biopsy sample from the test subject (Title and Abstract); and 1000X vertical coverage of the target region (page 316, column 1, para. 1).

Huang et al. shows using software for assessing microsatellite instability from catalogs of somatic mutations and calculating standard deviation for subsets of repeating units (page 6, para. 3); inputting classification categories into a classifier trained to distinguish between stable and unstable microsatellite loci (page 2, para. 9) where the classifier is trained to assign a stability status selected from unstable and stable to each respective microsatellite locus (page 2, para. 9) and the subject is classified as having a high level of microsatellite instability when at least a threshold number of microsatellite loci are assigned a status of unstable (page 4, para. 5); and the threshold number of microsatellite loci is at least 30% of the total number of microsatellite loci (page 4, para. 5).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to modify the method shown by Wang et al. to incorporate the methods of Lu et al. in view of Hinrichsen et al., and Huang et al. One would have been motivated to incorporate the method of Lu et al. because the reference exemplifies the characterization of microsatellite instability in

cancer cells using a large-scale analysis of cancer lines and normal individuals (Abstract). This would have accomplished the predictable result of broadening the range of accurate detection of MSI in cancer cells and distinguishing between MSI and MSS cancer cell lines (Abstract).

One would have been motivated to incorporate the method of Hinrichsen et al. because the reference exemplifies the use blood-based liquid biopsy methods to detect and characterize circulating cell-free tumor DNA in cancer patients (Abstract). This would have accomplished the predictable result of increasing the specificity and sensitivity of biomarker detection that can be correlated with tumor disease dynamics (Abstract).

One would have been motivated to incorporate the method of Huang et al. because the reference exemplifies the use of next-generation sequencing (NGS) technologies and software programmed to generate trained MSI classification algorithms capable of reliably determining MSI status from lists of somatic mutation calls (page 2, para. 3). This would have accomplished the predictable result of providing the capability to determine the MSI status using NGS sequencing data and software to train a classifier algorithm for assessing MSI status (page 8, para. 2).

17. Claim 3 is rejected under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., and Huang et al. as applied to claims 1, 2, 4-6, 8-11, 14-16, 19-21, 23, 24, and 154, 155, and 159 above, and further in view of Cheng et al. (Clinical Biochemistry. 2017. Vol. 50, pp. 496-501).

Dependent claim 3 further recites the method of claim 1, wherein the plurality of aligned nucleotide sequences comprises at least 250,000 aligned nucleotide sequences.

The combined methods of Wang et al., Lu et al., Hinrichsen et al., and Huang et al. are discussed above and incorporated fully here.

Wang et al. in view of Lu et al., Hinrichsen et al., and Huang et al. as applied to claims 1, 2, 4-6, 8-11, 14-16, 19-21, 23, 24, and 154, 155, and 159 above, do not show the plurality of aligned nucleotide sequences comprises at least 250,000 aligned nucleotide sequences.

Cheng et al. shows the analysis of cell-free genome sequence reads using 47.4 million to 125.8 million mappable non-duplicated reads for each sample (Supp. Page 5, Supp. Table 1).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to modify the method taught by Wang et al. in view of Lu et al., Hinrichsen et al., and Huang et al. as applied to claims 1, 2, 4-6, 8-11, 14-16, 19-21, 23, 24, and 154, 155, and 159 above, to incorporate the methods of Cheng et al. One would have been motivated to incorporate the method taught by Cheng et al. because the reference exemplifies the use of massively parallel DNA sequencing technology to generate a median of 80 million unique, non-duplicated reads mapped to the human reference genome (Supp. Page 3), which implies that the claim limitation of at least 250,000 aligned sequences would have been obvious. This would have accomplished the predictable result of increasing the

accuracy and sensitivity for identifying a tissue of origin for the cfDNA (page 500, column 2, para. 3).

18. Claims 7 and 12 are rejected under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., and Cheng et al. as applied to claims 1-6, 8-11, 14-16, 19-21, 23, 24, and 154, 155, and 159 above, and further in view of Zahir et al. (Journal of Ayub Medical College Abbottabad. 2014. Vol. 26(1), pp. 95-97).

Dependent claims 7 and 12 further recite the methods for claim 4 and 8, wherein for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus.

The combined methods of Wang et al., Lu et al., Hinrichsen et al., Huang et al., and Cheng et al. are discussed above and incorporated fully here.

Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., and Cheng et al. as applied to claims 1-6, 8-11, 14-16, 19-21, 23, 24, and 154, 155, and 159 above, do not show that for each respective microsatellite locus in the plurality of predetermined microsatellite loci, the reference number of repeat units representative of a stable construct is the mode of the number of repeat units at the respective microsatellite locus in aligned nucleotide sequences, in the plurality of aligned nucleotide sequences, encompassing the respective microsatellite locus.

Zahir et al. shows that measures of central tendency (mean, median, and mode; page 96, column 1, para. 3) are basic statistical concepts (page 95, column 2, para. 2) in biology and health sciences (Title).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to modify the methods shown by Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., and Cheng et al. as applied to claims 1-6, 8-11, 14-16, 19-21, 23, 24, and 154, 155, and 159 above, to incorporate the methods of Zahir et al. One would have been motivated to incorporate the methods of Zahir et al. because the reference exemplifies the application of statistical concepts and methods in biology, public health, and medicine (Abstract). This would have accomplished the predictable result of providing one possible measure of central tendency for calculating a statistic for the estimation of variability (page 96, column 1, para. 3).

19. Claim 13 is rejected under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., and Zahir et al. as applied to claims 1-12, 14-16, 19-21, 23, 24, and 154, 155, and 159 above, and further in view of Saunders et al. (Bioinformatics. 2012. Vol. 28(14), pp. 1811-1817).

Dependent claim 13 further recites the method of claim 1, wherein the one or more metrics comprises a likelihood score, and the corresponding metric value for the likelihood score is a statistical measure of a distribution of probabilities that each respective aligned nucleotide sequence in a subset of the set of aligned nucleotide sequences encompassing the respective microsatellite locus is a member of a distribution of aligned nucleotide sequences encompassing a stable construct at the

respective microsatellite locus, wherein the subset of aligned nucleotide sequences consists of the aligned nucleotide sequences encompassing the respective microsatellite locus that have a number of repeat units that falls within a threshold percentile of the smallest number of repeat units.

The combined methods of Wang et al., Lu et al., Hinrichsen et al., Huang et al., Cheng et al., and Zahir et al. are discussed above and incorporated fully here.

Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., and Zahir et al. as applied to claims 1-12, 14-16, 19-21, 23, 24, and 154, 155, and 159 above, do not show that the one or more metrics comprise a likelihood score as a statistical measure of a distribution of probabilities. Wang et al. shows that each respective aligned nucleotide sequence in a subset of the set of aligned nucleotide sequences encompassing the respective microsatellite locus is a member of a distribution of aligned nucleotide sequences encompassing a stable construct at the respective microsatellite locus, wherein the subset of aligned nucleotide sequences consists of the aligned nucleotide sequences encompassing the respective microsatellite locus that have a number of repeat units that falls within a threshold percentile of the smallest number of repeat units (page 573, column 2, para. 1).

Saunders et al. shows the one or more metrics comprise a likelihood score as a statistical measure of a distribution of probabilities (page 1813, Section 2.3).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to modify the methods shown by Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., and Zahir et al. as applied to claims 1-12, 14-16, 19-21, 23, 24, and 154, 155, and 159

above, to incorporate the methods of Saunders et al. One would have been motivated to incorporate the methods of Saunders et al. because the reference exemplifies the use of a novel Bayesian approach for somatic SNV and small indel detection from sequencing data of matched tumor-normal samples (Abstract). This would have accomplished the predictable result of providing sensitive and accurate small-variant calling at any practical level of tumor impurity (Title and Abstract).

20. Claim 22 is rejected under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et al., and Saunders et al. as applied to claims 1-16, 19-21, 23, 24, and 154, 155, and 159 above, and further in view of Hong et al. (Clinical & Experimental Metastasis. 2010. Vol. 27, pp. 83-90).

Dependent claim 22 further recites the method of claim 19, wherein the classifier comprises a k-nearest neighbors algorithm.

The combined methods of Wang et al., Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et al., and Saunders et al. are discussed above and incorporated fully here.

Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et al., and Saunders et al. as applied to claims 1-16, 19-21, 23, 24, and 154, 155, and 159 above, do not show that the classifier comprises a k-nearest neighbors algorithm.

Hong et al. shows the use of four different families of classification models, one of which is a classifier comprising a k-nearest neighbors algorithm (page 85, column 1, para. 1).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to modify the methods shown by Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et al., and Saunders et al. as applied to claims 1-16, 19-21, 23, 24, and 154, 155, and 159 above, to incorporate the methods of Hong et al. One would have been motivated to incorporate the methods of Hong et al. because the reference exemplifies the use the K-nearest neighbor classification model (page 85, column 1, para. 1). This would have accomplished the predictable result of using a supervised learning classifier algorithm for more efficient use of a limited sample size than the alternative option of simply splitting the samples into separate training and test sets (page 84, column 2, para. 6).

21. Claim 25 is rejected under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et al., Saunders et al., and Hong et al. as applied to claims 1-16, 19-24, and 154, 155, and 159 above, and further in view of Salipante et al. (Clinical Chemistry. 2014. Vol. 60(9), pp. 1192-1199).

Dependent claim 25 further recites the method of claim 23, wherein the threshold number of microsatellite loci is at least 50% of the total number of microsatellite loci in the plurality of microsatellite loci.

The combined methods of Wang et al., Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et al., Saunders et al., and Hong et al. are discussed above and incorporated fully here.

Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et al., Saunders et al., and Hong et al. as applied to claims 1-16, 19-24, and 154, 155,

and 159 above, do not show that the threshold number of microsatellite loci is at least 50% of the total number of microsatellite loci in the plurality of microsatellite loci.

Salipante et al. shows threshold values for stable and unstable microsatellite loci where MSI positive status is 50% or greater (page 1195, Figure 2; page 1196, column 1, para. 2).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to modify the methods shown by Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et al., Saunders et al., and Hong et al. as applied to claims 1-16, 19-24, and 154, 155, and 159 above, to incorporate the methods of Salipante et al. One would have been motivated to incorporate the methods of Salipante et al. because the reference exemplifies the use of next-generation sequencing for microsatellite instability detection (Title and Abstract). This would have accomplished the predictable result of enabling a highly accurate means for detection of MSI (page 1192, column 1, para. 4).

22. Claims 160-163 are rejected under 35 U.S.C. 103 as being unpatentable over Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et al., Saunders et al., Hong et al., and Salipante et al. as applied to claims 1-16, 19-25, and 154, 155, and 159 above, and further in view of Cotes-Ciriano et al. (Nature Communications. 2017. Vol. 8(15180), 1-12).

Dependent claim 160 further recites the method of claim 1, wherein the plurality of predetermined microsatellite loci comprises at least 25 microsatellite loci. Dependent claim 161 further recites the method of claim 1, wherein the plurality of predetermined microsatellite loci comprises at least 10 of the microsatellite loci listed in Table 2.

Dependent claim 162 further recites the method of claim 1, wherein the plurality of predetermined microsatellite loci comprises at least all of the microsatellite loci listed in Table 2. Dependent claim 163 further recites the method of claim 1, wherein the subject is a human.

The combined methods of Wang et al., Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et al., Saunders et al., Hong et al., and Salipante et al. are discussed above and incorporated fully here.

Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et al., Saunders et al., Hong et al., and Salipante et al. as applied to claims 1-16, 19-25, and 154, 155, and 159 above, do not show the plurality of predetermined microsatellite loci comprises at least 25 microsatellite loci; the plurality of predetermined microsatellite loci comprises at least 10 of the microsatellite loci listed in Table 2; the plurality of predetermined microsatellite loci comprises at least all of the microsatellite loci listed in Table 2; or the subject is a human.

Cotes-Ciriano et al. shows predetermined microsatellite loci comprising at least 25 microsatellite loci (page 5, Figure 2); predetermined microsatellite loci comprising at least 10 of the microsatellite loci listed in Table 2 (page 7, Figure 4; and Supp. Data Table 13); predetermined microsatellite loci comprising at least all of the microsatellite loci listed in Table 2 (page 7, Figure 4; and Supp. Data Table 13); and the subject is a human (page 7, Figure 4; and Supp. Data Table 13).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to modify the method shown by Wang et al. in view of Lu et al., Hinrichsen et al., Huang et al., Cheng et al., Zahir et

al., Saunders et al., Hong et al., and Salipante et al. as applied to claims 1-16, 19-25, and 154, 155, and 159 above, to incorporate the methods of Cotes-Ciriano et al. One would have been motivated to incorporate the methods of Cotes-Ciriano et al. because the reference exemplifies the use of large amounts of sequencing data to examine the molecular fingerprints of MSI in detail (Abstract). This would have accomplished the predictable result of producing a highly accurate exome-based predictive model for the MSI phenotype (Abstract).

Conclusion

23. This Office action is a Non-Final action. A shortened statutory period for reply to this action is set to expire THREE MONTHS from the mailing date of this action.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN W. BAILEY whose telephone number is (571) 272-8170. The examiner can normally be reached Mon - Thurs 0730 - 1800.

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 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.

/S.W.B./
Examiner, Art Unit 1671
/JOHN S BRUSCA/
Primary Examiner, Art Unit 1672

Remarks/Arguments

Status of the Claims

Claims 1-163 were previously pending as originally filed in the application. With this Amendment, claims 17, 18, 26-153, and 156-158 are canceled without prejudice. With this amendment, claims 3, 4, 8, 10-13, 15, 16, 19, 21-23, 154, 155, and 158-163 are amended to remove multiple dependencies.

Upon entry of the present amendment, claims 1-16, 19-25, 154-156, and 159-163 will be pending for examination on the merits. Accordingly, Applicant respectfully requests entry of the claim amendments.

Notice to File Missing Parts

The Notice to File Missing Parts miscalculates the fees due for this application. The Application as originally filed via EFS Web contained a total of 295 pages. Per the MPEP, the paper size equivalent of an application filed electronically via EFS web, for purposes of calculating the application size fee, is 75 percent of the total number of pages:

The paper size equivalent of the specification (including claims) and drawings of an application submitted via the Office electronic filing system will be considered to be seventy five percent of the number of sheets of paper present in the specification (including claims) and drawings of the application when entered into the Office file wrapper after being rendered by the Office electronic filing system for purposes of computing the application size fee required by 37 CFR 1.16(s).

MPEP § 607(II), emphasis omitted. Accordingly, 75 percent of 295 pages is 220 pages. Under 37 C.F.R. § 1.16(s), Applicants are charged for each additional 50 sheets that exceed 100 sheets. As per the USPTO fee schedule on the date the instant application was filed, this fee was \$400. Thus, because Applicants' specification included 120 paper size equivalent pages of application exceeding 100 pages, the proper fee was $3 \times \$400 = \$1200$. Applicants paid this fee at the time the application was filed, which is presumably the (\$1200) previous unapplied payment amount referenced in the Notice to File Missing Parts.

The Notice, however, indicates that Applicant should pay \$2000, for 67 electronically equivalent pages in excess of 250 application size fee. This corresponds to an application page size of 317 pages, which is incorrect. Moreover, this fee calculation does not account for the 25 percent reduction in page number, as specified in MPEP § 607(II), for electronically-filed applications.

Applicants assert that the proper excess page fee, of \$1200, was timely paid at the time the application was filed. Accordingly, Applicants respectfully request that the \$2000 fee set forth in the Notice of Missing Parts be reconsidered and withdrawn, and that the Office applies the \$1200 unapplied payment amount for the proper excess page fee of \$1200. Further, because the excess page fee was timely filed, the \$160 surcharge for late payment of the basic filing fee does not apply. Accordingly, Applicants respectfully request that the \$160 surcharge be reconsidered and withdrawn.

With this Preliminary Amendment, Applicants have reduced the total number of claims to 30 total claims, with 1 independent claim. Accordingly, Applicants believe that the updated excess claims fee should be \$1000, for 10 total claims over 20.

If Applicants' understanding above is incorrect, please deduct any deficiency in payment due from Deposit Account No. 500310 (Order No.: 123138-5013-US), in order to ensure a timely response to the Notice to File Missing Parts. However, Applicants do not acquiesce on the merits of the analysis above, and expressly reserve the right to petition any additional deductions made in this manner.

CONCLUSION

Except for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to further charge any necessary fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17, which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310 (Order No.: 123138-5013-US).

Prompt and favorable consideration of this Amendment and Response is respectfully requested.

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS LLP

Dated: November 20, 2020

Customer No.: 43850

Morgan, Lewis & Bockius LLP

One Market, Spear Street Tower

San Francisco, CA 94105

Telephone: (415) 442-1000

Facsimile: (415) 442-1001

By: /Andrew J. Antczak/

Andrew J. Antczak, Ph.D., Reg. No. 70,871

for

Brett A. Lovejoy, Ph.D., Reg. No. 42,813