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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/738,354	05/06/2022	Joshua BABIARZ	N.012.US.44	8319
110711	7590	07/07/2022	EXAMINER	
Natera, Inc. 201 Industrial Road Suite 410 San Carlos, CA 94070			BRUSCA, JOHN S	
			ART UNIT	PAPER NUMBER
			1631	
			NOTIFICATION DATE	DELIVERY MODE
			07/07/2022	ELECTRONIC

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

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

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

IP@natera.com

Office Action Summary

Application No.
17/738,354

Applicant(s)
BABIARZ et al.

Examiner
JOHN S BRUSCA

Art Unit
1631

AIA (FITF) Status	Yes
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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____. The restriction requirement and election have been incorporated into this action.
4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 1-15 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) 1-15 is/are rejected.
- 8) ☒ Claim(s) 1 is/are objected to.
- 9) ☐ Claim(s) _____ are subject to restriction and/or election requirements.

* 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 06 May 2022 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

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

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

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

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date _____
- 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 4) ☐ Other: _____

DETAILED ACTION

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 1-15 are pending.

Claim 1 is objected to.

Claims 1-15 are rejected.

Priority

3. Claims 1-15 are given the benefit of the claim to priority to Provisional Application No. 61/982,245 filed 21 April 2014.

Drawings

4. The drawings were received on 06 May 2022. These drawings are accepted.

Claim Objections

5. Claim 1 is objected to because of the following informalities: In line 6 the claim recites “the cell-free DNA” and should recite “cell-free DNA” because the first recitation of a term should not use a definite article. Appropriate correction is required.

Claim Interpretation

6. The terms “clonal SNV mutations” and “subclonal SNV mutations” in claims 4-6 are interpreted as discussed in the specification at paragraphs 111 and 748. Paragraph 48 states that plasma has a cumulative representation of SNV mutations. Plasma samples are therefore interpreted as comprising both clonal and subclonal SNV mutations.

Claim Rejections - 35 USC § 112

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

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

Claims 1-15 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

Claim 1 is indefinite for recitation in lines 6-7 of the phrase “from the cell-free DNA isolated from a plasma sample of the subject or DNA derived therefrom” because it is not clear how cell-free DNA is different than DNA derived therefrom. For the purpose of examination claim 1 has been interpreted to be limited to cell-free DNA isolated from a plasma sample.

Claims 2-15 are rejected for the same reason as claim 1 because they depend from claim 1 and fail to remedy the indefiniteness of claim 1.

Claims 1, 2, and 12 are indefinite for recitation of the phrase “high throughput sequencing” because the metes and bounds are not clear and the specification does not provide a limiting definition of the phrase. For the purpose of examination the claims have been interpreted as being limited to sequencing.

Claims 3-7 are rejected for the same reason as claim 2 because they depend from claim 2 and fail to remedy the indefiniteness of claim 2.

Claim 11 is indefinite for recitation of the phrase “patient-specific PCR primers” because the phrase is not defined in the specification and it is not clear if the primers are not capable of

hybridizing to DNA of any other individual or merely capable of hybridizing to DNA of a particular patient. For the purpose of examination claim 11 has been interpreted as being limited to primers that are capable of hybridizing to DNA of a patient.

Claim Rejections - 35 USC § 103

8. 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.

9. 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.

10. 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.

11. Claims 1, 3, 7, 9, and 11-14 are rejected under 35 U.S.C. 103 as being unpatentable over Forshew et al. (Science Translational Medicine vol. 4, article 136ra68 plus supplementary material (2012)) in view of Benesova et al. (Analytical Biochemistry vol. 433, pages 227-234 (2013)).

Independent claim 1 recites a process of identifying single nucleotide variant (SNV) mutations in a tumor sample of a subject by sequencing, performing at least a 20 multiplex amplification to generate amplicons using cell-free DNA from a plasma sample of the subject, and sequencing the amplicons to detect SNV mutations. Dependent claim 3 further recites a process of analyzing cell-free DNA that comprises circulating tumor DNA. Dependent claim 7 further recites a process of analyzing mutations in a tumor tissue sample of a subject. Dependent claim 9 further recites a process of a 20-50 multiplex amplification. Dependent claim 11 further recites a process of use of primers that hybridize to DNA of the subject. Dependent claim 12 further recites a process of using barcoding in the amplification. Dependent claim 13 further recites a process of detecting recurrence of cancer. An embodiment of dependent claim 14 further recites a process of analysis of colorectal cancer.

Forsheew et al. shows in the abstract and throughout analysis of cell-free DNA of individuals with tumors for mutation analysis by multiplex amplification using a pool of primer pairs followed by sequencing of amplicons. Forsheew et al. outlines the process in Figure 1, which shows a preamplification step that uses a single multiplex amplification of regions of interest followed by a second amplification followed by barcoded amplification and sequencing. Forsheew et al. shows on page 3 use of 48 primer pairs to amplify regions of interest. Forsheew et al. shows on pages 3-9 identification of mutations in the amplified regions of interest. Forsheew et al. shows in Figure 4 data of time series of observations to identify recurrences of cancer, for example see Figure 4-B.

Forsheew et al. does not show an initial step of identifying SNV mutations in a tumor sample or tumor tissue of a subject by sequencing. Forsheew et al. does not show analysis of colon cancer.

Benesova et al. shows analysis of cell-free DNA to analyze tumor DNA in a patient on pages 228-232. Benesova et al. shows in the first column of page 230 a process of initially determining a tumor-specific mutation in a primary tumor, followed by detection of the same mutation in cell-free DNA. Benesova et al. notes in the first column of page 228 that Figure 1 shows colon tumor analysis through cell-free DNA, as illustrated in Figure 1. Analysis of colorectal cancer is further discussed on pages 230-232

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to modify the process of Forshew et al. by first identifying a mutation in tumor tissue because Benesova et al. provides guidance to first identify a mutation in tumor tissue followed by analysis of the mutation using cell-free DNA. It would have been further obvious to analyze colorectal cancer using cell-free DNA because Benesova et al. provides guidance to do so.

12. Claims 4-6 and 8 are rejected under 35 U.S.C. 103 as being unpatentable over Forshew et al. in view of Benesova et al. as applied to claims 1, 3, 7, 9, and 11-14 above, and further in view of Marusyk et al. (Biochimica et Biophysica Acta vol. 1805 pages 105-117 (2010)).

Dependent claim 4 further recites a process of analyzing clonal SNV mutations. Dependent claim 5 further recites a process of analyzing subclonal SNV mutations. Dependent claim 6 further recites a process of analyzing both clonal and subclonal SNV mutations. Dependent claim 8 further recites a process of determining clonal heterogeneity of a sample.

Forshew et al. in view of Benesova et al. as applied to claims 1, 3, 7, 9, and 11-14 above does not explicitly discuss analysis of clonal and subclonal mutations.

Marusyk et al. reviews tumor clonal heterogeneity. Marusyk et al. shows intra tumor clonal diversity at section 3.1. Analysis of clonal heterogeneity and subclonal changes by sequencing of specific genes is discussed in section 4.1.

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to modify the process of Forshew et al. in view of Benesova et al. as applied to claims 1, 3, 7, 9, and 11-14 above by analysis of clonal and subclonal mutations because as discussed in the interpretation above plasma samples (as analyzed in Forshew et al. and Benesova et al.) comprise clonal and subclonal mutations and Marusyk et al. provides explicit guidance to analyze tumor heterogeneity comprising clonal and subclonal variations.

13. Claim 10 is rejected under 35 U.S.C. 103 as being unpatentable over Forshew et al. in view of Benesova et al. as applied to claims 1, 3, 7, 9, and 11-14 above, and further in view of Anderson et al. (WO 2004/051218).

Dependent claim 10 further recites a process of a 50-100 multiplex amplification.

Forshew et al. in view of Benesova et al. as applied to claims 1, 3, 7, 9, and 11-14 above does not show a process of a 50-100 multiplex amplification.

Anderson et al. shows multiplex amplifications in the abstract and throughout. Anderson et al. shows in the example at pages 36-39 examples of a multiplex amplification of 95 samples using low primer concentrations.

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to modify the process of Forshew et al. in view of Benesova et al. as applied to claims 1, 3, 7, 9, and 11-14 above by use of the 95 multiplex process of Anderson et al. to allow for analysis of a greater number of loci in a single amplification saving time and expense.

14. Claims 14 and 15 are rejected under 35 U.S.C. 103 as being unpatentable over Forshew et al. in view of Benesova et al. as applied to claims 1, 3, 7, 9, and 11-14 above, and further in view of Diehl et al. (Proceedings of the National Academy of Sciences USA vol. 102, pages 16368-16373 (2005)).

An embodiment of dependent claim 14 further recites a process of analysis of colorectal cancer. Dependent claim 15 further recites a process of analyzing a mutation that is less than or equal to 0.015% of the cell-free DNA.

Forshew et al. in view of Benesova et al. as applied to claims 1, 3, 7, 9, and 11-14 above show analysis of colorectal cancer in Benesova et al., but do not show analyzing a mutation that is less than or equal to 0.015% of the cell-free DNA.

Diehl et al. analyzes cell-free DNA for colorectal cancer DNA in the abstract and throughout. Diehl et al. shows sensitivity of the assay (detailed in figure 2) of amplified colorectal cancer DNA in Table 1 of as low as 0.001%.

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to modify the process of Forshew et al. in view of Benesova et al. as applied to claims 1, 3, 7, 9, and 11-14 above by use of the assay of Diehl et al. because Diehl et al. shows an assay with high sensitivity.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not

patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

16. Claim 1 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 11 and 18 of U.S. Patent No. 11,319,596. Although the claims at issue are not

identical, they are not patentably distinct from each other because claims 11 and 18 of U.S.

Patent No. 11,319,596 is anticipatory of instant claim 1 in view of claiming a species of the instant claim 1 regarding multiplex amplifications of 10-50 target loci relative to the instant at least 20 target loci. Regarding the instant claim 1 limitation of sequencing a tumor sample by whole exome sequencing or whole genome sequencing, the type of sequencing is obvious over issued claim 18 limited to whole exome sequencing of a tumor biopsy sample.

17. Claim 1 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 16 of copending Application No. 16/288,416 in view of Ku et al. (Expert Reviews in Molecular Diagnostics vol. 12, pages 241-251 (2012)). Claim 16 of Application No. 16/288,416 claims a species of the instant claim 1 regarding multiplex amplifications of 10-50 target loci relative to the instant at least 20 target loci. Regarding the limitation in instant claim 1 of sequencing by whole exome sequencing, such sequencing is obvious over Ku et al. which shows advantages of whole exome sequencing for targeting expressed genomic regions at page 243.

This is a provisional nonstatutory double patenting rejection.

18. Claim 1 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 13 and 10 of U.S. Patent No. 11,371,100. Although the claims at issue are not identical, they are not patentably distinct from each other because claims 13 and 10 of U.S. Patent No. 11,371,100 is anticipatory of instant claim 1 in view of claiming a species of the instant claim 1 regarding multiplex amplifications of 10-50 target loci relative to the instant at least 20 target loci. Regarding the instant claim 1 limitation of sequencing a tumor sample by whole exome sequencing or whole genome sequencing, the type of sequencing is obvious over issued claim 10 limited to whole exome sequencing of a tumor biopsy sample.

19. Claim 1 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 18 and 19 of copending Application No. 16/359,917 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because claim 18 of Application No. 16/359,917 shows a method of performing whole exome sequencing of a tumor sample of a subject and performing multiplex amplification of a cell-free sample of the subject followed by sequencing of the amplicons. Copending claim 19 shows a species of the limitation of instant claim 1 of at least 20 target loci targeted in a multiplex amplification by claiming at least 50 target loci targeted in a multiplex amplification. The combination of claim 18 and 19 makes instant claim 1 obvious.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

20. Claim 1 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 14 of copending Application No. 17/018,966 in view of Ku et al. (Expert Reviews in Molecular Diagnostics vol. 12, pages 241-251 (2012)). Claim 14 of Application No. 17/018,966 claims a species of the instant claim 1 regarding multiplex amplifications of at least 25 target loci relative to the instant at least 20 target loci. Regarding the limitation in instant claim 1 of sequencing by whole exome sequencing, such sequencing is obvious over Ku et al. which shows advantages of whole exome sequencing for targeting expressed genomic regions at page 243.

This is a provisional nonstatutory double patenting rejection.

21. A rejection based on double patenting of the “same invention” type finds its support in the language of 35 U.S.C. 101 which states that “whoever invents or discovers any new and useful process... may obtain a patent therefor...” (Emphasis added). Thus, the term “same

invention,” in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the claims that are directed to the same invention so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

22. Claims 1-15 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-15 of copending Application No. 17/692,469 (reference application). This is a provisional statutory double patenting rejection since the claims directed to the same invention have not in fact been patented.

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 JOHN S. BRUSCA whose telephone number is (571)272-0714. The examiner's fax number is (571) 273-0714. The examiner can normally be reached M-F 8:30 AM-5:00PM.

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.

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/JOHN S BRUSCA/
Primary Examiner, Art Unit 1631