UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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NEOGENOMICS LABORATORIES, INC.,
Petitioner,

v.

NATERA, INC.,
Patent Owner.

IPR
U.S. Patent No. 11,530,454

PETITION FOR *INTER PARTES* REVIEW
OF
U.S. PATENT NO. 11,530,454

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3. Claim 3: The method of claim 1, wherein the SNV mutations comprise one or more clonal SNV mutations. 35

4. Claim 4: The method of claim 1, wherein the SNV mutations comprise one or more subclonal SNV mutations. 36

5. Claim 5: The method of claim 1 wherein the SNV mutations comprise one or more clonal SNV mutations and one or more subclonal SNV mutations. 37

6. Claim 6: The method of claim 1, wherein the tumor sample of the subject is a tumor tissue sample. 37

7. Claim 8: The method of claim 1, wherein the targeted multiplex amplification amplifies 20 to 50 target loci each encompassing a different tumor-specific SNV mutation. 37

8. Claim 9: The method of claim 1, wherein the targeted multiplex amplification amplifies 50 to 100 target loci

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each encompassing a different tumor-specific SNV mutation. 40

9. Claim 10: The method of claim 1, wherein the method further comprises designing PCR primers or hybrid capture probes targeting the plurality of SNV mutations identified in the tumor sample. 40

10. Claim 11: The method of claim 1, wherein the method further comprises performing barcoding PCR prior to the sequencing. 40

11. Claim 12: The method of claim 1, wherein the method further comprises detecting recurrence and/or metastases of the cancer from the SNV mutations detected in the cell-free DNA. 41

12. Claim 13: The method of claim 1, wherein the cancer is colorectal cancer, lung cancer, bladder cancer, or breast cancer. 42

13. Claim 14 42

14. Claim 15: The method of claim 14, wherein the sequencing has a depth of read of at least 50,000 per target locus. 45

15. Claim 16: The method of claim 14, wherein the cell-free DNA comprises circulating tumor DNA. 45

16. Claim 17: The method of claim 14, wherein the SNV mutations comprise one or more clonal SNV mutations. 45

17. Claim 18: The method of claim 14, wherein the SNV mutations comprise one or more subclonal SNV mutations. 45

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20. Claim 22: The method of claim 14, wherein the targeted multiplex amplification amplifies 20 to 50 target loci each encompassing a different tumor-specific SNV mutation. 46

21. Claim 23: The method of claim 14, wherein the targeted multiplex amplification amplifies 50 to 100 target loci each encompassing a different tumor-specific SNV mutation. 46

22. Claim 24: The method of claim 14, wherein the method further comprises designing PCR primers or hybrid capture probes targeting the plurality of SNV mutations identified in the tumor sample. 46

23. Claim 25: The method of claim 14, wherein the method further comprises performing barcoding PCR prior to the sequencing. 46

24. Claim 26: The method of claim 14, wherein the method further comprises detecting recurrence and/or metastases of the cancer from the SNV mutations detected in the cell-free DNA. 47

25. Claim 27: The method of claim 14, wherein the cancer is colorectal cancer, lung cancer, bladder cancer, or breast cancer. 47

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1132	Sohrab P. Shah et al., *The Clonal and Mutational Evolution Spectrum of Primary Triple Negative Breast Cancers*, 486(7403) Nature 1-13 (2013) (Supplemental Table, unexpanded columns)

I. INTRODUCTION

NeoGenomics Laboratories, Inc. ("Petitioner") requests *inter partes* review and cancellation of all claims of U.S. Patent No. 11,530,454 ("the '454 patent"). The '454 patent, entitled "Detecting Mutations and Ploidy in Chromosomal Segments," issued on December 20, 2022 and is assigned to Natera, Inc. ("Patent Owner").

The '454 patent claims a routine and undeniably obvious method for monitoring cancer using cell-free DNA ("cfDNA"). The independent claims recite sequencing tumor DNA to identify tumor-specific mutations, followed by collecting a cfDNA sample from the blood stream of the cancer patient and then amplifying and sequencing the cfDNA to check if the tumor-specific mutations are present. Such a process for tracking cancer based on identifying the genetic fingerprint of a tumor and then simply looking for this signature in blood via standard techniques is, on its face, not remotely inventive.

Patent Owner, in fact, has already effectively admitted this in multiple prior proceedings over the years. Most important, Patent Owner is currently asserting the '454 patent against Petitioner in parallel district court proceedings in North Carolina. There, Petitioner identified as invalidating prior art the 2012 Forshew reference, which is the same reference relied upon here and that teaches a method insubstantially different from the claimed methods of the '454 patent. In the

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parallel district court proceedings, involving claims 1, 8, and 11, there was only ***one*** claim element that Patent Owner alleged was not identically present in Forshew.

Specifically, Patent Owner alleged that Forshew fails to teach performing sequencing at a "depth" of at least 50,000. EX1054.011-.012. Yet, with respect to this one element, which pertains to nothing more than increasing the number of DNA molecules that are sequenced at a given genetic locus, the evidence is overwhelming that increasing sequencing "depth" to improve sensitivity would have been nothing more than a routine and obvious step.

Forshew—which already teaches a sequencing depth above 15,000—provides a clear motivation to do this, teaching that "high[] read depth…could allow for enhanced mutation detection ***without change to protocols***." EX1003.011. [1] Patent Owner itself has made numerous express and unequivocal admissions that success would be expected. For instance, Patent Owner affirmed in prior litigation that it "was well known by 2009 that the number of molecules analyzed is one component of sensitivity, and that higher sensitivity could be achieved by sequencing more molecules." EX1088.032. Patent Owner's expert from that case, Dr. John Quackenbush, likewise testified on behalf of Patent Owner that

[1] Emphasis supplied unless otherwise noted.

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"POSAs prior to November 6, 2009 were ***well aware*** that sequencing more molecules, or increasing sequencing depth, improves sensitivity." EX1094 ¶ 119.

And, far from suggesting that a sequencing "depth" of 50,000 is non-obvious, the '454 patent itself gives this topic hardly any attention at all, treating sequencing depth as nothing but a standard parameter that could be varied over five orders of magnitude. EX1001 at 68:33-39. A depth of 50,000 is not once called out as inventive or special in the '454 patent.

In an about-face from its prior positions and its statements in the '454 patent itself, Patent Owner now alleges in parallel district court proceedings, and will presumably allege here, that increasing sequencing depth would have presented all sorts of challenges and that a person having ordinary skill in the art never would have tried it. EX1054.011-.012; EX1081 ¶¶ 81-118. Patent Owner even hired a different expert, Dr. Michael Metzker, to distance itself from its prior admissions about how obvious and conventional increasing sequencing depth was. Dr. Metzker now opines on behalf of Patent Owner that "[p]rior to 2015 there were many challenges in using next generation sequencing." EX1081 ¶ 94.

Yet, Patent Owner apparently neglected to recall that years earlier Dr. Metzker had opined on its behalf to the exact opposite effect before this very tribunal. Specifically, in IPR2018-01317, Dr. Metzker opined that, in the 2010 timeframe, "[a]t high sequence coverage all NGS platforms have excellent variant calling

accuracy." EX1082 ¶ 213. As to sequencing depth specifically, Dr. Metzker could not have been clearer, testifying with respect to an early sequencing platform that to "increase the accuracy of the Illumina GA sequencer, it ***would have been obvious*** in my opinion to target regions of a chromosome with high sequence coverage." EX1082 ¶ 214; EX002 ¶ 177. For the reasons set forth below, and as further explained in the declaration of Petitioner's expert Niall Lennon, Ph.D. (EX1002), all of the claims of the '454 patent would have been obvious over the prior art and should be cancelled.

II. TECHNOLOGY BACKGROUND

A. Cell-Free DNA

DNA is a double-stranded polymer comprised of covalently linked chains of nucleotides. EX1002 ¶ 55. There are four nucleotides, adenine ("A"), thymine ("T"), cytosine ("C"), and guanine ("G"), which form complementary base pairs: A with T, and C with G:

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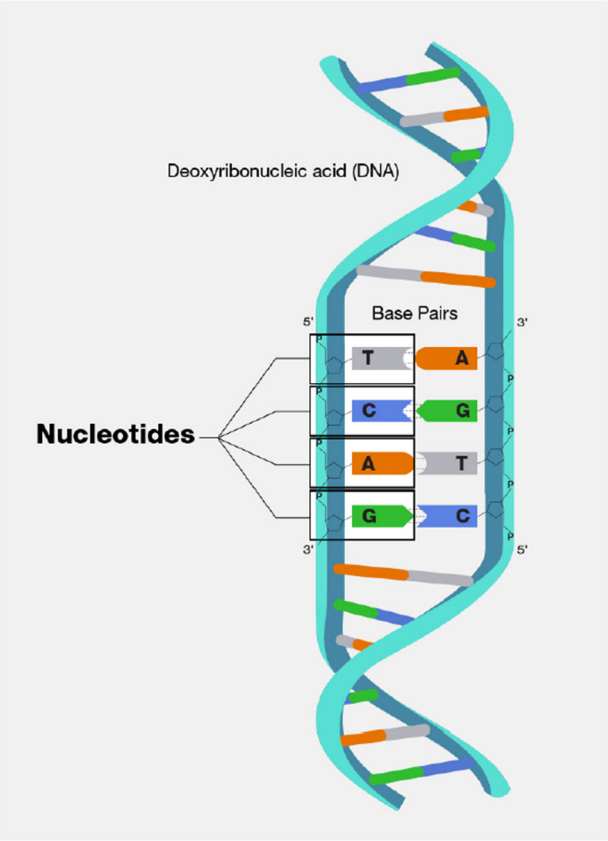

EX1026.002; *see also* EX1002 ¶¶ 55-57.

Most DNA, in humans, is found in large, complex structures called chromosomes located within the cellular nucleus. EX1027.001; EX1028.001; EX1002 ¶ 58. It has been known since the 1940s, however, that when cells die, chromosomal DNA is fragmented by natural processes and the resulting DNA fragments make their way into cell-free fluids like blood plasma—this DNA is cfDNA. EX1002 ¶¶ 58-59. When cancer cells die, tumor DNA likewise makes its way into these fluids, is called circulating tumor DNA ("ctDNA"), and can be used to monitor and diagnose cancers. *Id.* ¶¶ 59-61.

B. SNVs AND SNPs

DNA variants can occur naturally (different traits among people) or through mutations associated with a disease, such as cancer. *Id.* ¶¶ 62-64. These variants can be as simple as the difference between two nucleotides, called single nucleotide variants ("SNVs") or single nucleotide polymorphisms ("SNPs"). *Id.* ¶ 62. The '454 patent defines SNPs as "a single nucleotide that may differ between the genomes of two members of the same species" and notes "usage of the term should not imply any limit on the frequency with which each variant occurs." EX1001 at 28:13-17; EX1002 ¶ 64. The '454 patent does not define SNVs, but uses the term consistently with prior art, as indicating single nucleotide mutations of the individual's DNA. *See, e.g.*, EX1001 at 41:65-42:3, 171:29-43 (claim 1); EX1002 ¶ 63.

C. Multiplex PCR Amplification

Some applications of biotechnology, such as certain forms of DNA sequencing, require more DNA than is present in typical samples. EX1002 ¶ 65. Methods of amplifying (*i.e.*, making copies of) DNA have therefore found widespread use. *Id.* ¶¶ 65-77. One such method is polymerase chain reaction ("PCR"), wherein DNA fragments are amplified in cycles. *Id.* ¶ 65.

PCR generally requires denaturing double-stranded DNA into single strands (through heat or other means) to serve as two templates for copying. *Id.* ¶¶ 66-67.

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Next, primers, or pairs of short DNA molecules complementary to specific regions of each template, are annealed (*i.e.*, bound) to each template strand. *Id.* ¶¶ 66, 68. The choice of primers and the DNA regions they complement determines which portion of the DNA will be amplified. *Id*. Once annealed, the primer is extended (*i.e.*, built on) to form a complementary strand to the template strand. *Id.* ¶¶ 66, 69. This process can be repeated in cycles with the newly formed double stranded DNA being denatured to form four templates for copying. *Id.* ¶ 69.

Multiplex PCR is the use of multiple primer pairs to amplify many DNA locations ("loci") in a single reaction, which is faster, less expensive, and less cumbersome than amplifying each locus separately in individual PCR reactions. *Id.* ¶ 71. It also reduces the likelihood of missing rare molecules because it avoids the need to partition the sample into individual reactions that will each start with less genetic material. *Id.* ¶ 71. Multiplex PCR reactions were well-known in the art, including involving thousands of loci, and were commercialized by 2005. EX1001 at 97:13-20; EX1050 ¶¶ 267, 303, 515-516; EX1049 at 85:14-16, 48:25-29, 210:35-211:43; EX1071; EX1072; EX1060 ¶ 214; EX1083 ¶¶ 119, 175; EX1107.004-.005; EX1058 at Abstract; EX1058 ¶ 57; EX1109.001-.002; EX1002 ¶¶ 72-76. Various DNA polymerases were commercially available for PCR reactions, including high fidelity polymerases, by 2015. EX1121.001-.002; EX1002 ¶ 77.

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D. Sequencing

DNA sequencing is the process of determining the order of bases in a DNA sequence. EX1002 ¶¶ 78-79. In the early 2000s, next generation sequencing ("NGS"), also known as high throughput sequencing, technologies were created to increase sequencing capacity and decrease costs, becoming commercially available by 2008. EX1077.002; EX1124 at Abstract; EX1103.002; EX1002 ¶ 80. These technologies allowed for rapid identification of tumor mutations by at least 2013. EX1032.002; EX1002 ¶ 80. NGS uses parallel sequencing of many DNA fragments, processing millions of fragments simultaneously and producing millions of "sequence reads." EX1002 ¶ 81. Sequence reads, the individual base sequences of measured DNA fragments, are then joined together to form the sequence for the full region of interest. *Id.*

DNA amplification may be used in conjunction with DNA sequencing and increase sequencing accuracy. EX1002 ¶ 82; EX1056.005; EX1061.004.

As of 2015, NGS platforms had been used for both whole genome sequencing ("WGS") and whole exome sequencing ("WES"). EX1002 ¶¶ 83-84. WGS refers to a sequencing method wherein one seeks to sequence all or nearly all of an entire genome. *Id.* ¶ 83. WES, by contrast, refers to a method where one seeks to sequence only the portion of the genome that codes for proteins. *Id*. Both of these methods were also known for identifying SNVs in the tumor DNA of cancer

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patients. *Id.* ¶ 85. By April 2015, many factors, including introducing and refining NGS methods, had led to an exponential decrease in DNA sequencing costs. *Id.* ¶ 86.

E. Minimal Residual Disease Monitoring

Minimal residual disease ("MRD") monitoring is the monitoring of residual cancer that remains after a patient has undergone treatment, *e.g.*, surgery and/or treatment with radiation or chemotherapy. EX1130.002; EX1002 ¶ 87. MRD monitoring generally involves WGS or WES of the cancerous DNA to identify cancer-related (*e.g.*, tumor-specific) SNVs, and follow-up monitoring (involving multiplex PCR and sequencing) of these SNVs in cfDNA. EX1002 ¶¶ 88-93. This was developed to provide patient-specific care and allows detection of recurrent tumors without the need for invasive surgeries, and can also be used to monitor treatment progress as the level of cfDNA correlates with the size of the tumor. *Id.* ¶¶ 87-88. MRD monitoring was routinely conducted by at least 2013 through a range of different approaches. *Id.* ¶¶ 87-93.

F. Clonal Heterogeneity

Heterogeneity of tumors and tumor DNA is a consideration in MRD monitoring. *Id.* ¶ 94. Clonal heterogeneity describes a tumor that includes cells with different genetic make-up, caused by continuing mutations as the cancer cells propagate. *Id.* ¶¶ 94-95. Mutations found in all of the tumors' cells are "clonal,"

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while those found in only some are "sub-clonal." *Id.* ¶ 95. Heterogeneity can be the cause of cancer recurrence and resistance to treatment and has been studied in many cancers. *Id.* ¶ 96. Determining heterogeneity is done using the same techniques used to sequence cancerous cells, and heterogeneity can be monitored using cfDNA. *Id.* ¶ 97.

III. OVERVIEW OF THE ′454 PATENT

A. Priority Date

The '454 patent issued December 20, 2022 from Application No. 17/738,354 ("the '354 Application"), filed May 6, 2022. EX1001 at codes (21), (22), (45); EX1018; EX1002 ¶ 43. In a Court-ordered interrogatory response, Patent Owner declared the priority date of the '454 patent as "by April 21, 2015," which is the filing date of Application No. 14/692,703 ("the '703 application"). EX1008.010; EX1009.002; EX1001 at code (63), claims 1 and 14; EX1002 ¶ 39. The '703 application was the first application in the '454 patent's priority chain with any written description support whatsoever for "whole exome sequencing" or "whole genome sequencing," which is recited in the independent claims of the '454 patent. EX1002 ¶ 40. This support appears in Example 13, which was first included in the '703 application. EX1001 at 167:66-168:19; EX1010 ¶ 608; EX1002 ¶ 40.

Patent Owner may contend that references in provisional applications in the '454 patent's priority chain to "long read sequencing" and "phasing," constitute

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written description support for WES or WGS. *See e.g.*, EX1011 ¶ 98; EX1012 ¶ 97; EX1013.323; EX1014 ¶¶ 107, 372; EX1015 ¶¶ 107, 372; EX1016 ¶ 107; EX1017 ¶¶ 107, 394; EX1002 ¶ 41. Reliance on such disclosure, however, is unavailing because neither recitation of "long read sequencing" nor "phasing" constitutes a description or disclosure of WES or WGS because a POSA would have understood that both could have been, and often were, accomplished on much smaller portions of genomic material than whole exomes or whole genomes. *See, e.g.*, EX1014 ¶¶ 35, 372; EX1002 ¶ 41.

April 21, 2015, the filing date of the '703 application, is the priority date of the '454 patent. EX1002 ¶ 42.

B. Prosecution History Of The '454 Patent

The '354 Application that eventually issued as the '454 patent originally included 15 claims directed to methods for amplifying and sequencing DNA. EX1019; EX1002 ¶ 43. During examination, the Examiner issued a Non-Final Rejection, rejecting all then-pending claims except claim 2 as obvious under § 103 over Forshew and other prior art references. EX1020; EX1002 ¶ 44.

Then-pending claim 2, which included the limitation "wherein the high-throughput sequencing has a depth of read of at least 50,000 per target locus," was not the subject of rejection over the prior art. EX1019.001; EX1020.005-.007; EX1002 ¶ 44. Patent Owner responded to the obviousness rejection of claim 1 by

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amending it to incorporate a depth of sequencing limitation like that in then-pending claim 2. EX1021.001.

Patent Owner argued for allowance of independent claim 1, over the combination that included Forshew, on the basis of the limitation to a sequencing depth of at least 50,000 per target locus:

> Claim 2 stands free of the subject rejections. For the sole purpose of expediting prosecution and without acquiescing to the rejection, Applicant has amended independent claim 1 to incorporate the limitation of previous claim 2, thereby rendering the rejections moot. None of the cited references teaches or suggests sequencing each of the target loci with a depth of read of at least 50,000 per target locus. For at least these reasons, Applicant respectfully request withdrawal of the subject rejections against claims 1 and 3-14.

EX1022.003; EX1002 ¶ 45.

Then-pending claim 1 stood rejected over the combination of Forshew and Benesova. EX1022.002-.005. In response, Patent Owner argued that Forshew did not disclose the use of the claimed "multiplex targeted amplification," asserting that "Forshew had considered but dismissed multiplex targeted amplification." EX1022.004; EX1002 ¶ 46. Thus, Patent Owner argued that Forshew did not utilize multiplex PCR. As documented below, this assertion was false. *See infra* § X.A.1.c. Nevertheless, in view of this and other arguments Patent Owner made, the Examiner allowed the '454 patent claims. EX1024; EX1002 ¶ 47.

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C. Claims

All claims in the ’454 patent are challenged in this Petition. A listing of these claims is provided in Appendix A.

Briefly, the claims are directed to a process wherein a tumor sample from a cancer patient is broadly surveyed by “whole exome” or “whole genome” sequencing to identify tumor-specific SNV mutations. Appendix A; EX1002 ¶ 37. Next, one obtains a blood sample from the subject and attempts to amplify DNA fragments in the blood sample that harbor the SNV mutations that were identified through sequencing the tumor sample. *Id.* Finally, the amplified DNA fragments are subject to sequencing and analysis to detect the cancer-related tumor mutations in the blood sample. *Id.* The overall idea underlying these claims is an attempt to non-invasively detect or track cancer in a subject by looking for the genetic signature of a tumor in the bloodstream of a cancer patient.

IV. GROUNDS FOR STANDING

Petitioner certifies that the ’454 patent is IPR-eligible and Petitioner is not barred or estopped from requesting *inter partes* review of any ’454 patent claim.

V. MANDATORY NOTICES

A. Real Party-In-Interest

NeoGenomics Laboratories, Inc. is the real party-in-interest with respect to this petition for *inter partes* review.

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B. Related Matters

Patent Owner filed suit against Petitioner[2] for infringement of the '454 patent on December 20, 2022. *Natera, Inc. v. Inivata, Inc.*, Case No. 1:22-cv-01609 (D. Del.)[3]. Case No. 1:22-cv-01609 was then consolidated with an earlier-filed case in which Patent Owner had filed suit against Inivata for infringement of other patents. *Natera, Inc. v. Inivata, Inc.*, Case No. 1:21-cv-00056 (D. Del.)[4]. Patent Owner subsequently filed suit against Petitioner for infringement of the '454 patent on July 28, 2023. *Natera, Inc. v. NeoGenomics Labs., Inc.*, Case No. 1:23-cv-00629 (M.D.N.C.) ("North Carolina litigation").

In the North Carolina litigation, there has been minimal investment in developing invalidity positions as part of Patent Owner's preliminary injunction proceedings, and a full case schedule of fact and expert discovery lies ahead. EX1051; EX1053; EX1054. The case schedule has yet to be set by the court in

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[2] Inivata, Inc. and Inivata Ltd., wholly-owned subsidiaries of Petitioner, were acquired on June 18, 2021, the date Petitioner completed acquisition of the remaining equity interests following a minority equity investment in May 2020. EX1112.070.

[3] EX1113.

[4] EX1114.

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light of the pending preliminary injunction motion, and the Court has not construed any claims. *See infra* § XI.B.

C. Lead and Back-up Counsel

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D. Additional Service Information

Please address all correspondence to the lead and back-up counsel as shown above. Petitioner consents to electronic service at:

NeoGenomics@weil.com

VI. LEVEL OF ORDINARY SKILL IN THE ART

As explained in detail by Dr. Lennon, a POSA relevant to the ’454 patent as of April 21, 2015, would have had at least (1) a Master’s Degree and/or Ph.D. in biochemistry, molecular genetics, pharmacology, or an equivalent discipline with applications in genomics and (2) at least five years of academic or industrial laboratory experience. EX1002 ¶¶ 48-54.

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A POSA would have had a deep understanding of genomics, including nucleic acid detection, quantification, and genotyping and would understand the underlying scientific principles to such. *Id.* ¶ 50. A POSA also would have been apprised of then current literature on genomic assays, such as multiplex PCR, NGS techniques, and the use of cfDNA in genotyping. *Id.* ¶ 51. A POSA would also have generally understood the processes behind the development of DNA mutation-based illnesses, such as cancers, and would have been apprised of the recent literature in those fields. *Id.*

VII. CITED PRIOR ART

A. Forshew

Forshew, the primary reference relied upon herein, was published in 2012 with supplemental material, also available in 2012. EX1003; EX1002 ¶ 98. Forshew is therefore prior art to the ’454 patent under post-AIA § 102(a)(1).

Forshew describes methods for identifying SNVs likely to cause cancer in a tumor sample and then tracking those SNVs in blood plasma samples of the patient for relapse detection. EX1003.002-.010; EX1002 ¶ 99. Forshew explains that “[e]volutionary changes within the cancer can alter the mutational spectrum of the disease and its responsiveness to therapies,” which motivated Forshew’s team to develop “[s]ensitive methods for detecting cancer mutations in plasma [that] may

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find use in early detection screening, prognosis, monitoring tumor dynamics over time, or detection of minimal residual disease." EX1003.002; EX1002 ¶ 99.

Forshew's tagged-amplicon deep sequencing ("TAm-Seq") approach includes the following general steps:

- First, "[w]hole-genome sequencing of tumor material was used to identify tumor mutations in a patient with metastatic breast cancer undergoing two phases of chemotherapy." EX1003.010. For this experiment, "[t]en mutations were selected." EX1003.010.

- Second, target-specific primers were designed to amplify short genetic loci including the ten mutations. EX1003.016; EX1003.010.

- Third, using a sample of cell-free DNA from the cancer patient, the primers were employed to amplify the ten target loci together in a multiplex PCR reaction. This was followed by singleplex (individual) amplification to further purify the DNA sequences having the mutations. EX1003.010; EX1003.004.

- Finally, the amplified DNA was sequenced using next-generation sequencing, and the sequence data was analyzed to detect the tumor-specific SNVs in the plasma samples. EX1003.016-.017; EX1003.010.

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B. Secondary References Relied Upon Herein

While this Petition relies principally upon Forshew, the following secondary reference are also utilized herein:

- **Bashashati**: published in 2013 with supplemental material, also available in 2013. EX1004; EX1002 ¶ 107. Bashashati is therefore prior art to the ’454 patent under post-AIA § 102(a)(1).
- **Bai**: published in 2013. EX1005; EX1002 ¶ 113. Bai is therefore prior art to the ’454 patent under post-AIA § 102(a)(1).
- **Bentley**: published in 2010. EX1057 at code (43); EX1002 ¶ 117. Bentley is therefore prior art to the ’454 patent under post-AIA § 102(a)(1)
- **Narayan**: published in 2012. EX1086; EX1002 ¶ 119. Narayan is therefore prior art to the ’454 patent under post-AIA § 102(a)(1).

VIII. GROUNDS FOR THE CHALLENGES

Petitioner challenges claims 1-28 of the ’454 patent as follows:

1. **Ground 1:** Claims 1-6, 8-20, and 22-28 of the ’454 patent are unpatentable under § 103 over Forshew (EX1003);
2. **Ground 2:** Claims 3-5, 7, 17-19, and 21 of the ’454 patent are unpatentable under § 103 over Forshew in view of Bai (EX1005) and/or Bashashati (EX1004);

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3. **Ground 3:** Claims 14-20 and 22-28 of the ’454 patent are unpatentable under § 103 over Forshew in view of Bentley (EX1056) and/or Narayan (EX1086); and

4. **Ground 4:** Claims 17-19 and 21 of the ’454 patent are unpatentable under § 103 over Forshew in view of Bai and/or Bashashati and Bentley and/or Narayan.

IX. CLAIM CONSTRUCTION

For purposes of this Petition, Petitioner requests that the Board apply the following claim constructions, one of which is urged by Patent Owner in related proceedings. *Hospira, Inc. v. Amgen Inc.*, IPR2021-00528, Paper 7 at 7 (PTAB Aug. 17, 2021) (“all that rule [42.104(b)(3)] requires is for the Petition to identify ‘[h]ow the challenged claim is to be construed”). Petitioner reserves the right to respond to any proposed constructions raised by Patent Owner, or to revise its claim constructions in light of developments in related proceedings.

A. “Targeted Multiplex Amplification”

The Board should construe the term “targeted multiplex amplification,” to mean “simultaneously increasing the number of copies of many particular targeted molecules of DNA (or RNA), or targeted regions of DNA (or RNA) in a single reaction.” EX1001 at 34:52-62, 163:16-17; EX1002 ¶ 121.

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B. "Sequencing The Amplicons"

For the limited purposes of this petition, Petitioner relies on the claim construction for "sequencing the amplicons" urged by Patent Owner in the related North Carolina litigation, which is "sequencing amplification products containing the target loci." EX1002 ¶ 122. Under Patent Owner's interpretation, this claim element is not limited to directly sequencing the "amplicons" that result from the claimed "targeted multiplex amplification," but also encompasses the sequencing of products that have been subject to additional amplification processes following the "targeted multiplex amplification," such as a PCR process to add barcodes to the amplicons that emerge from the "targeted multiplex amplification." *Id.*

Under Patent Owner's claim construction for "sequencing the amplicons," the '454 patent is invalid. Further, as discussed below, to the extent this claim term is interpreted to require direct sequencing of the "amplicons" that result from the "targeted multiplex amplification" without any intervening amplification steps, the claims are still invalid.

X. THE '454 CLAIMS ARE UNPATENTABLE

A. Ground 1: Claims 1-6, 8-20, and 22-28 Are Unpatentable Under 35 U.S.C. § 103 Over Forshew In View of a POSA's Knowledge

As proven below, Forshew in view of a POSA's knowledge renders obvious claims 1-6, 8-20, and 22-28 of the '454 patent. EX1002 ¶ 134. With respect to the independent claims, in the district court case where independent claim 1 is

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challenged, Patent Owner does not deny that Forshew discloses all but a single claim element, and with respect to this one allegedly undisclosed claim element Patent Owner has repeatedly admitted that it was otherwise routine, well-known, and obvious. *See supra* § I. As to the dependent claims, they are typical dependent claims that likewise recite no inventive features and for which Patent Owner has presented no meaningful argument for patentability in parallel proceedings.

1. Claim 1:

a. [1.preamble]: A method for preparing a plasma sample of a subject having cancer or suspected of having cancer useful for detecting one or more single nucleotide variant (SNV) mutations in the plasma sample, the method comprising:

To the extent the preamble is limiting, Forshew discloses this limitation. EX1002 ¶¶ 135-139.

Forshew discloses that the "[p]lasma of cancer patients contains cell-free tumor DNA that carries information on tumor mutations and tumor burden" and "demonstrated use of TAm-Seq to noninvasively identify the origin of metastatic relapse in a patient with multiple primary tumors." EX1003.002; EX1002 ¶ 136.

As part of the TAm-Seq process, Forshew teaches using WGS to identify tumor mutations in a solid tumor sample. EX1003.010 ("Whole-genome sequencing of tumor material was used to identify tumor mutations in a patient with metastatic breast cancer undergoing two phases of chemotherapy."); EX1002 ¶ 137.

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The identified mutations included SNVs. EX1003.010, .017-.019, Tables S6-S7; EX1002 ¶ 138. Forshew then teaches preparing plasma samples useful for detecting these SNV mutations. EX1003.010 ("We performed TAm-Seq in duplicate, ***using DNA from 0.08 ml of plasma per amplification***, and tracked dynamics of all mutations in parallel."); *see also* EX1003.004, S1; EX1002 ¶ 137.

b. [1.a]: performing whole exome sequencing or whole genome sequencing on a tumor sample of the subject to identify a plurality of tumor-specific SNV mutations;

Forshew discloses "[w]hole-genome sequencing of tumor material [] to identify tumor mutations in a patient with metastatic breast cancer undergoing two phases of chemotherapy." EX1003.010; *see also id.*, Table S7; EX1002 ¶¶ 140-141, 145. The identified mutations were SNVs. EX1003.010, .017-.019, Tables S3, S6-S7; EX1002 ¶¶ 142-145.

c. [1.b]: performing targeted multiplex amplification to amplify 10 to 500 target loci each encompassing a different tumor-specific SNV mutation from cell-free DNA isolated from a plasma sample of the subject or DNA derived therefrom to obtain amplicons having a length of 50-150 bases, wherein the target loci are amplified together in the same reaction volume; and

Forshew discloses every component of this claim element. EX1002 ¶¶ 146-157.

Forshew discloses amplifying ten SNV mutations from a tumor sample that were identified based on WGS data, which are listed in Table S7. EX1003.010

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(WGS "of tumor material was used to identify tumor mutations…Ten mutations were selected, and short amplicons (<120 bp) were designed to cover the mutation loci (table S7)."), Table S7; EX1002 ¶¶ 147-149. Forshew further explains that this amplification was performed using cfDNA from a plasma sample, referring to collecting cfDNA "before and after treatment" and performing "TAm-Seq in duplicate, using DNA from 0.08 ml of plasma per amplification." EX1003.010; *see also* EX1003.002 ("Plasma of cancer patients contains cell-free tumor DNA that carries information on tumor mutations and tumor burden."); EX1003.011 (describing "[e]xtraction of DNA from…blood plasma"); EX1002 ¶¶ 150, 153.

Forshew further discloses that the ten mutations were amplified by a targeted multiplex amplification wherein all of the targets were amplified in the same reaction: "An initial preamplification step was performed for 15 cycles using a ***pool of the target-specific primer pairs***" which included "***each*** forward and reverse target-specific primer." EX1003.003 (Fig. 1B Legend), S2; *see also* EX1003.004 ("a limited-cycle preamplification step where ***all primer sets were used together***"); EX1002 ¶¶ 150, 152. Patent Owner's expert in district court litigation, Dr. Metzker, confirms that the amplification in Forshew is a targeted multiplex amplification. EX1052 at 65:15-18 ("Forshew (2012) does describe multiplex PCR"); *id.* at 66:19-24 ("In the preamplification step, it does use multiplex PCR."); EX1002 ¶ 151.

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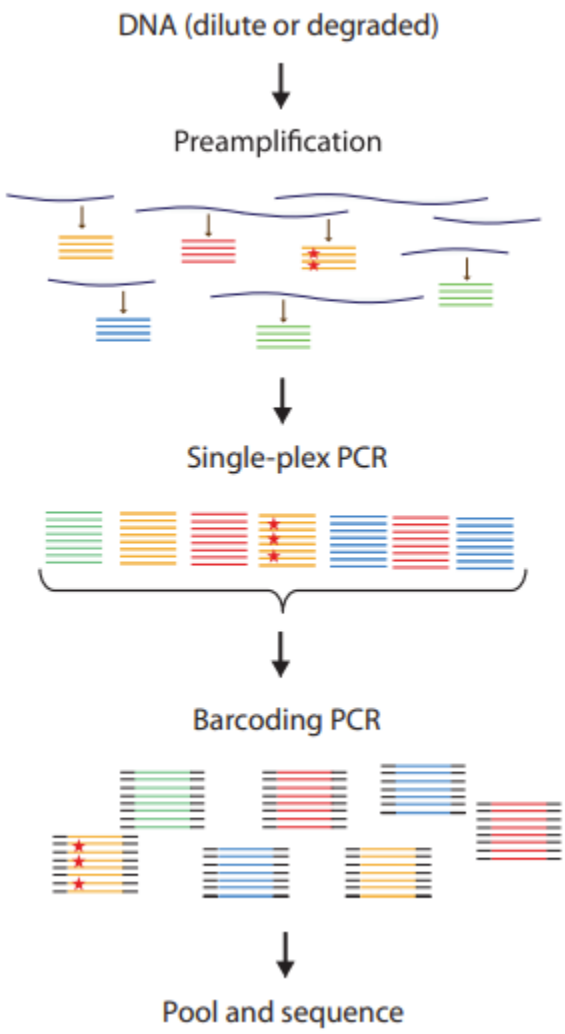
Finally, Forshew discloses amplicons with lengths of "<120 bp to cover each mutation." EX1003 at Table S7; EX1002 ¶ 154. The amplicons likewise include >50 bases in the listed primers defining the amplicons, which are identified by a list of start and stop locations on the genome for the amplicons. EX1003 at Table S1, S7; EX1002 ¶ 154. This discloses amplicons in the claimed 50-150 base range. EX1002 ¶ 154.

d. [1.c]: sequencing the amplicons to obtain sequence reads, and detecting one or more of the tumor-specific SNV mutations present in the cell-free DNA from the sequence reads, wherein the sequencing has a depth of read of at least 50,000 per target locus.

Forshew teaches the key components of this claim element, including sequencing followed by detecting mutations in the sequence data. EX1002 ¶¶ 158-159.

After the targeted multiplex amplification (*i.e.*, "Preamplification"), there is a "Single-plex PCR" and "Barcoding PCR:"



EX1003 at Fig. 1b; EX1002 ¶ 159. Then, the resulting DNA is pooled and sequenced. *Id.*; *see also* EX1003.004 ("We performed 100-base single-end sequencing (GAIIx sequencer, Illumina), with an additional 10 cycles using the barcode sequencing primer, generating ~30 million reads per lane."); EX1002 ¶ 159. Accordingly, Forshew discloses the "sequencing" component of this claim element. EX1002 ¶ 159.

Furthermore, the sequence data is analyzed to detect SNV mutations in the cfDNA. *Id.*; EX1003 at S2-S4, Table 1, Table 1 Legend, Table S7, Abstract;

EX1002 ¶ 159. Specifically, Forshew teaches using a bioinformatics pipeline for this purpose. EX1003.018; EX1002 ¶ 159. Thus, Forshew also discloses the "detecting" component of this claim element. EX1002 ¶ 159.

This element of claim 1 further requires a sequencing depth of at least 50,000. EX1002 ¶¶ 160-161. As below, to the extent Forshew is deemed to not disclose this element, a POSA would have found it obvious to modify Forshew to achieve the claimed invention. *Id.* Likewise, to the extent the claims are construed to require direct sequencing of the "amplicons" that emerge from the "targeted multiplex amplification" without any intermediate steps, a POSA would have found it obvious to modify Forshew to adopt this approach. *Id.* ¶¶ 189-195.

i. It Would Have Been Obvious To Increase Sequencing Depth To Increase Sensitivity

The use of a sequencing "depth of read" of at least 50,000 is the sole element of claim 1 that Patent Owner has suggested is not present in Forshew in parallel district court proceedings. EX1054.011-.012.

Sequencing "depth," as explained in the '454 patent, and as understood by a POSA, is a measure of how many sequence reads map to a given genetic locus. EX1002 ¶ 162; EX1001 at 100:9-15. A POSA would have been motivated to increase sensitivity by modifying Forshew so as to sequence more molecules and reach a depth of at least 50,000, and would have expected success. EX1002 ¶¶ 163-

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188. As below, this would have been an obvious approach in view of rapidly improving capabilities of sequencing instrumentation during the three-year timeframe between publication of Forshew and the April 2015 priority date of the '454 patent. This is clear from Forshew, the prior art, numerous admissions from Patent Owner and its experts, and even the '454 patent itself.

As an initial matter, Forshew's Table 1 discloses examples of sequencing depth of up to 15,400. EX1002 ¶ 163; EX1003.004, .006, Table 1 (showing duplicate samples with mean sequencing depth of 7,700, for total sequencing depth of 15,400). Forshew thus discloses sequencing depths on the order of tens of thousands, such that increasing to at least 50,000 would have been an obvious change. EX1002 ¶ 164. A POSA would have been motivated to make this change and had a reasonable expectation of success because sequencing more molecules in a given region of the genome allows one to sample the sequence associated with that region more frequently, hence increasing sensitivity of mutation detection. EX1002 ¶ 165. Forshew, in fact, teaches precisely this, stating *inter alia* that "higher read depth" and using "additional replicates" (increasing read depth) allows "enhanced mutation detection without change to protocols." EX1003.011; EX1002 ¶¶ 165-167. This alone proves obviousness.

Such teaching is not limited to Forshew, but is echoed in numerous prior art references, as Dr. Lennon explains. EX1002 ¶¶ 168-170; EX1086 (disclosing a

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sequencing depth of 108,467 reads per locus); EX1090 (same); EX1091.036 (same); EX1057 ¶¶ 85, 88 (teaching that with more reads, a lower minimum frequency of SNVs is detectable); EX1105.001, Supplemental Fig. 2 (discussing correlation between increasing reads and increasing sensitivity); EX1108.011 (same).

In fact, in 2012, work had been published validating the detection of over 50 variants at a sequencing depth above 50,000, including some variants that were a sequenced to a depth of up to 3 million. EX1101 at Table S3 (EX1102, EX1132) (sequencing tumor tissue to depths up to 3 million, with over 50 variants validated with sequencing depths over 50,000); EX1002 ¶ 169. If researchers in 2012 had successfully validated variants using a sequence depth of up to 3 million, any suggestion that in 2015 researchers would be fearful of sequencing to a depth of merely 50,000 cannot be given any weight. EX1101 at Table S3 (EX1102, EX1132). Regardless, the repeated prior disclosure in the art that one can increase sensitivity merely by increasing sequencing depth confirms that a POSA would have viewed such an approach as obvious and sure to succeed. EX1002 ¶¶ 165, 168-169 (and citing references).

Patent Owner itself has repeatedly affirmed this in prior cases. For example, in a case related to detection of organ transplant rejection using sequencing to detect cfDNA, Patent Owner affirmed that "[i]t was well-known by 2009 that the number of molecules analyzed is one component of sensitivity, and that higher

sensitivity could be achieved by sequencing more molecules." EX1088.032-.033; *see also id.* at .033 ("And as discussed above, it was well-known by 2009 that by sequencing more molecules, sensitivity will necessarily increase."); EX1002 ¶ 170.

Patent Owner's expert from that case, Dr. John Quackenbush, likewise testified that "POSAs prior to November 6, 2009 were ***well aware*** that sequencing more molecules, or increasing sequencing depth, improves sensitivity" and that "the detection limit is determined by sequencing error rate and sequencing read depth (i.e., how many molecules are sequenced), reflecting the fact that there was a ***well-known*** correlation between the number of molecules sequenced and sensitivity." EX1094 ¶ 119 (citing EX1105, EX1108); *see also* EX1084 at 98:10-99:6 (testifying on behalf of Patent Owner that there was nothing "nonconventional" about increasing sequencing depth, that this is a "standard practice in many fields," and that "to get higher sensitivity for detecting molecules, you simply sequence more molecules."); EX1002 ¶¶ 171-173.

Notably, the expert that Patent Owner now relies upon in parallel district court litigation in North Carolina involving the '454 patent, Dr. Metzker, has opined to this exact same effect before this very tribunal. In IPR2018-01317, Dr. Metzker opined that in the 2010 timeframe that to "increase the accuracy of the Illumina GA

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sequencer, it ***would have been obvious*** in my opinion to target regions of a chromosome with high sequence coverage."[5] EX1082 ¶¶ 91, 214; EX1002 ¶ 174.

Looking to the '454 patent itself confirms obviousness. The patent does not disclose 50,000 as a special—let alone inventive—read depth. Instead, it buries 50,000 among an undifferentiated list of 14 different possible sequencing depths that span four orders of magnitude, from 100 to 500,000. EX1002 ¶ 175; EX1001 at 68:33-39. Depth of read is nothing more than a known result-effective variable to provide improved sensitivity, and it would have been routine to optimize this variable to provide the required sensitivity of detection. *In re Aller*, 220 F.2d 454, 456 (CCPA 1955) ("where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation"). Far from being inventive, the claimed sequencing depth of 50,000 is *prima facie* obvious.

Nevertheless, in parallel district court litigation, Patent Owner has asserted that increasing sequencing depth in connection with the TAm-Seq process of

[5] The term "sequence coverage" is no different in substance from "sequence depth," as confirmed by Dr. Metzker himself, who opined on behalf of Patent Owner that the "term 'coverage' means the number of unique sequence reads at a given location (base pair) on a chromosome." EX1082 ¶ 206.

Forshew would have presented various challenges that would have dissuaded a POSA from pursuing this approach. EX1054.011-.012; EX1081 ¶¶ 81-118; 1002 ¶ 176. Dr. Metzker, for instance, opined on behalf of Patent Owner that "[p]rior to 2015, there were many challenges in using next generation sequencing" and "Forshew (2012)'s sample library preparation and sequencing workflow exceed the technique's ability to detect rare genetic DNA variants…the rare variants are lost in the 'noise' associated with the abundant errors found in the sequence read data." EX1081 ¶¶ 93-94; EX1002 ¶ 176. Patent Owner has asserted that "[s]equencing each SNV locus 50,000 times or more…would not reasonably be expected to identify rare variants in low-abundance ctDNA above the background 'noise' from sequencing-related error rates." EX1054.012; EX1002 ¶ 176.

This, however, is all without merit, and likewise directly contrary to Dr. Metzker's own testimony about how it would have been "obvious" to increase sequencing depth to enhance accuracy. EX1082 ¶ 214; EX1002 ¶ 177. Far from complaining about alleged "challenges" with NGS, Dr. Metzker previously testified on behalf of Patent Owner that as of 2009 the literature taught that at "high sequence coverage ***all*** NGS platforms have ***excellent variant calling accuracy*** (>95%) as assessed by the detection of known SNP variants." EX1082 ¶ 213 (citing EX1042); EX1002 ¶ 177. Likewise, in the North Carolina litigation, Dr. Metzker opined about the use of enzymes with built-in "proofreading" capabilities that would

overcome PCR errors that would allegedly cause problems for sequencing. EX1081 ¶ 304; EX1002 ¶ 177. A POSA would have understood how to address both systematic and random errors. EX1002 ¶ 178; EX1128.002; EX1127 at Abstract; EX1129 at Abstract.

Thus, there is no basis for any suggestion that sequencing technology in 2015 was so problematic that a POSA would avoid increasing sequencing depth to improve accuracy. If there were any truth to such a contention, Forshew never would have taught precisely doing so in 2012. In fact, as Dr. Lennon explains in detail, between 2012 and 2015, the relevant amplification and sequencing technology simply became more accurate, more efficient, and less costly, which would have only provided further motivation to increase sequencing depth. EX1002 ¶¶ 179-188.

ii. It Would Have Been Obvious To Modify Forshew To Omit Intermediate PCR Steps

To the extent the Board rejects the claim construction advanced by Patent Owner in the North Carolina litigation, and construes the claims to require sequencing of the amplicons generated directly after the targeted multiplex amplification, excluding any intermediate steps between the targeted multiplex amplification and sequencing, Forshew still renders this claim element obvious. As set forth below, it would have been obvious to modify Forshew to directly

sequence the amplicons that emerge from the targeted multiplex amplification without any intermediate PCR steps, omitting both the single-plex PCR and the PCR to introduce barcodes and sequencing adapters. EX1002 ¶ 189.

First, as to the single-plex PCR, Forshew itself makes clear that the preceding multiplex PCR was designed so as to avoid unwanted side products:

> The final concentration of each primer in the preamplification reaction was 50 nM, ***reducing the potential for interprimer interactions***, and 15 cycles of long-extension (4 min) polymerase chain reaction (PCR) were used to ***remain in the exponential phase of amplification***.

EX1003.004; *see also id.* at .016 ("Primer designs were screened against the hg19 reference genome to prevent cross-product generation, and were screened to prevent primer-dimer interactions and formation of intramolecular secondary structure"); EX1002 ¶ 190. Accordingly, a POSA would recognize that the single-plex PCR that was used in Forshew to improve purity was not needed. EX1002 ¶ 190. Further, as Patent Owner's own expert confirmed, "[i]f the number of cycles remains within the exponential amplification phase, the relative abundance of mutations will not be diluted." EX1081 ¶ 290; EX1002 ¶ 190. In this regard, Forshew's multiplex PCR was designed in such a way that it would preserve the relative abundance of mutations, enabling the resulting amplicons to be sequenced directly. EX1002 ¶ 190.

Second, as to the PCR to introduce barcodes and sequencing adapters, a POSA would have understood that the sample barcodes and sequencing adapters could have easily been incorporated into the sequence-specific primers used in the multiplex PCR amplification such that they would then be incorporated into the amplicons that result from the multiplex amplification step. EX1002 ¶ 191. This would have then allowed the amplicons from the multiplex amplification to be directly sequenced in the same manner as in Forshew. *Id.* ¶¶ 191-192.

A POSA would have been motivated to modify Forshew in the foregoing manner because a POSA would have understood that omitting the single-plex PCR and performing multiplex PCR amplification using primer pairs having sample barcodes and sequencing adapters would simplify the overall process so that it required only a single amplification step (as opposed to also requiring a separate amplification step to add the barcodes). EX1002 ¶ 192. A POSA would have had a reasonable expectation of success in pursuing this approach for at least two reasons. EX1002 ¶ 193. First, as noted above, Forshew already taught multiplex PCR conditions that would avoid unwanted side products and preserve relative abundance of mutations, such that the single-plex PCR that Forshew used to enhance purity would not be required. *Id.* Second, Forshew already discloses targeted multiplex amplification using target-specific

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primer pairs that include an additional sequence, namely, the "universal primer sequences (termed CS1 and CS2) appended at the 5'-end." *Id.*; EX1003.016.

This understanding is reflected in the prior art. EX1002 ¶ 194. Hoffmann (EX1069), for instance, teaches "[g]enomic DNA samples of interest are amplified using primers that include 5' extension providing binding sites for the 454A and B primers" that are required for sequencing. *Id.*; EX1069.003. The single amplification step is depicted in Hoffmann's Figure 2. EX1002 ¶ 194; EX1069 at Fig. 2.

2. Claim 2: The method of claim 1, wherein the cell-free DNA comprises circulating tumor DNA.

Disclosed. *See supra* § X.A.1; EX1002 ¶¶ 196-198.

3. Claim 3: The method of claim 1, wherein the SNV mutations comprise one or more clonal SNV mutations.

Clonal SNV mutations are those that are present in all cells of a tumor because they were present from the outset in the original cells that led to the tumor such that the mutations ultimately proliferate to all tumor cells. EX1002 ¶¶ 200-201. Forshew discloses the detection of a clonal SNV mutation (a *TP53* mutation), which was present in eight tissue regions sampled. *Id.* ¶¶ 199-203; EX1003.008, Fig. 4(A).

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4. Claim 4: The method of claim 1, wherein the SNV mutations comprise one or more subclonal SNV mutations.

Subclonal SNV mutations are those that are not present in all cells of a tumor because the mutation arose only after the tumor had originated and become partially grown, such that as the tumor grows further the mutation is present in only some cells of the tumor. EX1002 ¶ 205.

Forshew discloses detection of a subclonal SNV mutation, an *EGFR* mutation only present in two of the eight tissue regions sampled. EX1002 ¶ 206; EX1003.008, Fig. 4(A). The difference between the *EGFR* SNV between tumor samples would have established the presence of a subclonal mutation to a POSA. EX1002 ¶ 206. At a minimum, Forshew in view of the knowledge of a POSA renders this claim obvious because a POSA would have understood that cancerous tumors mutate constantly, and that some of those mutations occur only in a subset of the tumor cells. *Id.* ¶¶ 204, 207. As all SNVs can be detected through whole genome sequencing of the tumor and healthy tissue, a POSA would have understood that some of the detected SNVs would be subclonal. *Id.* A POSA would have been motivated to monitor subclonal SNVs for the benefit of improved detection, prognosis, and treatment. *Id.*

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5. Claim 5: The method of claim 1 wherein the SNV mutations comprise one or more clonal SNV mutations and one or more subclonal SNV mutations.

Forshew in view of a POSA's knowledge renders obvious the method of claim 1, wherein the SNV mutations comprise one or more clonal SNV mutations and one or more subclonal SNV mutations. EX1002 ¶ 208. As discussed above in connection with claims 3-4, Forshew teaches and renders obvious detecting both clonal and subclonal SNV mutations in circulating tumor DNA from plasma samples. *See supra* §§ X.A.3-4; EX1002 ¶¶ 209-210.

6. Claim 6: The method of claim 1, wherein the tumor sample of the subject is a tumor tissue sample.

Disclosed. *See supra* § X.A.1.b; EX1002 ¶¶ 211-212.

7. Claim 8: The method of claim 1, wherein the targeted multiplex amplification amplifies 20 to 50 target loci each encompassing a different tumor-specific SNV mutation.

Forshew in view of a POSA's knowledge renders this claim obvious. EX1002 ¶ 213. In parallel district court proceedings, Patent Owner presented no challenge to the obviousness of this claim other than to contend that claim 1 was not obvious based on the sequencing "depth" element. *See supra* § I.

As documented above in connection with claim 1, Forshew teaches multiplex amplification of 10 SNV targets in connection with its breast cancer experiments. *See supra* § X.A.1.b; EX1002 ¶ 214. As explained by Dr. Lennon, Forshew further specifically discloses conducting targeted multiplex amplification of 20 and 48

target amplicons as part of the TAm-Seq protocol. EX1002 ¶ 215; EX1003.004 (disclosing 48 primer pairs to amplify 5995 bases); *id.* at Table S1 (20 pairs of primers). Further, Forshew discloses the detection of 23 point mutations in plasma samples from ovarian cancer patients using TAm-Seq. EX1002 ¶ 216; EX1003 at Table S6; *see supra* § X.A.1.c. These disclosures represent a teaching of the multiplex amplification step of TAm-Seq being conducted using higher numbers of amplicons, including within the range of 20 to 50 multiplex. EX1002 ¶¶ 215-217.

At a minimum, Forshew renders obvious the ability to use even greater multiplex amplification as part of the TAm-Seq protocol because a POSA would have known that significantly greater multiplex amplification was already well-established. EX1002 ¶ 218. This knowledge is reflected in the prior art, including even in Patent Owner's own patents. *Id.* ¶¶ 218-219; EX1083 ¶ 119; EX1096 ¶¶ 19, 64, 201, 223, 258; EX1040.007. For instance, in Patent Owner's U.S. Patent No. 11,519,035, Patent Owner admitted that "the general belief in the art is that multiplexing PCR for sequencing is limited to about 100 assays in the same well." EX1049 at 48:25-29; EX1002 ¶ 219. If there was a "general belief" that one could perform a multiplex PCR for sequencing of up to 100 targets, then 20 to 50 would have presented no trouble.

In fact, it was known in the art to perform multiplex PCR for sequencing of a number of targets far in excess of 100. Patent Owner's own expert in the parallel

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district court proceedings, for instance, has opined before this tribunal in IPR2018-01317 that years before the priority date it was known to amplify up to 9,216 targets in a single tube for sequencing. EX1082 ¶ 98 ("The pre-pre-amplification step uses PCR amplification with 9,216 primer pairs, to amplify 9,216 target sequences."); EX1002 ¶ 220. In the district Court, Dr. Metzker reaffirmed his opinions from years earlier:

> Q. Okay. So in the PCR -- in the Fluidigm reference that you opined upon, that is teaching a single-tube multiplex PCR of over 9,000 targets for sequencing; correct?
>
> A. It does have a preamplification step that does target at multiplex PCR.
>
> Q. Of over 9,000 targets; correct?
>
> A. That's what they report.

EX1052 at 87:24-88:6; *see also* EX1002 ¶ 220; EX1083 ¶ 119. As Dr. Lennon explains, numerous other references teach multiplex PCR of far more than 20 targets. EX1002 ¶¶ 218-220. As such, a POSA would have had a reasonable expectation of pursuing such an approach. And the motivation to do so is natural: including more targets in the process allows one to track a broader spectrum of cancer-related mutations and hence better track and detect the cancer over time. *Id.* ¶ 221.

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8. Claim 9: The method of claim 1, wherein the targeted multiplex amplification amplifies 50 to 100 target loci each encompassing a different tumor-specific SNV mutation.

As discussed with respect to claims 1 and 8, Forshew teaches using TAm-Seq with 48 sequence-specific primer pairs to amplify 5995 bases. EX1002 ¶ 223; EX1003.004, Fig. 1A; *see supra* §§ X.A.1.c, X.A.7. Additionally, for the same reasons stated above in connection with claim 8, Forshew in view of the knowledge of the POSA renders obvious amplifying higher numbers of target loci, including 50 to 100. *See supra* § X.A.7; EX1002 ¶¶ 222, 224.

9. Claim 10: The method of claim 1, wherein the method further comprises designing PCR primers or hybrid capture probes targeting the plurality of SNV mutations identified in the tumor sample.

Forshew discloses, as discussed for claim 1, designing "[t]arget-specific primers [] with universal primer sequences (termed CS1 and CS2) appended at the 5'-end (table S1)." EX1002 ¶¶ 225-228; EX1003 at S2, Figure S1 ("PCR strategy and primer design."); *see supra* § X.A.1.c.

10. Claim 11: The method of claim 1, wherein the method further comprises performing barcoding PCR prior to the sequencing.

Forshew discloses that both "[p]latform-specific adaptors and barcodes are attached by PCR following the single-plex amplification step" and that the sequencing adaptors are necessary for sequencing. EX1003 at Table S2, .004; *see also id.* at .004 ("Sequencing adaptors were separately attached at either end and the

products [then] mixed together, ***such that single-end sequencing generated*** separate sets of forward and reverse reads."); EX1002 ¶¶ 229-230, 232. This is shown in Forshew Figure S1. EX1003 at Fig. S1; EX1002 ¶ 230.

As discussed above with respect to claim 1, to the extent the claims are construed to exclude intermediate PCR steps between the targeted multiplex amplification and sequencing, a POSA would have found it obvious to include the barcode(s) in the sequence-specific primers used in the targeted multiplex amplification, as this would allow the amplification step to be performed using only a single PCR amplification step, simplifying the process. EX1002 ¶ 231; *see supra* § X.A.1.c.

11. Claim 12: The method of claim 1, wherein the method further comprises detecting recurrence and/or metastases of the cancer from the SNV mutations detected in the cell-free DNA.

Forshew teaches using "TAm-Seq to noninvasively identify the origin of metastatic ***relapse*** in a patient with multiple primary tumors" and that "a method that measures multiple mutations in parallel can have a low likelihood of a false-negative result even if the detection rate for each mutation is less than 50%." EX1002 ¶¶ 233-234, 236; EX1003.002; EX1003.011. Forshew further explains that it uses "TAm-Seq to monitor tumor dynamics, and tracked 10 concomitant mutations in plasma of a metastatic breast cancer patient over 16 months." EX1003.002; EX1002 ¶¶ 233-234, 236. The ability to monitor mutations associated with cancers

was well-known in the art. *See, e.g.*, EX1104 (disclosing monitoring *EGFR* mutations in recurrent cancer); EX1002 ¶ 235.

12. Claim 13: The method of claim 1, wherein the cancer is colorectal cancer, lung cancer, bladder cancer, or breast cancer.

Forshew discloses analysis "of tumor material [] to identify tumor mutations in a patient with ***metastatic breast cancer***." EX1003.010; EX1002 ¶¶ 237-239; *see supra* § X.A.1.

13. Claim 14

a. [14.preamble]: A method for preparing a plasma sample of a subject having cancer or suspected of having cancer useful for detecting one or more single nucleotide variant (SNV) mutations in the plasma sample, the method comprising:

Disclosed. *See supra* § X.A.1.a; EX1002 ¶¶ 240-242.

b. [14.a]: performing whole exome sequencing or whole genome sequencing on a tumor sample of the subject to identify a plurality of tumor-specific SNV mutations;

Disclosed. *See supra* § X.A.1.c; EX1002 ¶¶ 243-244.

c. [14.b]: performing targeted multiplex amplification to amplify 10 to 500 target loci each encompassing a different tumor-specific SNV mutation from cell-free DNA isolated from a plasma sample of the subject or DNA derived therefrom to obtain amplicons, wherein the target loci are amplified together in the same reaction volume; and

Disclosed. *See supra* § X.A.1.c; EX1002 ¶¶ 245-247.

d. [14.c]: sequencing the amplicons to obtain sequence reads, and detecting one or more of the tumor-specific SNV mutations present in the cell-free DNA from the sequence reads, wherein the method is capable of detecting an SNV mutation that is present in less than or equal to 0.015% of the cell-free DNA comprising the SNV locus.

Claim element 14.c is identical to claim element 1.c, until the "wherein" limitation. For the reasons stated above, the "sequencing" and "detecting" limitations of this element are taught in Forshew. *See supra* § X.A.1.d; EX1002 ¶ 248; *see also id.* ¶ 247. Likewise, if required, direct sequencing of amplicons would have been obvious. *See supra* § X.A.1.d; EX1002 ¶ 264.

As to the requirement for detecting an SNV that is present at a level less than or equal to 0.015%, Figure S3 of Forshew shows frequencies that could be detected with different confidence levels above the background read rate, including frequencies of 0.015% and below (*i.e.*, frequencies of 0.00015 and below). EX1003 at Fig. S3; *see also id.* at .004; EX1002 ¶ 251.

To the extent Patent Owner contends Forshew does not disclose sensitivity of 0.015%, it would have nonetheless been obvious in view of Forshew. EX1002 ¶¶ 249-263. As documented above in connection with the sequencing "depth" element of claim 1, it would have been obvious to increase sensitivity simply by increasing sequencing depth. *See supra* § X.A.1.c. Forshew expressly teaches that one would have been motivated to do this because "higher read depth" allows

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"for ***enhanced mutation detection*** without change to protocols." EX1003.011; EX1002 ¶¶ 249, 250, 252, 254.

Further, obtaining greater sensitivity by increasing sequencing depth was well-known in the art and there is no question that a POSA would have had a reasonable expectation of successfully achieving a sensitivity of 0.015% because this had already been accomplished long before the priority date. EX1002 ¶¶ 252-253, 255; EX1057; EX1062.010, Fig. 2, legend; EX1090; EX1091.036; EX1101; EX1105.001, Supplemental Fig. 2; EX1108.011. Forshew, for instance, teaches that mutations had long since been detected, including in ctDNA, by a slew of different methods down to a level of 1 in 10,000, which corresponds to a sensitivity of 0.01%. EX1003.010; EX1002 ¶ 252. These included studies focused on circulating tumor DNA, thus establishing not only that mutations could be detected with the claimed sensitivity in such samples, but that researchers were motivated to do so. As an example, the Diehl reference that is cited in Forshew specifically taught detection of mutations at 0.015%. EX1062.010 ("the fraction of mutant DNA fragments dropped to 0.015%"); EX1002 ¶ 255.

Likewise, as Dr. Lennon explains, as early as 2012, the Narayan reference taught a detection limit of 0.014% for mutations in circulating tumor DNA through the use of DNA sequencing. EX1086.004 ("Using this approach, we were able to reduce the frequency of miscalls of specific mutations from known wild-type

samples to a median value of 0.014%"); EX1002 ¶ 256. As Narayan explains, the "deep sequencing approach described above shows the successful application of principles that we believe could form the basis of a practical diagnostic test to measure tumor-derived DNA levels in blood." EX1086.006; EX1002 ¶ 256. Patent Owner has made similar arguments in other proceedings. EX1002 ¶ 256.

While claim 14 has not been at issue in the district court, Patent Owner may nonetheless raise similar arguments here for sensitivity as it raised in district court for "sequencing depth." *See supra* Section X.A.1.d.i. Should Patent Owner do so, Dr. Lennon thoroughly rebuts such arguments. EX1002 ¶¶ 257-263.

14. Claim 15: The method of claim 14, wherein the sequencing has a depth of read of at least 50,000 per target locus.

For the same reasons discussed above with respect to claim 1, Forshew discloses and, at a minimum, renders obvious this claim. *See supra* § X.A.1.d; EX1002 ¶¶ 265-266.

15. Claim 16: The method of claim 14, wherein the cell-free DNA comprises circulating tumor DNA.

Disclosed. *See supra* § X.A.2; EX1002 ¶¶ 267-268.

16. Claim 17: The method of claim 14, wherein the SNV mutations comprise one or more clonal SNV mutations.

Disclosed. *See supra* § X.A.3 EX1002 ¶¶ 269-270.

17. Claim 18: The method of claim 14, wherein the SNV mutations comprise one or more subclonal SNV mutations.

Disclosed. *See supra* § X.A.4; EX1002 ¶¶ 271-272.

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18. Claim 19: The method of claim 14, wherein the SNV mutations comprise one or more clonal SNV mutations and one or more subclonal SNV mutations.

Disclosed. *See supra* § X.A.5; EX1002 ¶¶ 273-274.

19. Claim 20: The method of claim 14, wherein the tumor sample of the subject is a tumor tissue sample.

Disclosed. *See supra* § X.A.6; EX1002 ¶¶ 275-276.

20. Claim 22: The method of claim 14, wherein the targeted multiplex amplification amplifies 20 to 50 target loci each encompassing a different tumor-specific SNV mutation.

For the same reasons discussed above with respect to claim 8, Forshew discloses and renders obvious this claim. *See supra* § X.A.7; EX1002 ¶¶ 277-278.

21. Claim 23: The method of claim 14, wherein the targeted multiplex amplification amplifies 50 to 100 target loci each encompassing a different tumor-specific SNV mutation.

For the same reasons discussed above with respect to claim 9, Forshew discloses and renders obvious this claim. *See supra* § X.A.8; EX1002 ¶¶ 279-280.

22. Claim 24: The method of claim 14, wherein the method further comprises designing PCR primers or hybrid capture probes targeting the plurality of SNV mutations identified in the tumor sample.

Disclosed. *See supra* § X.A.9; EX1002 ¶¶ 281-282.

23. Claim 25: The method of claim 14, wherein the method further comprises performing barcoding PCR prior to the sequencing.

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For the same reasons discussed above with respect to claim 11, Forshew discloses and renders obvious this claim. *See supra* § X.A.10; EX1002 ¶¶ 283-284.

24. Claim 26: The method of claim 14, wherein the method further comprises detecting recurrence and/or metastases of the cancer from the SNV mutations detected in the cell-free DNA.

Disclosed. *See supra* § X.A.11; EX1002 ¶¶ 285-286.

25. Claim 27: The method of claim 14, wherein the cancer is colorectal cancer, lung cancer, bladder cancer, or breast cancer.

Disclosed. *See supra* § X.A.12; EX1002 ¶¶ 287-288.

26. Claim 28: The method of claim 14, wherein the method is capable of detecting an SNV mutation that is present in 0.005% to 0.015% of the cell-free DNA comprising the SNV locus.

For the same reasons as claim 14.c, Forshew discloses and, at a minimum, renders obvious this claim. *See supra* § X.A.1.d; EX1002 ¶¶ 289-291.

B. Ground 2: Claims 3-5, 7, 17-19, And 21 Are Unpatentable Over Forshew In View Of Bai And/Or Bashashati, and a POSA's Knowledge

1. Claims 3 and 17: Clonal SNV Mutations

Claims 3 and 17 recite that "the SNV mutations comprise one or more clonal SNV mutations." As noted above, Forshew specifically discloses the detection of a clonal SNV mutation (a *TP53* mutation), which was present in eight tissue regions sampled. *See supra* § X.A.3.

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Nevertheless, to the extent Forshew is deemed not to disclose "clonal mutations," claims 3 and 17 would have been rendered obvious by Forshew in view of Bashashati and/or Bai. EX1002 ¶¶ 292-301. As Dr. Lennon explains, both clonal and subclonal mutations were a well-known and common categories of cancer-related mutation. EX1002 ¶ 299. A POSA would have understood that to monitor and track cancer effectively, one would need to be able to identify the various categories of cancer-related mutations, including clonal mutations. *Id*. This is clear from, for instance, Bashashati and Bai. *Id*.

For instance, Bashashati teaches generally that "cancers are assumed to originate from a monoclonal composition (the ancestral clone), with subsequent evolution leading to selective expansions of genomically distinct subclones." EX1004.002; EX1002 ¶ 299. Bashashati goes on to report at length regarding the distribution of different mutations (including clonal mutations) within the tumor. EX1004; *id.* at .002 ("A panel of shared, identical mutations, indicative of a single ancestral clonal origin, was evident…"); EX1002 ¶ 300. Likewise, Bai, which focuses on lung cancer, explains that the formation of lung cancer "is a multistage process by which monoclonal cancer cells gradually become heterogeneous owing to clonal evolution and genetic/epigenetic instability." EX1005.001; EX1002 ¶ 300.

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Thus, a POSA would have understood that cancer tumors generally encompass both clonal mutations that were present at the outset of tumor formation, along with subclonal variants that develop later over the lifecycle of the tumor. EX1002 ¶ 301. To effectively track and monitor cancer, a POSA would have found it obvious and would have been motivated to identify and detect the clonal mutations (along with the subclonal mutations). *Id*. A POSA would have had a reasonable expectation of successfully doing so because Forshew, Bashashati, and Bai all taught detection of clonal (and subclonal) cancer mutations generally in both tumor and cfDNA, including by the use of sequencing. *See, e.g.*, EX1004.002 ("Next-generation sequencing technology has enabled the study and quantification of clonal evolution and intratumoural diversity in cancer…."); EX1002 ¶ 301. Clonal mutations are merely a particular variety of mutation distinguished by time of origin with respect to tumor formation. EX1002 ¶ 299.

2. Claims 4 and 18: Subclonal SNV Mutations

Claims 4 and 18 recite that "the SNV mutations comprise one or more subclonal SNV mutations." As documented above, Forshew discloses detection of a subclonal SNV mutation: an *EGFR* mutation only present in two of the eight tissue regions sampled. *See supra* § X.A.4.

To the extent Forshew is deemed not to disclose subclonal mutations, claims 4 and 18 would have been obvious over Forshew in view of Bashashati and/or Bai.

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EX1002 ¶¶ 302-304. As set forth above for claims 3 and 17, Bashashati and Bai teach that tumors generally include both clonal and subclonal mutations. *See supra* § X.B.4; EX1002 ¶ 304. As such, a POSA would have been motivated to track and detect subclonal mutations because they are part and parcel of cancer tumors. EX1002 ¶ 304. Further, a POSA would have had a reasonable expectation of successfully doing so. *Id*. Indeed, Bashashati did precisely this. *See, e.g.*, EX1004.002 ("In addition, for a subset of cases (four patients), plasma (pre-operative and pre-anaesthetic) was used to identify the presence of clonally dominant and subclonal mutations through deep sequencing of ctDNA."); *id.* at .006 ("Observations of subclonal NF1 deletions reinforced evidence from the mutation data that important driver mutations may be acquired late in the evolutionary history of the tumour."); EX1002 ¶ 304.

3. Claims 5 and 19: Clonal and Subclonal SNV Mutations

Claims 5 and 19 recite that "the SNV mutations comprise one or more clonal SNV mutations and one or more subclonal SNV mutations." As above, Forshew discloses detection of both a clonal SNV mutation (a *TP53* mutation), which was present in eight tissue regions sampled (*see supra* § X.A.3) and a subclonal SNV mutation, an *EGFR* mutation only present in two of the eight tissue regions sampled (*see supra* § X.A.4).

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To the extent Forshew is deemed not to disclose one or more clonal SNV mutations and one or more subclonal mutations, claims 5 and 19 would have been obvious over Forshew in view of Bashashati and/or Bai. EX1002 ¶¶ 305-307. As set forth above in connection with claims 3 and 17 (*see supra* § X.B.1) and claims 4 and 18 (*see supra* § X.B.2), Bashashati and Bai teach that tumors generally include both clonal and subclonal mutations; EX1002 ¶ 307. As also set forth above, a POSA would have been motivated to track and detect clonal and subclonal mutations because they are part and parcel of cancer tumors and would have had a reasonable expectation of successfully doing so. *See supra* § X.B.1-2; EX1002 ¶ 307.

4. Claims 7 and 21: Clonal Heterogeneity

Claims 7 and 21 recite determining "clonal heterogeneity of the tumor sample," which pertains to determining the extent to which different regions of a tumor are composed of different variations of that particular cancer. As the '454 patent explains, "many cancers are heterogeneous meaning that different cells in a tumor are genetically distinct from other cells in the same tumor." EX1001 at 24:63-65; EX1002 ¶ 309. Accordingly, Example 13 discloses an example of assessing "tumor heterogeneity" wherein samples from various "regions" of a cancerous lung are collected and then analyzed by "whole exome sequencing" to determine the relative amounts of mutation present in each region. EX1001 at

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168:6-23; *see also id.* at 41:57-61, 42:4, 42:59-62, 41:65-42:6, Figs. 51A-B, 53A-B, 54A; EX1002 ¶ 309.

As Dr. Lennon explains, well before the '454 patent, it was known that tumor tissue was genetically heterogeneous. EX1002 ¶ 310; *see also, e.g.*, EX1003.002, .011; EX1005.002-.003, Figs. 1 and 2; EX1004.001, .007-.008. Forshew itself teaches, for instance, that "mutation profiles in different metastatic clones can differ significantly from each other or the parent primary tumor" and that there was thus a need to identify the range of mutations present in the cancer patient to improve monitoring and treatment. EX1003.002; EX1003.011; EX1002 ¶ 311. To this end, Forshew further teaches determining the heterogeneity of tumor samples, from an ovarian cancer patient at relapse, disclosing, for instance, that the *TP53* mutation could be in the left and right ovaries and omental mass at different frequencies. EX1003 at Fig. 4A, Fig. 4A, legend ("Percentages indicate mutant AFs."), Table 1; EX1002 ¶ 313; *id.* ¶ 312. A POSA would have understood this as establishing heterogeneity as to the alleles present within tumor tissue, and would have understood as well that this teaches heterogeneity as to the alleles present in different portions of the same tumor. EX1002 ¶ 313.

To the extent Patent Owner nonetheless contends that Forshew does not render obvious claims 7 and 21 because Forshew does not teach determining heterogeneity within an individual tumor, this nonetheless would have been obvious

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in view of Bai and/or Bashashati. EX1002 ¶¶ 314-318. Bai, for instance, discloses that "[m]utant frequencies varied widely throughout individual tumors, ranging between 5%-100% by DHPLC and 1%-100% by ARMS." EX1005.003; EX1002 ¶ 315. Bai further reports that a percentage of "samples were identified to carry intratumoral *EGFR* mutational heterogeneity by DHPLIC and ARMS." EX1005.003; EX1002 ¶ 315. Likewise, Bashashati teaches analyzing a fallopian tube lesion and determining that it "was composed of heterogeneous subclones" with further analysis revealing "two coexisting populations" in the lesion. EX1004.008; EX1002 ¶ 317. These different mutations were tracked in cfDNA using personalized NGS assays, thus monitoring clonal heterogeneity. EX1004.005 ("Cases 1 and 5 were enriched for the presence of mutations in the plasma that were also present in all intrapatient tumour samples, and thus part of the ancestral clone (Fisher exact test, $p < 0.05$; Figure 2)."); EX1002 ¶ 317.

A POSA seeking to practice Forshew's method in 2015 would have been motivated to determine clonal heterogeneity of a tumor because this would have provided a more complete picture of the genetic makeup of the cancer, which would have aided in the task of monitoring and tracking the cancer. EX1002 ¶ 294; EX1003.002, .010; EX1005.006; EX1004.001, Abstract. There is no question of reasonable expectation of success because multiple researchers had successfully determined clonal heterogeneity of a tumor. EX1002 ¶ 295.

C. Ground 3: Claims 14-20 and 22-28 Are Unpatentable Over Forshew In View Of Bentley and/or Narayan, and a POSA's Knowledge

1. Claim 14

As noted above, claim 14 would have been obvious over Forshew in view of a POSA's knowledge. *See supra* § X.A.13; EX1002 ¶ 319. Nevertheless, to the extent Forshew is deemed not to disclose detecting an SNV mutation present in less than or equal to 0.015% of the cfDNA, claim 14 would have been rendered obvious by Forshew in view of Bentley and/or Narayan. EX1002 ¶¶ 319-328.

Both Bentley and Narayan teach detection with this degree of sensitivity. Narayan teaches that a detection limit of 0.014% for mutations in circulating tumor DNA can be reached using DNA sequencing methods like TAm-Seq with high read depths. EX1086.003-.004 (disclosing "median depth of 108,467 reads per locus" with the result of "reduc[ing] the frequency of miscalls of specific mutations from known wild-type samples to a median value of 0.014%"); *see also* EX1086.001; EX1002 ¶ 320; *supra* § X.A.13.d. Bentley similarly teaches the correlation between the depth of read and the sensitivity in detecting mutations, at different levels of confidence, including that SNPs with a frequency between 0.014% and 0.018% can be detected with 95-99% confidence with a sequencing depth of 40,000, and at a frequency between 0.005% and 0.007% with 95-99% confidence with a

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sequencing depth of 100,000. EX1057 ¶ 88 (Table 2); *see also* EX1057 ¶ 85; EX1002 ¶ 321.

As Dr. Lennon explains, a POSA would have understood the desirability of detecting an SNV mutation present in less than or equal to 0.015% of the cfDNA comprising the SNV locus, and have been motivated to attain that level of sensitivity. EX1002 ¶¶ 325-326; EX1003.011; EX1086.004; EX1057 ¶ 88. Bentley and Narayan both also teach the desirability of the recited level of sensitivity in detecting SNVs, and that this can be met by increasing the depth of sequencing. EX1002 ¶¶ 320-321; EX1086.001, .003-.004; EX1057 ¶ 85, 88, 88 (Table 2). A POSA also would have understood them to be in the same field as the ’454 patent, each being directed to detecting rare genetic mutations using sequencing following DNA amplification and to be reasonably pertinent to the particular problem that the ’454 patent addresses. EX1002 ¶¶ 322-324; EX1001 at 24:63-65, 168:6-23, claim 14; EX1003.002-.004, .010-.011; EX1057 ¶ 90; EX1086.002-.004.

Thus, a POSA would have understood that increasing sequencing depth would have provided increased sensitivity and would have had a reasonable expectation of successfully detecting SNV mutations that are present in less than or equal to 0.015% of cfDNA, because this had already been accomplished in the art, including as disclosed in Bentley and Narayan. EX1002 ¶¶ 320-321, 327; EX1086.001, .003-.004; EX1057 ¶ 85, 88, 88 (Table 2).

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For these as well as the reasons above in Section X.A.13, claim 14 would have been obvious over Forshew in view of Bentley and/or Narayan and a POSA's knowledge. EX1002 ¶¶ 319-328.

2. Claims 15-20 and 22-28

For the same reasons above, claims 15-20 and 22-28 would have been obvious over Forshew in view of Bentley and/or Narayan, and a POSA's knowledge. *See supra* §§ X.A.13-X.B.26, X.C.1; EX1002 ¶ 329.

D. Ground 4: Claims 17-19 And 21 Are Unpatentable Over Forshew In View Of Bai and/or Bashashati and Bentley and/or Narayan, and a POSA's Knowledge

For the same reasons above, claims 17-19 would have been obvious over Forshew (*see supra* §§ X.A.16-X.A.18), and claims 17-19 and 21 would have been obvious over Forshew in view of Bai and/or Bashashati (*see supra* §§ X.B.1-X.B.4). EX1002 ¶¶ 330, 339.

Nevertheless, to the extent Forshew in view of Bai and/or Bashishati is deemed to fall short as to the recited detection sensitivity, the further combination with Bentley and/or Narayan would render the claims obvious for the same reasons above. *See supra* § X.C; EX1002 ¶¶ 331-339; EX1086.001, .003-.004; EX1057 ¶¶ 85, 88, 88 (Table 2); EX1003.011.

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XI. THE BOARD SHOULD REACH THE MERITS OF THIS PETITION

A. The Facts and Law Weigh Against Discretionary Denial under § 325(d)

The *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH* test does not support discretionary denial of institution under § 325(d). IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020) (precedential).

While Forshew was of record and considered during examination, the Examiner made several critical errors, and it is clear that the consideration of Forshew was defective and inadequate. *See supra* § III.B. Specifically, the Examiner erred materially, failing to appreciate that: (1) Forshew's pre-amplification step is multiplex amplification; and (2) a greater depth of sequencing and the resulting increased sensitivity would have been obvious because sequencing depth was a known result effective variable for increased sensitivity. *Id.*

After the Examiner rejected the claims as obvious over Forshew, Patent Owner argued Forshew did not disclose the use of the claimed "multiplex targeted amplification," asserting that "Forshew had considered but dismissed multiplex targeted amplification." EX1022.004.

Patent Owner's statement, however, was erroneous. Forshew ***does*** disclose multiplex targeted amplification. EX1003 at Supplement, Fig. 1B; EX1002 ¶ 150. This was confirmed repeatedly by Patent Owner's own expert, Dr. Metzker, in the North Carolina litigation:

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> Q. And you do agree that the Forshew (2012) paper that does disclose the use of a multiplex amplification; correct?
>
> A. ***Forshew (2012) does describe multiplex PCR***.
>
> * * *
>
> Q. You do agree, though, that the Forshew (2012) publication we've been looking at, that it does use multiplex targeted application; correct?
>
> A. In the preamplification step, ***it does use multiplex PCR***.

EX1052 at 65:15-18, 66:19-24. Thus, the Examiner materially erred by accepting Patent Owner's false statement and not maintaining the rejection of claims over Forshew.

While this error is enough to warrant that the Board now reconsider the validity of the '454 patent, the Examiner made yet another even more critical error during examination. Specifically, the Examiner inexplicably failed to issue a rejection of then-pending claim 2, which recited the use of a "sequencing depth" of at least 50,000. The Examiner appears to have neglected claim 2 entirely during examination. This was critical because, as summarized above, Patent Owner eventually incorporated the "sequencing depth" limitation of then-pending claim 2 into the independent claims and secured allowance. *See supra* § III.B.

Allowing the claims on the basis of the sequencing "depth" element after giving this topic no scrutiny was material error. *Halliburton Energy Servs. Inc. v. US Well Servs. LLC*, IPR2021-01316, Paper 9 at 13-15 (PTAB Feb. 22, 2022)

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(instituting review after finding material error in examiner allowing claims on basis of added limitations from non-rejected claim where limitations were in the prior art). As above, Forshew, which was front and center during examination expressly teaches that increasing sequencing depth was obvious and natural, explaining that "[h]igher read depth" can be used to achieve "enhanced mutation detection without change to protocols." EX1003.011; EX1002 ¶ 167. The Examiner utterly failed to recognize this teaching. Likewise, there is no indication whatsoever that the Examiner considered a POSA's voluminous knowledge (detailed above) that depth of sequencing was a known result effective variable for increased sensitivity. EX1002 ¶¶ 168-169.

As confirmation of just how significant the Examiner's oversight was, Patent Owner has time and again explicitly argued that increasing sequencing "depth" was routine, conventional and obvious. EX1002 ¶ 170. Patent Owner, for instance, has argued that "[i]t was well-known by 2009 that the number of molecules analyzed is one component of sensitivity, and that higher sensitivity could be achieved by sequencing more molecules." EX1088.032-.033; *see also id.* at .033 ("And as discussed above, it was well-known by 2009 that by sequencing more molecules, sensitivity will necessarily increase.").

Patent Owner's expert witnesses have likewise endorsed the obviousness of similar claim limitations. For example, Dr. Quackenbush opined that "POSAs

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prior to November 6, 2009 were well aware that sequencing more molecules, or increasing sequencing depth, improves sensitivity," and that "the detection limit is determined by sequencing error rate and sequencing read depth (i.e., how many molecules are sequenced), reflecting the fact that there was a well-known correlation between the number of molecules sequenced and sensitivity." EX1094 ¶ 119; EX1002 ¶¶ 171-173. Patent Owner's expert in parallel district court litigation affirmed to this tribunal that in the 2010 timeframe, to "increase the accuracy of the Illumina GA sequencer, it would have been ***obvious***…to target regions of a genome with high sequence coverage." EX1082 ¶¶ 91, 214; EX1002 ¶ 173.

Notably, during prosecution, Patent Owner failed to provide the Examiner with any evidence documenting its extensive prior statements confirming the obviousness of increasing sequencing "depth." This additional fact illustrates the defective primary examination and further establishes that the Board should now take this opportunity to reconsider the validity of the '454 patent.

As the Examiner materially erred on two counts, both accepting Patent Owner's false claim regarding the prior art and neglecting to consider a plainly obvious claim limitation, there can be no basis for discretionary denial of institution under § 325(d).

Moreover, while nominally of record during examination due to their inclusion in an IDS, none of Bai, Bashashati, nor Narayan were the basis of a

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rejection, alone or in combination with any other reference. Bentley was not apparently of record, but is a continuation-in-part of Appl. No. 12/445,666, published as US2010/0086914, which nominally was of record by inclusion in an IDS. Neither Bentley nor its parent application were the basis of a rejection. Failure to reject claims over these references was also material error. *Satco Prods. Inc. v. Regents of the Univ. California*, IPR2021-00662, Paper 13 at 25 (PTAB Nov. 8, 2021) (finding material error in failure to apply references during examination). Such nominal consideration by Examiner is insufficient. *Id.* (Examiner initialing asserted references insufficient where numbers are large); EX1001 at 1-30 ("References Cited").

B. Fintiv Does Not Support Discretionary Denial

The parallel district-court proceedings do not justify discretionary denial under the § 314(a) factors identified in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (precedential) ("*Fintiv*"), as applied in *CommScope Technologies LLC v. Dali Wireless, Inc.*, IPR2022-01242, Paper 23 (PTAB Fed. 27, 2023) and *OpenSky Indus., LLC v. VLSI Tech. LLC*, IPR2021-01064, Paper 102 at 49 (PTAB Oct. 4, 2022) (precedential).[6]

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[6] *See also* USPTO Memorandum, Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation

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1. Factor 1: Likelihood Of A Stay

This factor weighs in favor of institution. As numerous district courts have recognized, "Congress intended for district courts to be liberal" in granting stays pending PTAB proceedings. *See, e.g.*, *IOENGINE, LLC v. PayPal Holdings, Inc.*, 2019 U.S. Dist. LEXIS 141545, at *10-11 (D. Del. Aug. 21, 2019) (liberal stay policy applies to IPR and CBM proceedings); 157 Cong. Rec. S1363 (daily ed. Mar. 8, 2011) (Sen. Schumer) (Congress placed "a very heavy thumb on the scale in favor of a stay being granted"). This case is no exception. *See, e.g.*, *NFC Tech. LLC v. HTC Am., Inc.*, 2015 WL 1069111, at *7 (E.D. Tex. Mar. 11, 2015) ("[A]fter the PTAB has instituted review proceedings, the parallel district court litigation ordinarily should be stayed.").

Moreover, district courts in North Carolina and Delaware routinely grant motions to stay pending IPR. *See, e.g.*, *Valencell, Inc. v. Apple Inc.*, 5-16-cv-00001 (E.D.N.C. Jun. 28, 2017) (granting motion to stay pending IPR); *Implus Footcare, LLC v. Maverick Sports Medicine, Inc. d/b/a Pro-Tec Athletics*, 5-15-cv-00659

("Memorandum") (June 21, 2022), available at https://www.uspto.gov/sites/default/files/documents/interim_proc_discretionary_denials_aia_parallel_district_court_litigation_memo_20220621_pdf.

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(E.D.N.C. Oct. 10, 2016) (same); *ThreatModeler Software Inc. v. IriusRisk, Inc.*, 1-22-cv-00912 (D. Del. Nov. 20, 2023) (same).

Further, as discussed below with respect to Factor 3, the district court cases are in very early stages and no invalidity contentions or summary judgment motions have been filed, making the possibility of a stay realistic. *Valencell, Inc. v. Apple Inc.*, 5-16-cv-00001, at 5 (E.D.N.C. Jun. 28, 2017) (granting motion to stay despite pending motions for summary judgment and to supplement invalidity contentions); *Implus Footcare, LLC v. Maverick Sports Medicine, Inc. d/b/a Pro-Tec Athletics*, 5-15-cv-00659 (E.D.N.C. Oct. 10, 2016) (granting motion to stay where "the case is at a very early stage, discovery is not complete, and a trial date has not been set"); *ThreatModeler Software Inc. v. IriusRisk, Inc.*, 1-22-cv-00912 (D. Del. Nov. 20, 2023) ("a stay pending final resolution of…IPR proceedings is in the best interest of the parties and promotes judicial economy because discovery is in its early stages"); *Sentient Sensors, LLC v. Xilinx, Inc.*, 1-22-cv-00173 (D. Del. Oct. 3, 2023) (granting motion to stay where "fact discovery in the above-captioned litigation is not complete, and whereas substantial work remains in this case including depositions, expert discovery, claim construction, and dispositive motions, and this case is at an early phase in the proceedings"). There is no reason a stay should be denied here and this factor favors institution.

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2. Factor 2: Proximity Of Trial Date To Final Written Decision

This factor favors institution. The trial in the consolidated District of Delaware litigation is scheduled for October 26, 2025 and there is no scheduled trial date in the North Carolina litigation. EX1115.014; EX1115.016; Memorandum at 3. The median time to trial from filing for civil actions in Middle District of North Carolina is 42.4 months. EX1118.022. With a filing date of July 28, 2023, this indicates a projected trial date in February 2027.

Thus, trial would likely occur (if at all) no earlier than October 26, 2025. *Mylan Pharms. Inc. v. Bayer Pharma Aktiengesellschaft*, IPR2022-00517, Paper 15 at 8-9 (PTAB Aug. 9, 2022) (evaluating median time to trial for factor 2). Petitioner expects a decision on institution within approximately 6 months, with a Final Written Decision a year after that, giving a projected statutory deadline of about mid-June, 2025, which is over four months before the scheduled trial date in the consolidated District of Delaware litigation. Therefore, this factor favors institution.

3. Factor 3: Investment In The Parallel Proceeding

This factor favors institution, or is at least neutral. The investment analysis focuses on work "completed at the time of the institution decision" that concerns "the merits of the invalidity positions." *Fintiv* at 9-10; *Sand Revolution II, LLC v.*

Cont'l Intermodal Group – Trucking LLC , IPR2019-01393, Paper 24 at 10 (PTAB June 16, 2020) (informative).

There has been essentially no relevant investment in the consolidated District of Delaware litigation. The parties have only recently served initial document requests, no documents have been produced, invalidity contentions have not been served, claim construction has not started, no depositions have been taken, nor has expert discovery begun. Initial invalidity contentions are not due until February 2024 and claim construction will not begin until at least March 2024 and would continue into September 2024. EX1115.007-.009. Further, "the most burdensome parts of the case—filing and responding to pretrial motions, preparing for trial, going through the trial process, and engaging in post-trial motions practice—all lie in the future." *CyWee Grp. Ltd. v. Samsung Elecs. Co. Ltd.*, No. 2:17-cv-00140-WCB-RSP, 2019 WL 11023976, at *6 (E.D. Tex. Feb. 14, 2019). NeoGenomics has filed a § 101 Motion to Dismiss, but this is irrelevant to *inter partes* review. EX1117.

The investment in the North Carolina litigation is highly limited, and significant work lies ahead. There has been minimal investment in developing invalidity positions as part of Patent Owner's preliminary injunction proceedings, but a full case schedule of fact and expert discovery lies ahead. EX1051; EX1053; EX1054. The case schedule has yet to be set by the court in light of the pending

preliminary injunction motion. There will still be fact and expert depositions, expert reports, and claim construction, as well as further document review and production and written discovery. Again, "the most burdensome parts of the case…all lie in the future." *CyWee Grp.,* 2019 WL 11023976, at *6.

Whatever emphasis Patent Owner may place on investment made during the preliminary injunction proceedings falls short as the circumstances here are similar to those in *Sand Revolution*. There, the panel found that "aside from the district court's *Markman* Order, much of the district court's investment relates to ancillary matters untethered to the validity issue itself" and "much work remains in the district court case as it relates to invalidity." *Sand Revolution* at 11. Here, the majority of the limited investment goes to issues other than invalidity and, to the extent invalidity is addressed, much goes to issues that cannot be addressed in this proceeding such as §101 eligibility, § 112 written description, and improper inventorship. EX1053. Further, the obviousness challenge to invalidity is limited to one of two independent claims and to only three claims of twenty-eight in total. EX1053.008; EX1001. Again, NeoGenomics has filed a § 101 Motion to Dismiss, but this is irrelevant to *inter partes* review. EX1116.

Thus, this third factor favors institution.

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4. Factor 4: Overlap of Issues

This factor favors institution, or is at least neutral. In the parallel proceeding in North Carolina, Patent Owner's obviousness challenge to invalidity as set forth in its preliminary injunction motion is limited to one of two independent claims and to only three claims of twenty-eight in total. In the parallel proceeding in Delaware, Patent Owner has merely asserted that Petitioner[7] "has infringed and continues to infringe at least one claim of the '454 patent." EX1113 ¶ 39. However, the obviousness challenge in the petition goes to both independent claims and all twenty-eight claims in the '454 patent. As the obviousness challenge in the petition concerns twenty-five claims not addressed in the parallel proceeding in North Carolina, the overlap of issues is minimal, and this fourth factor favors institution.

5. Factor 5: Whether Petitioner And Defendant In Parallel Proceeding Are The Same

This factor is neutral, because it is often the case for a patent asserted in district court to be challenged at the Board.

6. Factor 6: Other Circumstances, Including the Merits

This factor strongly favors institution. As set forth above, the Petition sets forth "[c]ompelling, meritorious challenges…in which the evidence, if unrebutted at trial, would plainly lead to a conclusion that one or more claims are unpatentable by

[7] See footnote 3 above.

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a preponderance of the evidence." *OpenSky* at 49 (citing Memorandum). For the reasons set forth herein, grounded on the evidence of record, it is highly likely that the Petitioner will prevail with respect to at least one challenged claim, and Petitioner therefore sets forth a compelling, meritorious challenge. *Id.* Thus, the Board should institute *inter partes* review because "compelling, meritorious challenges will be allowed to proceed at the PTAB even where district court litigation is proceeding in parallel." *Id.* (quoting Memorandum at 4).

XII. CONCLUSION

Petitioner respectfully submits that the Board should institute IPR and cancel the challenged claims.

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APPENDIX A: CHALLENGED CLAIM LISTING

No.	Limitation
1	A method for preparing a plasma sample of a subject having cancer or suspected of having cancer useful for detecting one or more single nucleotide variant (SNV) mutations in the plasma sample, the method comprising: (a) performing whole exome sequencing or whole genome sequencing on a tumor sample of the subject to identify a plurality of tumor-specific SNV mutations; (b) performing targeted multiplex amplification to amplify 10 to 500 target loci each encompassing a different tumor-specific SNV mutation from cell-free DNA isolated from a plasma sample of the subject or DNA derived therefrom to obtain amplicons having a length of 50-150 bases, wherein the target loci are amplified together in the same reaction volume; and (c) sequencing the amplicons to obtain sequence reads, and detecting one or more of the tumor-specific SNV mutations present in the cell-free DNA from the sequence reads, wherein the sequencing has a depth of read of at least 50,000 per target locus.
2	The method of claim 1, wherein the cell-free DNA comprises circulating tumor DNA.
3	The method of claim 1, wherein the SNV mutations comprise one or more clonal SNV mutations.
4	The method of claim 1, wherein the SNV mutations comprise one or more subclonal SNV mutations.
5	The method of claim 1, wherein the SNV mutations comprise one or more clonal SNV mutations and one or more subclonal SNV mutations.
6	The method of claim 1, wherein the tumor sample of the subject is a tumor tissue sample.
7	The method of claim 1, wherein the method further comprises determining clonal heterogeneity of the tumor sample.

8	The method of claim 1, wherein the targeted multiplex amplification amplifies 20 to 50 target loci each encompassing a different tumor-specific SNV mutation.
9	The method of claim 1, wherein the targeted multiplex amplification amplifies 50 to 100 target loci each encompassing a different tumor-specific SNV mutation.
10	The method of claim 1, wherein the method further comprises designing PCR primers or hybrid capture probes targeting the plurality of SNV mutations identified in the tumor sample.
11	The method of claim 1, wherein the method further comprises performing barcoding PCR prior to the sequencing.
12	The method of claim 1, wherein the method further comprises detecting recurrence and/or metastases of the cancer from the SNV mutations detected in the cell-free DNA.
13	The method of claim 1, wherein the cancer is colorectal cancer, lung cancer, bladder cancer, or breast cancer.
14	A method for preparing a plasma sample of a subject having cancer or suspected of having cancer useful for detecting one or more single nucleotide variant (SNV) mutations in the plasma sample, the method comprising: (a) performing whole exome sequencing or whole genome sequencing on a tumor sample of the subject to identify a plurality of tumor-specific SNV mutations; (b) performing targeted multiplex amplification to amplify 10 to 500 target loci each encompassing a different tumor-specific SNV mutation from cell-free DNA isolated from a plasma sample of the subject or DNA derived therefrom to obtain amplicons, wherein the target loci are amplified together in the same reaction volume; and (c) sequencing the amplicons to obtain sequence reads, and detecting one or more of the tumor-specific SNV mutations present in the cell-free DNA from the sequence reads, wherein the method is capable of detecting an SNV mutation that is present in less than or equal to 0.015% of the cell-free DNA comprising the SNV locus.
15	The method of claim 14, wherein the sequencing has a depth of read of at least 50,000 per target locus.

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16	The method of claim 14, wherein the cell-free DNA comprises circulating tumor DNA.
17	The method of claim 14, wherein the SNV mutations comprise one or more clonal SNV mutations.
18	The method of claim 14, wherein the SNV mutations comprise one or more subclonal SNV mutations.
19	The method of claim 14, wherein the SNV mutations comprise one or more clonal SNV mutations and one or more subclonal SNV mutations.
20	The method of claim 14, wherein the tumor sample of the subject is a tumor tissue sample.
21	The method of claim 14, wherein the method further comprises determining clonal heterogeneity of the tumor sample.
22	The method of claim 14, wherein the targeted multiplex amplification amplifies 20 to 50 target loci each encompassing a different tumor-specific SNV mutation.
23	The method of claim 14, wherein the targeted multiplex amplification amplifies 50 to 100 target loci each encompassing a different tumor-specific SNV mutation.
24	The method of claim 14, wherein the method further comprises designing PCR primers or hybrid capture probes targeting the plurality of SNV mutations identified in the tumor sample.
25	The method of claim 14, wherein the method further comprises performing barcoding PCR prior to the sequencing.
26	The method of claim 14, wherein the method further comprises detecting recurrence and/or metastases of the cancer from the SNV mutations detected in the cell-free DNA.
27	The method of claim 14, wherein the cancer is colorectal cancer, lung cancer, bladder cancer, or breast cancer.
28	The method of claim 14, wherein the method is capable of detecting an SNV mutation that is present in 0.005% to 0.015% of the cell-free DNA comprising the SNV locus.

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 et seq., the undersigned certifies that this document complies with the type-volume limitations. This document contains 13,983 words as calculated by the "Word Count" feature of Microsoft Word 2016, the word processing program used to create it.

Respectfully submitted,

WEIL, GOTSHAL AND MANGES LLP

Dated: December 19, 2023

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,530,454 WITH NEOGENOMICS LABORATORIES, INC'S EXHIBIT LIST, POWER OF ATTORNEY AND EXHIBITS 1001-1132** are being served on December 19, 2023, via Priority Express Mail (Fed Ex) pursuant to 37 C.F.R. § 42.105 and § 42.6(e) to the Patent Owner at the address below:

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