

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS INC.,
Petitioner,

v.

PERSONALIS, INC.,
Patent Owner.

IPR2024-00170
Patent No. 11,584,968

**PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 11,584,968**

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TABLE OF CONTENTS

	<u>Page</u>
I. INTRODUCTION	1
II. GROUNDS FOR STANDING.....	5
III. MANDATORY NOTICES	5
A. Real Party-In-Interest	5
B. Related Matters.....	5
C. Lead and Back-up Counsel and Service Information	7
D. Additional Service Information.....	7
IV. THE '968 PATENT	7
V. LEVEL OF ORDINARY SKILL IN THE ART.....	8
VI. BACKGROUND KNOWLEDGE OF A POSA	9
A. Genes and Mutations	9
B. Nucleic Acid Sequencing	10
C. Personalized Biomedical Monitoring.....	11
VII. KEY PRIOR ART	14
A. Chan.....	14
B. Ley	14
C. Okosun-II.....	14
VIII. GROUNDS FOR THE CHALLENGES	15
IX. LISTING OF CHALLENGED CLAIMS	16
X. CLAIM CONSTRUCTION	20
A. Preamble (Claim 1)	20

	<u>Page</u>
B. “mosaic variant” (Claim 1)	21
C. “(d) wherein said report comprises....” (Claim 1) / “wherein said predicting, diagnosing, and/or prognosing of (d) comprises....” (Claim 12) / “providing a recommendation...” (Claim 8)	23
D. “capture probe” (Claim 13)	24
XI. THE BOARD SHOULD CANCEL THE CHALLENGED CLAIMS	26
A. Ground 1: Chan anticipates claims 1-4, 7, and 9-12	26
1. Claim 1	26
2. Claim 2	32
3. Claim 3	33
4. Claim 4	33
5. Claims 7 and 10	34
6. Claim 9	34
7. Claim 11	34
8. Claim 12	34
B. Ground 2: Chan renders claims 1-13 obvious	35
1. Claim 2	35
2. Claims 5 and 6	36
3. Claim 8	37
4. Claim 13	37
C. Ground 3: Ley renders claims 1-13 obvious.	38
1. Overview of Ley	38

	<u>Page</u>
2. Adaptations of Ley’s Approach to Solid Tumors.....	39
3. Claim 1	43
4. Claim 2	52
5. Claim 3	57
6. Claim 4.....	57
7. Claims 5 and 6.....	57
8. Claim 8.....	58
9. Claim 9.....	58
10. Claim 11	58
11. Claim 12.....	59
12. Claims 7, 10, and 13	59
D. Ground 4: Okosun-II anticipates claims 1, and 8-13.	59
1. Claim 1	59
2. Claim 8.....	65
3. Claim 9.....	66
4. Claim 11	66
5. Claim 12.....	67
6. Claim 13.....	67
E. Ground 5: Okosun-II renders claims 1-13 obvious.....	68
1. Claim 1	68
2. Claim 2.....	69
3. Claim 3.....	72

	<u>Page</u>
4. Claim 4.....	72
5. Claims 5 and 6.....	72
6. Claims 7, 10, and 13	73
F. There is no evidence of secondary considerations.....	75
G. The Board should not exercise its discretion under Section 325(d).	76
XII. CONCLUSION.....	78

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH,</i> IPR2019-01469, Paper 6.....	76, 77
<i>Apple Inc. v. Telefonaktiebolaget LM Ericsson,</i> IPR2022-00457, Paper No. 7	78
<i>In re DiStefano,</i> 808 F.3d 845 (Fed. Cir. 2015)	23
<i>Foresight Diagnostics Inc. v. Personalis, Inc.,</i> Nos. IPR2023-00224, -00317, -00545, -00546	6
<i>Foresight Inc. v. Personalis Inc.,</i> IPR2023-00224, Paper No. 11	25, 26, 28
<i>Fox Factory, Inc. v. SRAM, LLC,</i> 944 F.3d 1366 (Fed. Cir. 2019)	76
<i>In re Ngai,</i> 367 F.3d 1336 (Fed. Cir. 2004)	24
<i>Personalis, Inc. v. Foresight Diagnostics Inc.,</i> No. 1:22-cv-01913-CNS-NRN	passim
<i>Personalis, Inc. v. Foresight Diagnostics Inc.,</i> No. 1:23-cv-01623-CNS-NRN	5, 6
<i>Praxair Distribution, Inc. v. Mallinckrodt Hosp. Prod. IP Ltd.,</i> 890 F.3d 1024 (Fed. Cir. 2018)	23, 24
<i>Rowe v. Dror,</i> 112 F.3d 473 (Fed. Cir. 1997)	20
<i>Yita LLC v. MacNeil IP</i> LLC, IPR2023-00172, Paper No. 12	76

Page

Statutes

35 U.S.C. §102(b)(1).....15

35 U.S.C. §325(d) 76

Rules

37 C.F.R. §42.8(b)(2).....5

PETITIONER’S EXHIBIT LIST

EX1001	U.S. Patent No. 10,584,968 issued to West
EX1002	Rebecca J. Leary <i>et al.</i> , “Development of Personalized Tumor Biomarkers Using Massively Parallel Sequencing,” <i>Science Translational Medicine</i> (2010) (<i>Leary</i>)
EX1003	Quake <i>et al.</i> , WO 2011/057061 (<i>Quake</i>)
EX1004	Reserved
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EX1007	Lira Mamanova <i>et al.</i> , “Target-enrichment strategies for next-generation sequencing,” <i>Nature</i> (2010) (<i>Mamanova</i>)
EX1008	Chan et al., “Cancer Genome Scanning in Plasma: Detection of Tumor-Associated Copy Number Aberrations, Single-Nucleotide Variants, and Tumoral Heterogeneity by Massively Parallel Sequencing,” <i>Clinical Chemistry</i> , January 1, 2013
EX1009	Reserved
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EX1011	Reserved
EX1012	Timothy J. Ley <i>et al.</i> , “DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome,” <i>Nature</i> (2008) (<i>Ley</i>)
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EX1017	Reserved
EX1018	Reserved
EX1019	Reserved
EX1020	Reserved
EX1021	Declaration of Ingrid Hsieh-Yee, Ph.D.
EX1022	Reserved
EX1023	<i>Curriculum Vitae</i> of John Quackenbush
EX1024	https://www.garvan.org.au/research/kinghorn-centre-for-clinical-genomics/learn-about-genomics/for-gp/genetics-refresher-1/types-of-variants
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EX1030	Reserved

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EX1032	Reserved
EX1033	Reserved
EX1034	Reserved
EX1035	Reserved
EX1036	Reserved
EX1037	Infringement Claim Chart for U.S. Patent No. 10,450,611; Ex. D to Patent Owner’s FAC
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EX1047	Reserved
EX1048	Reserved

EX1049	Reserved
EX1050	Reserved
EX1051	Reserved
EX1052	Reserved
EX1053	Reserved
EX1054	Reserved
EX1055	Reserved
EX1056	Reserved
EX1057	Reserved
EX1058	Reserved
EX1059	Reserved
EX1060	Reserved
EX1061	Reserved
EX1062	Reserved
EX1063	Reserved
EX1064	Reserved
EX1065	Reserved
EX1066	Reserved
EX1067	Reserved
EX1068	Reserved
EX1069	Reserved

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EX1073	Reserved
EX1074	Reserved
EX1075	Reserved
EX1076	Reserved
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EX1102	J. Okosun, <i>et al.</i> , "Integrated genomic analysis identifies recurrent mutations and evolution patterns driving the initiation and progression of follicular lymphoma," Nature America (2014) (Okosun II)
EX1103	Michael A. Chapman, <i>et al.</i> , "Initial genome sequencing and analysis of multiple myeloma, Nature (2011)
EX1104	William Lee, <i>et al.</i> , "The mutation spectrum revealed by paired genome sequences from a lung cancer patient," 27 May 2010 (Lee 2010)
EX1105	Li Ding <i>et al.</i> , "Genome remodelling in a basal-like breast cancer metastasis and xenograft," Nature (2010) (Ding 2010)

EX1106	Yan-Fang Guan, <i>et al.</i> , "Application of next-generation sequencing in clinical oncology to advance personalized treatment of cancer," Chinese J Cancer, 2012 Oct. 31 (10):463-470 (Guan)
EX1107	<i>Personalis v. Foresight</i> , First Amended Complaint, D. Colo., Case No. 1:23-cv-01623, Dkt. 21, filed August, 31, 2023
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EX1113	Supplementary Information (from Okosun II)
EX1114	Furneaux Declaration (from IPR2023-00224, -00317)
EX1115	West Declaration (from IPR2023-00224, -00317)
EX1116	Patent Owner Response from IPR2023-00224
EX1117	Dawson Supplementary Materials
EX1118	Christopher T. Saunders, <i>et al.</i> , "Strelka: accurate somatic small-variant calling from sequenced tumor-normal sample pairs, Bioinformatics, May 10, 2012
EX1119	Ex. F. to First Amended Complaint (Case 2)
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EX1122	Patent Owner Preliminary Response from IPR2023-00224 ('394)
EX1123	Patent Owner Preliminary Response from IPR2023-00317 ('033)
EX1124	Patent Owner Response from IPR2023-00317 ('033)
EX1125	USPTO Proposed Rules (88 Fed. Reg. 24503)
EX1126	<i>Personalis v. Foresight</i> , Personalis' Opposition to Defendant's Motion to Consolidate Related Cases, D. Colo., Case No. 1:22-cv-01913, Dkt. 66-1

I. INTRODUCTION

Foresight Diagnostics Inc. (“Petitioner” or “Foresight”) requests *inter partes* review and cancellation of claims 1-13 of U.S. Patent No. 11,584,968 (“the ’968 patent”), entitled “Methods for Using Mosaicism in Nucleic Acids Sampled Distal to Their Origins” and assigned to Personalis, Inc. (“Patent Owner,” or “Personalis”).

The parties are currently engaged in co-pending litigation in the District of Colorado and in co-pending proceedings before the Board. *See infra* Section III.B. The co-pending litigation involves two related cases, the first of which was filed in August 2022, and which is currently stayed pending instituted IPRs (the “Case 1 IPRs”) on each of the four patents-in-suit. Two weeks after the Board instituted review on Foresight’s first two Case 1 petitions, Personalis filed another patent infringement suit, accusing the same features of the same diagnostic test of infringing three related patents, including the ’968 patent.¹ Ex1107.

In its complaint, Personalis argues that the alleged inventions of the ’968 patent constitute:

[A]nalyzing a biological sample obtained from a subject being screened for a cancer by using whole genome sequencing (WGS) of the patient’s tumor DNA and matching normal samples to identify a set of single

¹ Foresight’s motion to consolidate and stay the second case is currently pending in the Colorado litigation. Ex1121.

nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms, or other variants present only in the patient's tumor and then looking for those variants in cell-free DNA (cfDNA) from a subsequently obtained blood or other sample in order to predict, diagnose, and/or prognose a status or outcome of a cancer in that patient.

Ex1107, ¶18. Thus, Personalis conceded that its infringement theory requires the term “mosaic variant” to encompass essentially any tumor-specific somatic mutation in a cancer patient. *Id.* ¶¶18, 43-44. As a result, under Personalis's understanding, the claims require (i) performing whole genome sequencing (“WGS”) on a patient's tumor DNA and matched normal sample, such as blood; (ii) comparing the obtained sequence information to identify “mosaic variants,” i.e., essentially any somatic mutations present in the tumor sample that were not present in the normal DNA; and (iii) serially monitoring the patient's cancer for those mutations over time. By the time the provisional application cited on the face of the '968 patent was filed² in October 2014, such methods had long been routine in the art. The Petition establishes this with three exemplary references: Ley, Chan, and Okosun-II.

² Foresight does not concede that the provisional application provides adequate support for the claims.

Ley was a landmark study that “presented the first whole-genome sequence” of an acute myeloid leukemia patient’s “tumour sample (sequenced at >30-fold coverage) and a normal skin sample.” Ex1120.1. “The normal sample allowed the team to filter out somatic mutations from germline ones, a crucial step towards distilling the genetic lesions that were driving the disease.” *Id.* Highlighting the significance of Ley’s work, it was named “Milestone 6” in *Nature*’s immersive publication “Milestones in Genetic Sequencing,”³ and was declared “[a] sequencing revolution in cancer.” *See id.* *Nature* further explained that “[t]he groundbreaking work by Ley et al. confirmed what many had suspected: unbiased, genome-wide sequencing can unmask novel genes that likely contribute to tumorigenesis and offers a palette of potentially druggable targets,” findings which were rapidly applied to analyze “[t]he genomic landscapes of different cancer types....” *Id.*

Significantly, Example 4 of the ’968 patent – the only example colorably relevant to what Personalis contends was invented – attempts to pass off as its own (in 2014) essentially the same experiment that Ley published in 2008. Titled “Detecting Variants in Leukemia by Tumor Versus Normal Analysis,” the example⁴ proposes:

³ Available at <https://www.nature.com/immersive/d42859-020-00099-0/index.html> (last accessed 11/21/23).

⁴ Example 4 appears to be prophetic and includes no results or data.

Nucleic acids are extracted from both the plasma and the leukocytes, the nucleic acids are sequenced, and variants are detected in the samples. In this example, the sequence identified in the cfDNA is the “normal” sample and the leukocytes are the “tumor” sample. The sequences are compared and variants that occur only in the leukemia are identified.

Ex1001, 53:44-54:3. The only difference between this example, Ley, and the claims is minor: the choice of cfDNA as a “normal” sample, whereas Ley used normal tissue. And as explained further below, the choice of appropriate sources of tumor nucleic acids and germline control nucleic acids for experiments of this sort was a matter of routine design well before 2014.

Chan and Okosun-II – studies which post-date Ley and pre-date the ’968 patent – discuss exemplary applications of paired tumor versus normal WGS to identify tumor-specific variants (“mosaic variants” under Personalis’s construction in litigation, *see infra* Section X.B), which are then monitored over time in follow-up samples. Chan analyzed paired hepatocellular carcinoma (“HCC”) tumor samples and matching leukocytes to identify tumor-specific variants, and then serially monitored them by analyzing the cfDNA present in plasma samples. *See* Grounds 1-2. Okosun-II investigated follicular lymphoma (“FL”) and analyzed paired lymph node tumor biopsies and matching peripheral blood to identify tumor-specific variants, before performing follow-up analysis using serially obtained tumor

biopsies. *See* Grounds 4-5. Taken together, the Chan and Okosun-II grounds anticipate 11 of the 13 challenged claims and render the others obvious.

For the reasons set forth below, and as further explained in the declaration of Petitioner’s expert genome scientist John Quackenbush, Ph.D., Ex1100 (“Quackenbush”), the challenged claims should be cancelled.

II. GROUNDS FOR STANDING

Petitioner certifies that the ’968 patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging its claims on the grounds identified in this petition.

III. MANDATORY NOTICES

A. Real Party-In-Interest

Petitioner Foresight Diagnostics Inc. is the real party-in-interest with respect to this petition for *inter partes* review.

B. Related Matters

Petitioner identifies the following related proceedings pursuant to 37 C.F.R. §42.8(b)(2):

- *Personalis, Inc. v. Foresight Diagnostics Inc.*, No. 1:22-cv-01913-CNS-NRN (District of Colorado) (“Case 1”)
- *Personalis, Inc. v. Foresight Diagnostics Inc.*, No. 1:23-cv-01623-CNS-NRN (District of Colorado) (“Case 2”)

IPR2024-00170

Patent No. 11,584,968

- *Foresight Diagnostics Inc. v. Personalis, Inc.*, Nos. IPR2023-00224, -00317, -00545, -00546 (Patent Trial and Appeal Board)

Case 1 in the District of Colorado is currently stayed pending the above referenced IPR proceedings. Foresight has moved to consolidate Case 1 and Case 2, and to extend the stay to Case 2. Ex1121. That motion is pending.

The '968 patent issued from application No. 17/494,513, which claims priority to divisional application No. 16/132,123, filed on September 14, 2018, now Patent. No. 11,142,802, which is a continuation of application No. 14/929,075, filed on October 30, 2015, now Patent No. 10,125,399, and provisional Application No. 62/072,936, filed on October 30, 2014.

C. Lead and Back-up Counsel and Service Information

LEAD COUNSEL	BACK-UP COUNSEL
Andrew E. Krause (Reg. No. 76,276) IRELL & MANELLA LLP 1800 Avenue of the Stars, Suite 900 Los Angeles, California 90067 Telephone: (310) 277-1010 Facsimile: (310) 203-7199 AKrause@irell.com ForesightIPRs@irell.com	Amir Naini (Reg. No. 45,770) NAINI P.C. 2632 Wilshire Blvd., Suite 268 Santa Monica, California 90403 Telephone: (310) 592-3030 Facsimile: (310) 453-9008 Amir@nainipc.com Alan Heinrich (<i>pro hac vice</i> to be requested) IRELL & MANELLA LLP 1800 Avenue of the Stars, Suite 900 Los Angeles, California 90067 Telephone: (310) 277-1010 Facsimile: (310) 203-7199 AHeinrich@irell.com Jordan Nafekh (<i>pro hac vice</i> to be requested) IRELL & MANELLA LLP 1800 Avenue of the Stars, Suite 900 Los Angeles, California 90067 Telephone: (310) 277-1010 Facsimile: (310) 203-7199 JNafekh@irell.com

D. Additional Service Information

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

IV. THE '968 PATENT

The '968 patent issued on February 21, 2023 from Application No. 17/494,513. Ex. 1001. According to Patent Center, the '968 Application was asserted to fall under the AIA's first inventor to file provisions:

IPR2024-00170
Patent No. 11,584,968

Application type	Earliest publication #	Intl. registration # (Hague)
Utility	US 2022-0056538 A1 	-
Examiner	Download PDF 	Intl. registration publication date
JOSEPH T WOITACH	Earliest publication date	-
Group art unit	02/24/2022	
1672	Assignee for publication	
Class/subclass	-	
514/049.000	Confirmation #	
AIA (first inventor to file)	8186	
Yes		
Entity status		
Small		

V. LEVEL OF ORDINARY SKILL IN THE ART

As Dr. Quackenbush explains, a POSA in the field of the '968 patent:

[W]ould have had an advanced degree (such as an M.D. or the equivalent of a Ph.D. in a life or physical sciences, engineering, or mathematics discipline), and through further education or postdoctoral experience, an understanding of various sequencing and next generation sequencing methods, sample preparation methods, targeted enrichment methods, bioinformatics methods for interpreting sequencing data, and methods for identifying genetic variants in a sample. A POSA also would have had an understanding of clinical applications of sequencing technology to conditions associated with nucleic acid variation, such as cancer, non-invasive prenatal testing, and transplant rejection. Additionally, a POSA would have had an understanding of cancer biology as it relates to mutations associated with

tumor diagnosis, progression, and treatment, as well as awareness of the various types of mutations that can occur in and influence the course of a patient's cancer.

Quackenbush ¶36.

VI. BACKGROUND KNOWLEDGE OF A POSA

A. Genes and Mutations

Genes contain the set of instructions for the development and maintenance of the cells of all organisms. Genes are made of deoxyribonucleic acid ("DNA") and are located on chromosomes. Certain alterations, sometimes called "mutations," "variations," "variants," or "polymorphisms," can occur in all genes and portions of the human genome, contributing both to normal patterns of human variation as well as individual risk for developing diseases. Polymorphisms can include many types of genomic alteration, including insertions, deletions, point mutations, translocations, rearrangements, and copy number variations. The entire collection of an individual's genetic variants is referred to as their "genotype." Quackenbush ¶¶40-51.

Genetic mutations can be inherited (i.e., passed on from their parents to their offspring) or acquired (i.e., developed for the first time in a new cell). Inherited mutations are called "germline" mutations. Acquired, or non-inherited, mutations are called "somatic" mutations. Somatic mutations unique to a particular tumor can be a useful tool for detecting, tracking, and monitoring a patient's cancer. *Id.* ¶52.

Mutations known in the art included single nucleotide polymorphisms (“SNPs”), copy number variants (“CNVs”), and insertions or deletions (“indels”). An SNP (sometimes called a single nucleotide variant (“SNV”)) is a change in one DNA base pair that may result in the substitution of one amino acid for another in the protein that is encoded by the gene. A POSA would have also been familiar with translocations, which involve the relocation of a gene from one chromosomal location to another. By 2014, many publicly accessible databases existed in which a POSA would have been able to search for a large number of catalogued cancer-associated mutations. *Id.* ¶¶53-55.

B. Nucleic Acid Sequencing

A POSA would have been familiar with multiple techniques for nucleic acid “sequencing,” i.e., determining the order of the bases in a nucleic acid molecule at the base-by-base level. For many years, sequencing was performed using “Sanger” sequencing, which terminates the synthesis of a template strand of DNA at different lengths. These different length DNA strands can be “read” to derive the DNA sequence. *Id.* ¶¶56-60.

By around 2005, a new approach to sequencing called “next generation sequencing” (“NGS”), sometimes also called “massively parallel sequencing” or “sequencing by synthesis,” had been developed to allow multiplex sequencing of many different sequences simultaneously. By approximately 2008, techniques for

NGS were well-known and commercially available. *See, e.g.*, Ex. 1013. NGS is a high-throughput method for determining the base-by-base sequences of nucleic acid molecules, such as DNA. NGS is exponentially faster, cheaper, and more efficient than Sanger sequencing, though both techniques provide accurate sequence information. Quackenbush ¶¶61-67.

C. Personalized Biomedical Monitoring

Once “[w]hole-genome sequencing [became] possible at reasonable cost and timeframe,” Ley “use[d] this approach for the unbiased discovery of tumour-specific somatic mutations that alter the protein-coding genes.” Ex1012. Ley established that a useful approach to cancer monitoring is to first fully characterize the patient’s tumor using WGS to identify polymorphisms of interest, and then serially monitor those polymorphisms to track the tumor over time. As Dr. Quackenbush explains, a POSA would have appreciated that in Ley’s approach, the results of the initial WGS step would help clinicians avoid “miss[ing] key mutations,” and allow them to create a specific set of probes to capture regions of interest harboring the identified mutations for further sequencing. Quackenbush ¶¶81-84. Shortly thereafter, Leary and McBride demonstrated the successful use of the same concept, using structural variants (as opposed to SNPs/SNVs in Ley) to serially monitor tumor DNA in the blood plasma of patients presenting with solid tumors. *Id.* ¶85. Those skilled in the art further developed ways to report the information obtained via such clinical

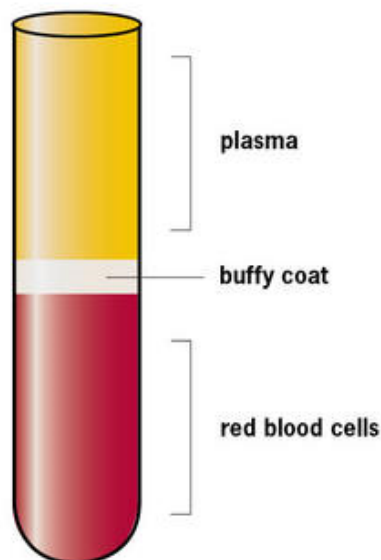
protocols, and ways to leverage that information, e.g. by identifying appropriate clinical trials or targeted therapies. *Id.* ¶¶86, 91-94.

Moreover, the use of WGS to develop targeted monitoring assays was not limited to cancer, because the fundamental properties of nucleic acids that enable this mode of analysis are universal. For example, by 2009, methods of analyzing nucleic acids to aid the diagnosis of transplant rejection had been developed. Ex. 1003. Those methods, similar to those applied in cancer surveillance, were based on the fact that a transplanted organ will have a different genetic fingerprint (a different genotype, coming from the organ donor) than the transplant recipient, and that once identified, that fingerprint may be used to detect transplant rejection by monitoring the levels of cell free DNA (cfDNA) observed in the transplant recipient's blood. The underlying science is that the cfDNA will be a mix of DNA from the recipient and the donor and that the unique variants in the donor's DNA will allow that DNA to be detected following transplantation. *See generally id.* ¶¶40-50, 69-70. *See id.* ¶¶47-48, 73-75; Quackenbush ¶¶87-90.

Cell-free DNA ("cfDNA") refers to small fragments of DNA present in the bloodstream, which comes from both healthy and diseased cells. This generally comes from DNA released during apoptosis, or the death of cells, in the body. During apoptosis, cells undergo various cell death processes. The fragmented DNA, along with other parts of the cells, are released into the bloodstream, and eventually cleared

out of the body with other bodily waste products. Therefore, there is always cfDNA being released into and circulating through the bloodstream before it is cleared out of the body. Quackenbush ¶¶88-89

To facilitate NGS analysis of patient samples, whole blood is often centrifuged to separate it into components for further analysis. These include plasma, buffy coat, and red blood cells. The plasma is commonly used as a source of cell-free DNA and the buffy coat fraction is an abundant source of leukocytes. *See* Ex1001, 53:60-62; Ex. 1109.29 (“Buffy coat is a leukocyte-enriched fraction of whole blood. Preparing a buffy-coat fraction from whole blood is simple and yields approximately 5-10 times more DNA than an equivalent volume of whole blood.”). Quackenbush ¶85, n.4.



VII. KEY PRIOR ART

The references of the grounds are prior because each was published and accessible to the interested public before the priority date of the '968 patent.

A. Chan

Chan (Ex1008) is an article that was published in *Clinical Chemistry*. Dr. Hsieh-Yee confirms that Chan was accessible to interested persons when it “was published online on October 11, 2012, and became discoverable on PubMed on October 16, 2012,” which is confirmed by Chan’s citation in a commentary article on October 31, 2012. Ex1021 ¶39. The online publication was “later published in the print version of vol.59, no. 1 of *Clinical Chemistry* in January 2013, and the copyright registration shows this issue was published on December 31, 2012.” *Id.* See also Quackenbush ¶95.

B. Ley

Ley is an article that was published in *Nature* by November 6, 2008. Ex1012; Quackenbush ¶97.

C. Okosun-II

Okosun-II is an article published in *Nature Genetics* by February 2014, and which was published online on December 22, 2013. Ex1102 at 176. Initial data on the key findings published in this article were published on November 16, 2012 in Okosun et al., “Whole Genome Sequencing in Sequential Biopsies Reveals the

Genetic Evolution of Follicular Lymphoma to Transformed Follicular Lymphoma,” (Okosun-I) which was an abstract in *Blood*, the journal of the American Society of Hematology. Ex1101. Quackenbush ¶96.

While the Petition relies on Okosun-II, Dr. Quackenbush has also mapped the findings of Okosun-I to the claims to the extent Personalis attempts to invoke any prior art exception under 35 U.S.C. §102(b)(1). Quackenbush ¶236.

VIII. GROUNDS FOR THE CHALLENGES

Petitioner challenges the claims of the '968 patent on the following grounds:

	Challenged Claims	Ground: Prior Art
1	1-4, 7, 9-12	§102: Chan (Ex1008)
2	1-13	§103: Chan (Ex1008)
3	1-13	§103: Ley (Ex1012)
4	1, 8-9, 11-13	§102: Okosun-II (Ex1102)
5	1-13	§103: Okosun-II (Ex1102)

IX. LISTING OF CHALLENGED CLAIMS

1. A method of analyzing a biological sample obtained from a subject being screened for a cancer, wherein the biological sample is from a non-fetal source, the method comprising:
 - (a) obtaining a first set of sequence reads and a second set of sequence reads by sequencing nucleic acid molecules derived from a first set of nucleic acid molecules and a second set of nucleic acid molecules, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules, wherein said first set of sequence reads and said second set of sequence reads are generated using whole genome sequencing, and wherein (i) said first set of nucleic acid molecules is extracted from tissue sample of said subject, and (ii) said second set of nucleic acid molecules is extracted from leukocytes from a blood sample;
 - (b) using said first set of sequence reads and said second set of sequence reads to identify mosaic variants specific to said tissue sample of said subject in said first set of sequence reads that is not present in said second set of sequence reads;

- (c) subsequent to (b), identifying said mosaic variants specific to said tissue sample of said subject in a first additional sample of said subject, wherein said first additional sample is obtained from a source that is different than said tissue sample and at a time point that is different than said tissue sample; and
 - (d) providing a report based on an identification of said mosaic variants specific to said tissue sample of said subject in said first additional sample, wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a cancer in said subject.
2. The method of claim 1, further comprising identifying mosaic variants specific to said tissue sample of said subject in a second additional sample of said subject, wherein said second additional sample comprises cell-free DNA, which second additional sample is obtained at a time point that is different than said tissue sample and said first additional sample.
3. The method of claim 2, wherein said first and/or second additional sample comprises a blood sample, a saliva sample, a buccal swab, a urine sample, a semen sample, or a cerebrospinal fluid sample of said subject.
4. The method of claim 2, wherein said mosaic variants specific to said tissue sample of said subject are selected from the group consisting of: copy number variation, small 10 insertions and deletions (inDels), single nucleotide

polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

5. The method of claim 2, wherein said mosaic variants specific to said tissue sample of said subject are causal or predisposing for a cancer.

6. The method of claim 2, wherein said mosaic variants specific to said tissue sample of said subject are non-causal for a cancer.

7. The method of claim 2, further comprising enriching said extracted nucleic acid molecules of said tissue sample, blood sample, first additional sample, or second additional sample.

8. The method of claim 1, further comprising providing a recommendation for a therapeutic intervention based on an identification of said mosaic variants specific to said tissue sample of said subject.

9. The method of claim 1, wherein said tissue sample comprises a metastatic tissue sample, a mixed tissue sample, a biopsy, or a core needle biopsy.

10. The method of claim 1, further comprising enriching said extracted nucleic acid molecules of said tissue sample, blood sample, or first additional sample.

11. The method of claim 1, wherein said mosaic variants specific to said subject are selected from the group consisting of: copy number variation, small

insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

12. The method of claim 1, wherein said predicting, diagnosing, and/or prognosing of (d) comprises one or more of the following: (i) diagnosing a cancer, (ii) identifying a cancer, (iii) determining a stage of a cancer, (iv) assessing risk of a cancer, (v) assessing risk of cancer recurrence, (vi) assessing reproductive risk, (vii) assessing efficacy of a drug, (viii) assessing risk of an adverse drug reaction, (ix) predicting optimal drug dosage, (x) predicting drug resistance, or any combination thereof.

13. The method of claim 1, wherein said mosaic variants specific to said tissue sample of said subject are identified using capture probes in said first additional sample of step (c).

X. CLAIM CONSTRUCTION

A. Preamble (Claim 1)

The preamble of claim 1, “[a] method of analyzing a biological sample obtained from a subject being screened for a cancer, wherein the biological sample is from a non-fetal source,” is not entitled to patentable weight because it merely recites an intended use of the structurally complete series of method steps recited in the body of the claim. *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997) (preamble is not limiting “where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention.”).

To the extent that the preamble is entitled to patentable weight, the phrase “a subject being screened for cancer,” should be interpreted to include a subject that has already been diagnosed with cancer. As the ’968 patent explains, “it can be difficult to detect [] diseases early, when a medical response may be most effective, and it can be difficult to monitor the progression of disease after it has been detected, especially if it requires screens which are expensive and/or invasive.” Ex1001, 1:18-24. Thus, “screening” for cancer includes at a minimum monitoring the disease after it has already been detected. Quackenbush ¶100.

B. “mosaic variants” (Claim 1)

The Petition applies the understanding of “mosaic variants” that Patent Owner has applied in its First Amended Complaint for infringement against Petitioner. Specifically, Patent Owner stated:

As those in the art understand, somatic cancer-causing variations are a type of mosaic variant. This is reflected for instance, in a publication by Wilson et al.:

The most well-studied example of somatic mosaicism is cancer; all tumors represent a subset of cells within an individual that have accumulated mutations resulting in uncontrolled cell growth and survival advantage (16). Both benign and malignant tumors constitute evidence of how common somatic mosaicism is in the human body. .

..

Furthermore, NGS is also useful in identifying mutations underlying cancers (78). *Cancer is a condition of mosaicism in two folds*: first, mosaicism is achieved by accumulation of mutations that confer survival advantage to the mutant cells and give rise to tumors (16); second, each mutant cell accumulates additional genetic alterations, due to lack of cell cycle checkpoints and DNA repair mechanisms, creating mosaicism within tumors (tumor heterogeneity) (79). Multiple NGS studies have successfully identified these two types of mosaicism, leading to a better understanding of different molecular subtypes of cancer and allowing for targeted therapy for each specific tumor and/or patient (80).

Cohen Wilson and Trinh Ye, *Detecting Somatic Mosaicism: Considerations and Clinical Implications*, 87 Clinical Genetics 554, at 55, 558 (2015).

Ex1107, ¶43 (emphasis original). Patent Owner went on to contend that “[t]he patents,” including the ’968 patent, “are consistent with this understanding and likewise **make clear that somatic cancer-causing variations are a type of mosaic variant.**” *Id.* ¶44.

Claim 5 of the ’968 patent states that “said mosaic variants” of claim 1 are “causal or predisposing for a cancer,” which aligns with the definition advanced by Patent Owner in the sections of its complaint against Petitioner cited above. Claim 6 of the ’968 patent states that “said mosaic variants” of claim 1 are “non-causal for a cancer.” Thus, under Patent Owner’s understanding of the claims, the claimed “mosaic variants” include somatic mutations that are causal for a cancer as well as somatic mutations that are non-causal for a cancer. Accordingly, Patent Owner’s understanding of the claims advanced in its infringement complaint, when taken in light of its own dependent claims, requires that the term “mosaic variants” encompasses both somatic cancer-causing variations and somatic non-causal cancer mutations. *See also* Ex1108.18, 34, 137 (“[T]he claimed methods are not restricted to the identification of cancer driver genes. As discussed in claims 16 and 17, the methods of the claims allow for the detecting of mosaic variants that are causal or predisposing of cancer, as well as mosaic variants that are not causal for cancer.”).

Thus, Patent Owner's understanding of the term "mosaic variants," requires the claimed "mosaic variants" to encompass any somatic mutation present in a cancer nucleic acid sample (i.e., either causal or non-causal somatic mutations, or both) that is not present in a normal nucleic acid. Quackenbush ¶¶101-103.

C. "(d) wherein said report comprises...." (Claim 1) / "wherein said predicting, diagnosing, and/or prognosing of (d) comprises...." (Claim 12) / "providing a recommendation..." (Claim 8)

"Claim limitations directed to printed matter are not entitled to patentable weight unless the printed matter is functionally related to the substrate on which the printed matter is applied." *Praxair Distribution, Inc. v. Mallinckrodt Hosp. Prod. IP Ltd.*, 890 F.3d 1024, 1031 (Fed. Cir. 2018). The doctrine is not limited to content that is literally printed; the Federal Circuit holds that a "claim limitation is directed to printed matter 'if it claims the content of information.'" *Id.* (citing *In re DiStefano*, 808 F.3d 845, 848 (Fed. Cir. 2015)).

Claim 1 recites "providing a report ... wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome...." Claim 12 recites, "wherein said predicting, diagnosing, and/or prognosing of [claim 1](d) comprises one or more of" "diagnosing," "identifying," "determining a stage," "assessing," and/or "predicting," various criteria. Similarly, claim 8 recites "providing a recommendation for a therapeutic intervention based on an identification of said mosaic variants."

Thus, these claim elements merely recite conveying information, such as a prediction, diagnosis, and/or prognosis of disease status, outcome, or stage, or a therapy recommendation, which is based on an actor's mental analysis of the "identification of mosaic variants." The conveyance of such information has no functional relationship to the substrate on which it is conveyed, so it is not entitled to patentable weight. *In re Ngai*, 367 F.3d 1336, 1339 (Fed. Cir. 2004) ("Ngai is entitled to patent his invention of a new RNA extraction method.... He is not, however, entitled to patent a known product by simply attaching a set of instructions to that product.").

It is appropriate for the Board to consider this issue on claim construction: "Because claim limitations directed to mental steps may attempt to capture informational content, they may be considered printed matter lacking patentable weight in an obviousness analysis." *Praxair Distribution, Inc.*, 890 F.3d at 1033.

D. "capture probe" (Claim 13)

The '968 patent explains that the main feature of a "capture probe" is that it "typically...comprises a nucleic acid binding site." Ex1001, 35:30-37. The nucleic acid binding sites may comprise a sequence "that hybridizes to at least a portion of the one or more nucleic acid molecules ... in the sample or subset of nucleic acid molecules." *Id.*, 35:49-53. Thus, the '968 patent explains, "capture probes may comprise a nucleic acid binding site that hybridizes to one or more genomic regions."

Id., 35:53-54; *see also id.*, 35:61-62 (“The capture probes may comprise one or more nucleotides.”). As Dr. Quackenbush explains, based on this intrinsic record, a POSA would have understood the term “capture probe” in the ’968 patent to encompass at least PCR primers (referred to herein as “PCR primer capture probes”) and solution-based hybridization baits (e.g., biotinylated oligonucleotide baits) (referred to herein as “solution-based hybridization capture probes”). Quackenbush ¶¶104-107. In related proceedings involving Personalis patents that define “capture probes” using the same language in their specifications the Board adopted this construction in its Decisions to Institute. *See, e.g., Foresight Inc. v. Personalis Inc.*, IPR2023-00224, Paper No. 11 at 28-29.

XI. THE BOARD SHOULD CANCEL THE CHALLENGED CLAIMS**A. Ground 1: Chan anticipates claims 1-4, 7, and 9-12.****1. Claim 1**

Chan anticipates claim 1. Quackenbush ¶¶108-126.

Claim 1 recites “A method of analyzing a biological sample from a subject being screened for cancer, wherein the biological sample is from a non-fetal source, the method comprising” enumerated steps a-d. As discussed in detail below, Chan discloses such a method, and thus anticipates claim 1.

Chan’s method titled “Cancer Genome Scanning in Plasma: Detection of Tumor-Associated Copy Number Aberrations, Single-Nucleotide Variants, and Tumoral Heterogeneity by Massively Parallel Sequencing,” satisfies the preamble. Ex1008.211. Chan recruited human subjects for cancer scanning (i.e., screening multiple times): “Four hepatocellular carcinoma patients and a patient with synchronous breast and ovarian cancers were recruited. DNA was extracted from the tumor tissues, and the preoperative and postoperative plasma samples of these patients were analyzed with shotgun MPS.” *Id.* Thus, Chan’s screening involves the analysis of samples from non-fetal sources. Quackenbush ¶¶108-112.

a) “[1] obtaining a first set of sequence reads and a second set of sequence reads by sequencing nucleic acid molecules derived from a first set of nucleic acid molecules and a second set of nucleic acid molecules, [2] wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds

to said second set of nucleic acid molecules, [3] wherein said first set of sequence reads and said second set of sequence reads are generated using whole genome sequencing, and [4] wherein (i) said first set of nucleic acid molecules is extracted from tissue sample of said subject, and (ii) said second set of nucleic acid molecules is extracted from leukocytes from a blood sample”

In sum, step 1(a) requires performing WGS on nucleic acid molecules extracted from (i) a tissue sample from the subject; and (ii) leukocytes from a blood sample. Chan discloses step 1(a) by performing WGS on matched (i) tumor tissue from hepatocellular carcinoma (HCC); and (ii) buffy coat DNA, which is the fraction of a centrifuged blood sample that contains leukocytes. Ex1008.211 (“DNA was extracted from [HCC] tumor tissues, and the preoperative and postoperative plasma samples of these patients were analyzed with shotgun MPS.”); *id.*, 218 (describing identification of mosaic variants by comparing tumor and germline DNA using WGS: “The MPS data from the tumor DNA and the buffy coat DNA from each of the 4 HCC patients were compared, and SNVs present in the tumor DNA but not in the buffy coat DNA were mined with a stringent bioinformatics algorithm.”). Quackenbush ¶¶113-114.

With respect to step 1(a)[i], Chan “sequenced tumor DNA and buffy coat DNA to mean depths of 29.5-fold (range, 27-fold to 33-fold) and 43-fold (range, 39-

fold to 46-fold) haploid genome coverage, respectively.” Ex1008.218. This sequencing obtains the claimed sets of sequence reads. Quackenbush ¶¶115-116.

With respect to step 1(a)([2]), the sequence reads of step 1(a)([1]) were obtained by sequencing DNA molecules, and the sequence reads necessarily correspond to the sample from which the DNA molecules were obtained. Thus, the first set of sequence reads corresponds to the nucleic acid sequence of the tumor DNA molecules and the second set of sequence reads corresponds to the buffy coat DNA molecules. Quackenbush ¶117.

With respect to Step 1(a)([3]), Chan’s “massively parallel sequencing” to generate the aforementioned sequence reads constitutes “whole genome sequencing.” Specifically, [t]o inform subsequent genomewide scanning in the plasma, Chan first subjected the HCC patients’ tumors to an initial paired tumor/normal sequencing step, in which a genome-wide comparison identified “SNVs present in the tumor DNA but not in the buffy coat DNA” based on sequencing to >29-fold haploid coverage of each sample. Ex1008.218; *id.*, 212 (“Sequencing libraries of the genomic DNA samples were constructed with the Paired-End Sample Preparation Kit (Illumina),” which involved shearing genomic DNA into 200-bp fragments. *Id.* The prepared DNA libraries were then sequenced “by 51 x 2 cycles or 76 x 2 cycles of sequencing on a HiSeq 2000 system (Illumina) with the TruSeq SBS Kit (v2).”). Quackenbush ¶¶118-120.

With respect to step 1(a)([4]), Chan performed whole-genome sequencing on (i) “DNA [] extracted from the tumor tissues” of HCC patients and (ii) the patients’ buffy coat DNA, which is DNA from the fraction of a blood sample that contains leukocytes. Ex. 1008.211, 218. Quackenbush ¶121.

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

After obtaining whole-genome sequencing reads, Chan discloses step 1(b) because it performs a bioinformatics analysis that identifies mosaic variants specific to the tissue (tumor) sample by comparing SNVs in tumor and normal tissue to identify such variants that are unique to the tumor, and thus not present in the germline sequence reads. Ex1008.211, 218. Chan explains that “[t]he MPS [i.e., WGS] data from the tumor DNA and the buffy coat DNA from each of the 4 HCC patients were compared, and *SNVs present in the tumor DNA but not in the buffy coat DNA were mined* with a stringent bioinformatics algorithm.” *Id.*, 218. Chan explained that “[t]he number of tumor-associated SNVs,” which constitute mosaic variants under Patent Owner’s understanding of the claim, “ranged from 1334 to 3171 in the 4 HCC cases.” *Id.* Quackenbush ¶122.

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

After tumor-specific SNVs (i.e., mosaic variants) in the HCC patients based on the paired tumor/germline WGS assay, Chan discloses Step 1(c) by identifying at least some of the previously identified mosaic variants in additional samples. Those samples include (i) a preoperative plasma sample; and (ii) a post-operative plasma sample. Ex1008.211, 215, 218. Each constitutes an additional sample obtained from a source that is different from the tumor tissue sample (at a minimum because such samples are from blood plasma and from different timepoints). And both such samples were taken at a time point that is different than said tissue sample (which was taken during surgery): the preoperative plasma samples were taken “before . . . surgical resection with curative intent from [the] 4 HCC patents,” and the postoperative plasma samples were taken “1 week after surgical resection with curative intent from [the] 4 HCC patients.” Ex1008.215. Quackenbush ¶123.

After identifying the mosaic variants – in the form of tumor-specific SNVs – Chan then evaluated “[t]he proportions of such SNVs that were detectable in plasma,” and listed them in Table 2. Ex1008.218. “Before treatment, 15%-94% of the tumor-associated SNVs were detected in plasma.” *Id.*, 218. After treatment, the

mosaic variants – tumor specific SNVs – were detected in plasma as at a rate of 1%-5% (1.5%, 2.3%, 1%, and 5.5% in patients HCC1-HCC4, respectively). *Id.*, 218 (Table 2); *id.*, 219 (“These fractional concentrations...were reduced after surgery (Table 2).”). Quackenbush ¶124.

Table 2. Fractional concentrations of tumor-derived DNA in plasma determined by SNV analysis.							
Case	No. of SNVs detected in tumor tissue	Time point	No. of tumor-associated SNVs sequenced from plasma (percentage of SNVs seen in tumor tissue)	No. of plasma DNA sequence reads showing SNVs (<i>p</i>)	No. of plasma DNA sequence reads showing wild-type sequence (<i>q</i>)	Deduced fractional concentration of tumor-derived DNA by SNV analysis $\left(\frac{2p}{p+q}\right)$	Deduced fractional concentration of tumor-derived DNA by GAAL analysis
HCC1	2840	Before surgery	2569 (94%)	11 389	31 602	53%	52%
		After surgery	44 (1.5%)	91	46 898	0.4%	0.9%
HCC2	3105	Before surgery	1097 (35%)	1490	57 865	5.0%	5.6%
		After surgery	72 (2.3%)	206	66 692	0.6%	0.9%
HCC3	3171	Before surgery	461 (15%)	525	48 886	2.1%	4.3%
		After surgery	31 (1%)	67	58 862	0.2%	1.4%
HCC4	1334	Before surgery	201 (15%)	248	18 527	2.6%	7.6%
		After surgery	74 (5.5%)	149	22 144	1.3%	2.7%

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

To the extent step 1(d) is entitled to patentable weight, Chan discloses it by providing a report based on the identification of mosaic variants – tumor specific SNVs – in preoperative and postoperative plasma samples. Ex1008.218 (Table 2). This report shows the “Fractional concentrations of tumor-derived DNA in plasma determined by SNV [mosaic variant] analysis,” and shows that for each of the HCC patients analyzed, the number of tumor-associated SNVs sequenced from plasma

decreased following “surgical resection with curative intent” as compared to presurgical plasma samples. *Id.*, 215, 218. The decrease in fraction of tumor specific SNVs (the mosaic variants) present after surgery constitutes a report that predicts, diagnoses, and/or prognoses the stats or outcome of the patient’s cancer, namely whether the surgery increased or decreased the level of HCC biomarkers present in the patient. Here, the decrease in detected mosaic variants (tumor specific SNVs) in the post-operative plasma indicates that the surgery was successful at least in reducing such biomarkers. *See id.*, 221 (“This approach would allow qualitative and quantitative aspects of such aberrations to be followed serially, as evidenced by the changes we observed in the pre- and postsurgery plasma samples. The method would also allow tumor load to be assessed, as indicated by the correlation between the fractional tumor DNA concentration measured and the size of the tumor.”). Quackenbush ¶125.

2. Claim 2

As explained with respect to Step 1(c) above, Chan discloses identifying tumor specific SNVs (mosaic variants specific to the HCC tissue sample) of each patient in two additional plasma samples, obtained pre- and post-operatively. Thus, Chan analyzes at least three samples at three time points: (1) the pre-operative plasma samples; (2) the surgically resected tumor sample; and (3) the post-operative plasma sample. Ex. 1008.215, 218. Chan’s preoperative and postoperative plasma

samples alternatively satisfy the claimed first and second additional samples. Quackenbush ¶128.

Moreover, Chan's plasma samples comprise cell-free DNA. *See* Ex1008 at 212 (“Cell-free DNA molecules from 4.8 mL of plasma were extracted...for subsequent preparation of the DNA-sequencing library.”). *See* also Ex1001, 53:62 (“The plasma contains cfDNA.”). Quackenbush ¶¶129-130.

3. Claim 3

As explained with respect to claim 2, above, the first and second additional samples disclosed by Chan are plasma samples, which are extracted from blood samples. The '968 patent acknowledges that a blood sample may consist of extracted fractions (e.g., plasma, buffy coat, red blood cells) of the blood sample. *Cf.* Ex1001 at 3:12-13 (“In some embodiments, the blood sample is a whole blood sample.”); Quackenbush ¶¶131-133.

4. Claim 4

As explained above with respect to claims 1 and 2, Chan discloses identifying mosaic variants specific to the tumor tissue sample in the form of tumor specific single nucleotide variants, which are also known as single nucleotide polymorphisms. Quackenbush ¶¶134-136.

5. Claims 7 and 10

Chan discloses enriching the extracted DNA samples (from tumor tissue and buffy coat) in the preparation of sequencing libraries for its WGS assay: “The adapter-ligated DNA was enriched with 12-cycle PCR.” Ex1008. 2112. Chan also discloses enriching the plasma samples used in the first and second additional samples: “Because the plasma DNA molecules were short fragments and the amounts of total DNA in the plasma samples were relatively small, we omitted the fragmentation steps and used a 15-cycle PCR when constructing the DNA libraries from the plasma samples.” *Id.* Quackenbush ¶¶137-139. 143-145.

6. Claim 9

Chan’s tumor tissue sample was a surgically resected HCC biopsy, and necessarily contained a mixture of normal and cancerous liver cells. Quackenbush ¶¶140-142.

7. Claim 11

As explained above with respect to claim 1, Chan discloses identifying mosaic variants to the tumor tissue sample in the form of tumor specific single nucleotide variants(aka single nucleotide polymorphisms). Quackenbush ¶¶146-148.

8. Claim 12

To the extent Claim 12 is entitled to patentable weight, Chan’s methods satisfy it. Chan’s predicting, diagnosing, and/or prognosing at a minimum comprises (i)

diagnosing the patient's HCC cancer as HCC and (ii) identifying the patient's HCC cancer as HCC because the plasma samples it sequences are analyzed to determine their relationship to SNVs detected in tumor tissue. *See* Ex1008.218, Table 2. Quackenbush ¶¶149-151.

B. Ground 2: Chan renders claims 1-13 obvious.

As discussed above, Chan anticipates independent claims 1 and 2. Chan renders the challenged claims obvious for at least the following additional reasons.⁵ which further render obvious the claims from which they depend.

1. Claim 2

As explained with respect to Step 1(c) above, Chan discloses identifying tumor-specific SNVs (mosaic variants specific to the HCC tissue sample) of each patient in two additional plasma samples, obtained pre- and post-operatively, thus anticipating claim 2. Chan further renders obvious claim 2 because it suggests that a POSA would have been motivated to serially obtain many plasma DNA samples over time to screen the patient for cancer over the course of their disease. Ex1008.221 (“This approach would allow qualitative and quantitative aspects of such aberrations to be followed serially, as evidenced by the changes we observed in the pre- and postsurgery plasma samples.”). Thus, Chan itself motivates

⁵ These reasons further render obvious the claims from which the enumerated claims depend.

analyzing multiple plasma samples containing cell-free DNA in order to serially monitor tumor-specific mosaic variants. A POSA would have reasonably expected success in performing such serial analysis, given Chan's demonstrated prior success in performing the same analysis on the pre- and post-operative plasma samples. Quackenbush ¶¶153-155.

2. Claims 5 and 6

Because the '968 patent does not disclose any information regarding the identification of a particular mosaic variant as "causal" or "non-causal," beyond the tautology that a mosaic variant may be either causal or non-causal, at a minimum, the mosaic variants identified by Chan necessarily constitute either causal or non-causal mutations. Moreover, Chan explained that "[i]n this work, we used tumor-associated SNVs as tumor markers and did not focus on elucidating the biology of the mutational landscape of the studied cancers" because its focus was "to develop a noninvasive approach to assess the tumor burden of the body." Ex1008.222. But Chan goes on to explain why a POSA would have found it obvious to do so, and that a POSA would have reasonably expected success in doing so: "We expect, however, that most of the tumor-associated SNVs we detected were 'passenger' rather than 'driver' mutations." *Id.* Thus, the SNVs included a mixture of non-causal (passenger) and causal (driver) mutations. Chan explained that a POSA would have wanted to identify passenger mutations because they "provide[] a numerical

advantage that has the potential for more sensitive, precise, and representative detection of tumor DNA in plasma,” aiding tumor burden assessments. *Id.* Chan also explains that “selective analyses of driver mutations may allow more readily the identification of medically actionable targets.” *Id.* Quackenbush ¶¶157-160.

3. Claim 8

To the extent claim 8 is entitled to patentable weight, Chan renders it obvious. As noted above, Chan explained that “selective analyses of driver mutations may allow more readily the identification of medically actionable targets.” Ex1008.222. A POSA would have understood that a “medically actionable target” is a type of causal mosaic variant for which a targeted or companion therapy existed, and thus such therapy would have been obvious to administer. Moreover, Chan’s analysis of post-surgical plasma mosaic variant levels would have rendered obvious therapeutic intervention, such as follow-up surgery, if such levels indicated a rising tumor burden. Quackenbush ¶¶161-163.

4. Claim 13

As discussed with respect to claim 1, Chan expressly discloses identifying tumor-specific mosaic variants in a plasma sample of step (c) using whole-genome sequencing. Chan further renders obvious the use of capture probes to identify the tumor-specific mosaic variants in an additional plasma sample, such as a post-operative plasma sample. Specifically, Chan explains that “[o]ne can also envision,”

after initial analysis of shotgun whole-genome sequencing data to identify mosaic variants, “targeting such sequences for serial monitoring purposes.” In order to target such sequences for serial monitoring purposes, Chan proposes the use of “solution-phase hybridization-based capture approaches,” which had “already been successfully used to enrich plasma DNA for noninvasive prenatal diagnoses.” Ex1008.223. In light of this experience, a POSA would have reasonably expected success in the use of similar capture techniques to enrich cancer-specific mosaic variants from plasma DNA. *Id.* (“[W]e see that the targeted and shotgun approaches can be used in combination for cancer detection and monitoring.”). Quackenbush ¶¶164-166.

C. Ground 3: Ley renders claims 1-13 obvious.

Ley in view of a POSA’s knowledge would have rendered the challenged claims obvious.

1. Overview of Ley

Because Ley analyzed AML, a type of leukemia, the “tumor sample” was derived from bone marrow or blood, rather than tissue as in the claims. For the germline reference sample, Ley used skin (a tissue biopsy), given that blood cells would serve as a suboptimal source of germline DNA in a leukemia patient because leukemia is a cancer of the blood cells. Quackenbush ¶168.

Example 4 of the '968 patent confirms the foundational nature of Ley's study, as it purports to describe as inventive an experiment that is remarkably similar to what Ley disclosed six years prior by conducting "tumor versus normal analysis" in leukemia, where the leukemia "nucleic acid sample [is] taken from a leukocyte" and the "normal" sequence is taken from the cell free DNA. "The sequences are compared and variants that occur only in the leukemia are identified." Ex. 1001 at 53:53-54-:3 ("Example 4: Detecting Variants of Leukemia by Tumor Versus Normal Analysis"). The only difference between this example – which is not inventive – and Ley is the use of cfDNA from the blood plasma as the normal sample, whereas Ley uses a skin biopsy, which is a trivial and non-inventive design choice that would have been well within the knowledge of a POSA. Example 4, like Ley, differs from the claim insofar as the tumor sample is blood (rather than tissue) in a leukemia, but confirms that the claimed application to solid tumors is merely an obvious variation of Ley's method, as explained in further detail below. Quackenbush ¶169.

2. Adaptations of Ley's Approach to Solid Tumors

Following Ley, many studies by many groups implemented the same general concept of (i) WGS of matched tumor/normal DNA to identify tumor-specific variants of interest and (ii) monitoring the tumor-specific variants in the patient to screen their cancer. Quackenbush ¶170.

For example, Meyerson reported that “[c]omplete sequencing of the genome of cancer tissue to high redundancy, using germline DNA sequence from the same patient as a comparison, has the power to discover the full range of genomic alterations....” Ex. 1031.687. The first of seven references Meyerson cites for this proposition is Ley. Quackenbush ¶171.

Similarly, Chapman observed that “[a] powerful way to understand the molecular basis of cancer is to *sequence* either *the entire genome* or the protein-coding exome, *comparing tumour to normal from the same patient to identify the acquired somatic mutations*.” Ex1103.467 Importantly, Chapman establishes the broad applicability of paired tumor/normal WGS assays to identify tumor specific mutations (i.e., mosaic variants), and cites exemplary “[r]ecent reports,” including Ley, which “have described the sequencing of whole genomes from a single patient.” *Id.* With Ley clearly providing inspiration, Chapman “report[ed] the massively parallel sequencing of 38 tumour genomes and their comparison to matched normal DNAs.” *Id.* Quackenbush ¶172.

Another of the “recent reports” cited by Chapman is Lee 2010 (its Note 5),⁶ which performed WGS on paired tumor and adjacent normal tissue of a lung cancer

⁶ For its part, Lee also cites Ley as an example of “[r]ecent cancer sequencing efforts [that] have used next-generation sequencing technologies to provide a genome-wide view of mutations in leukemia, breast cancer and cancer cell lines.”

patient. Ex. 1104.473 (“Here we present the complete sequences of a primary lung tumour (60x coverage) and adjacent normal tissue (46x). Comparing the two genomes); *id.*, Table 1. Lee compared the two genomes to identify tumor-specific mosaic variants, including SNVs. *Id.* The authors observed that “systematic comparison between a primary tumour and its matched normal genome gives a global view of the various forces shaping the complex mutation landscape of a solid tumor.” *Id.*, 476. Quackenbush ¶173.

Yet another of the “recent reports” mentioned by Chapman is Ding 2010, which described the genomic analysis of four DNA samples from a breast cancer patient implementing “[m]assively parallel DNA sequencing technologies” for its “unprecedented ability to screen entire genomes for genetic changes associated with tumour progression.” Ex1105.999. Ding compared its results to Ley’s. *Id.*, 1005. Quackenbush ¶174. Ding performed WGS generating over 110 billion base pairs of sequence data from the “genomic DNA derived from blood, primary tumour, brain metastasis and xenograft samples, respectively, with corresponding haploid coverages of 38.8x, 29.0x, 32.0x and 23.8x.” Ex1105.999-1000. Mosaic variants, including point mutations and small indels, were identified by comparing the

sequencing data for the peripheral blood (normal, “N”) sample⁷ with the primary tumor (“T”), metastases (“M”) and xenograft (“X”) tumor. *Id.*, 1002 (Table 2). Quackenbush ¶175.

These studies document the level of skill in the art, establishing that a POSA would have found it obvious to apply and extend the general method of Ley – identification of tumor-specific mutations based on comparison of paired tumor/germline WGS data followed by serial monitoring of such mutations over time – to a variety of cancers, including solid tumors. When working with cancers that present with solid tumors, a POSA would have known, and would have found it obvious, to use a tumor sample (i.e., a biopsy) as a source of tumor DNA, and a blood sample containing leukocytes as a source of germline DNA, which would have

⁷ A POSA would have known that the peripheral blood comprises leukocytes. Ex1109.29 (stating that “[a] 200 µl sample of whole human bloods” contains a concentration of $\sim 5 \times 10^6$ leukocytes/ml). Moreover, a POSA would have found it obvious to extract DNA from buffy coat, which is “a leukocyte-enriched fraction of whole blood,” to obtain DNA for a sequencing experiment because “[p]reparing a buffy-coat fraction from whole blood is simple and yields approximately 5-10 times more DNA than an equivalent volume of whole blood.” *Id.* Quackenbush ¶175.

been an obvious and predictable variation of the methods initially disclosed by Ley. Quackenbush ¶176.

3. Claim 1

Ley in view of the knowledge of a POSA renders claim 1 obvious. Quackenbush ¶¶168-198.

To the extent limiting, the preamble is rendered obvious by Ley in view of the knowledge of a POSA. Ley discloses analysis of samples from a subject being screened for cancer, given that the assay sequenced the patient's tumor's genome (at multiple times) and compared "its matched normal counterpart obtained from the same patient's skin." Ex1012.66. Through this analysis, Ley "discovered ten genes with acquired mutations; two were previously described mutations that are thought to contribute to tumour progression, and eight were new mutations present in virtually all tumour cells at presentation and relapse...." *Id.* The method of Ley analyzes samples from a non-fetal source, as AML is a disease that effects adults. *Id.*, 66. And following Ley, studies within the knowledge of a POSA confirmed that the same analysis applied to samples taken contemporaneously with the patients' disease and treatment. *See e.g.*, Ding (Ex1105), Chan (Ex1008), Okosun (Exs1101-1102). Quackenbush ¶¶177-180.

a) Step 1(a)

Step 1(a) requires performing whole-genome sequencing (WGS) on nucleic acid molecules extracted from (i) a tissue sample from the subject; and (ii) leukocytes from a blood sample. Ley renders obvious step 1(a) by performing WGS on matched (i) tissue sample in the form of a skin sample; and (ii) AML tumor DNA. As explained above, Ley's method is applicable to cancers which present as solid tumors (whereas Ley analyzed AML, a blood cancer), and in such case a POSA would have found it obvious to perform the WGS step on nucleic acid molecules extracted from (i) a tumor (tissue) sample from the subject; and (ii) leukocytes from a whole blood or buffy coat sample. Indeed, an example of such an approach within the knowledge of a POSA was successfully implemented by Ding, which compared a breast cancer tumor sample with paired normal peripheral blood, which includes leukocytes, using a WGS assay. Ex. 1105. Ding thus confirms that a POSA would have had a reasonable expectation of success in modifying Ley by altering the sample types to utilize the method in the screening of solid tumors, because the combination would be the simple application of known techniques to utilize similar, known sequencing and bioinformatics technology in the same way. Quackenbush ¶181.

With respect to step 1(a)([1]), Ley renders obvious the use of WGS to sequence two sets of nucleic acid molecules from a subject to generate sequencing data, which includes sequencing reads. Quackenbush ¶¶182-183.

With respect to step 1(a)([2]), Ley renders obvious generating sets of sequence reads that correspond to the respective set of nucleic acid molecules from which they were generated in the WGS assay. Quackenbush ¶184.

With respect to step 1(a)([3]), Ley renders obvious generating the aforementioned sequence reads using WGS. Quackenbush ¶185.

With respect to step 1(a)([4]), Ley in view of the knowledge of a POSA renders obvious performing WGS on (i) a tissue sample from a solid tumor; and (ii) germline DNA from a leukocyte-containing blood sample. As discussed above, Ley discloses performing its WGS on (i) an AML tumor sample; and (ii) a skin sample as a paired source of germline DNA. As explained above, applying Ley's methods to solid cancers, such as breast cancer tumors, would have been obvious to a POSA, and would have involved the simple application of known techniques. To do so, a POSA would have found it obvious to modify Ley's method by (i) extracting the tumor nucleic acid molecules from a tissue sample affected by a cancer (e.g., a breast cancer tumor biopsy); and (ii) extracting the paired normal nucleic acid molecules from leukocytes from a blood sample. This is confirmed by Ding's performance of such a method by 2011 using paired breast cancer tumor and peripheral blood.

Ex1105; *see* Ex. 1109.299 (confirming that whole blood contains leukocytes). Moreover, a POSA would have found it obvious to extract DNA from buffy coat, which is “a leukocyte-enriched fraction of whole blood,” to obtain DNA for a sequencing experiment. Quackenbush ¶186.

b) Step 1(b)

Ley renders obvious step 1(b) by comparing the sequence reads from the tumor sample to the sequence reads from the germline sample to identify mosaic variants specific to the tumor that are not present in the normal, germline sample. As explained above, it would have been obvious to perform this analysis using a tissue sample as a tumor sample, and a blood sample comprising leukocytes as a germline sample, for example in the context of a solid tumor. *See* Ex1105 (WGS of primary breast cancer tumor versus peripheral blood germline); Ex1031.686 (“[t]he samples generally used for germline genome analysis [are] peripheral blood mononuclear cells.”); *see also* Ex1008 (paired HCC tumor/buffy coat normal WGS); Exs. 1101-1102 (paired FL lymph node biopsy/peripheral blood WGS). Quackenbush ¶187.

For example, Ley discloses that its tumor/normal WGS revealed a number of genetic variants in the tumor sample that were not present in the germline reference. In particular, a variety of “SNVs” are described in Table 1, which identifies SNVs that were identified in the tumor sample, in the skin sample, and thus the corresponding number of SNVs that were detected in the tumor sample but not the

skin sample (e.g., 3,811,115 SNVs detected with respect to hg18 in the tumor, 2,918,446 detected in the skin, and thus 892,669 mosaic variants present in the tumor but not the skin). Quackenbush ¶188.

Table 1 Tumour and skin genome coverage from patient 933124		
	Tumour	Skin
Libraries	4	3
Runs	98	34
Reads obtained	5,858,992,064	2,122,836,148
Reads passing quality filter	3,025,923,365	1,228,177,690
Bases passing quality filter	98,184,511,523	41,783,794,834
Reads aligned by Maq	2,729,957,053	1,080,576,680
Reads unaligned by Maq	295,966,312	138,276,594
SNVs detected with respect to hg18 (no Y)	3,811,115	2,918,446
SNVs (chr 1-22) detected with respect to hg18	3,681,968 (100.0%)	2,830,292 (100.0%)
SNVs also present in dbSNP	2,368,458 (64.3%)	2,161,695 (76.4%)
SNVs also present in Venter genome	1,499,010 (40.7%)	1,383,431 (48.9%)
SNVs also present in Watson genome	1,573,435 (42.7%)	1,456,822 (51.5%)
SNVs not in dbSNP/Venter/Watson	1,223,830 (33.2%)	591,131 (20.9%)
SNVs not in dbSNP/Venter/Watson/skin	925,200 (25.1%)	—
HQ SNPs	46,494 (100.0%)	46,572 (100.0%)
HQ SNPs where reference allele is detected	42,419 (91.2%)	38,454 (82.6%)
HQ SNPs where variant allele is detected	43,164 (92.9%)	39,220 (84.2%)
HQ SNPs where both alleles are detected	42,415 (91.2%)	38,454 (82.6%)
Assessments are shown of the haploid and diploid coverage of the tumour and skin genomes from AML patient 933124. Chr, chromosome; hg18, human genome version 18; HQ, high quality.		

Ley subsequently filters SNV calls using its bioinformatics protocols to focus more specifically on a high-quality subset of tumor specific SNVs (mosaic variants) that were present in the tumor but not in the normal skin sample. Specifically, “[b]ecause the number of sequence variants initially detected by Maq was high, we developed improved filtering tools to effectively separate true variants from false positives.” Ex1012.67-68. Ultimately, Ley compares the sequencing data from the tumor and normal samples to identify mosaic variants, and focused later analyses on ten mosaic variants that occur in the tumor sample but not the normal sample. (Ley

refers to these mosaic variants as “acquired” or “somatic mutations”). *See, e.g., id.*, 70. Quackenbush ¶190.

Ley describes the identification of mosaic variants in the tumor sample in the section titled “Identification of somatic mutations in coding sequences.” Ex1012.68. Ley found that “[t]he patient had 3,813,205 sequence variants in her tumour genome,” which Ley filtered down to 2,647,695 using its bioinformatics workflow, and “2,584,418 (97.6%) were also detected in the skin genome (Fig. 2).” *Id.* Ley then performed further filtering on the 63,277 mosaic variants identified in the tumor sample but not in the skin sample, resulting in 8 validated SNVs (mosaic variants) for further study. *Id.* (Fig. 2). Quackenbush ¶191.

And Ley further described “Detecting insertions and deletions (indels)” to identify additional mosaic variants that were present in the tumor sample but not in the normal sample. Ex1012.69. Ley’s “efforts resulted in the identification of 726 putative small indels,” which were further reviewed and filtered to a set of 28 putative indels. *Id.* “Of these putative indels, 22 were validated but were found present in both tumour and skin..., two were false positive calls, two had no coverage, and two were previously validated somatic insertions in *NPM1* (4bp) and *FLT3* (30 bp).” *Id.* Thus, Ley identified 6 mosaic variants in the form of indels present in the tumor sample but not in the skin sample. Quackenbush ¶192.

In further studies, Ley focused on 10 mosaic variants comprising “[a] total of ten non-synonymous somatic mutations [that] were identified in this patient’s tumour genome” but not in the normal tissue sample: the 8 validated SNVs and the two previously known indels in NPM1 and FLT3. Ex1012.70. The application of a similar bioinformatics workflow to sequencing data generated from WGS of paired solid tumor and normal blood/leukocytes, reflected in the knowledge of a POSA by Ding – would have been an obvious application of known methods in a known way to achieve predictable results, namely the identification of mosaic variants present in a tumor sample that were not present in a matched germline sample. Quackenbush ¶193.

c) Step 1(c)

Ley renders obvious identifying tumor-specific mosaic variants from an additional tumor sample that was obtained from a different source at a different time as compared to the initial tumor sample. Specifically, Ley discloses identifying the tumor-specific mosaic variants identified in step 1(b) in a relapse tumor sample. Quackenbush ¶194.

Ley discloses analyzing an additional biological sample of the subject, *e.g.*, a sample from a “relapse tumor,” to generate a sequencing library, a process in which Ley specifically focuses on identifying the aforementioned validated mosaic variants (such as the eight validated SNPs). For example, Ley uses PCR probes

corresponding to the genetic variants identified in the patient tumor plus two additional PCR probes corresponding to exons in cancer-associated genes known to have common genetic variants to selectively amplify sequences from both the original tumor and skin samples as well as one additional sample obtained from the patient's relapsed disease, and to thereby generate amplicons comprising a sequencing library. Ex. 1012.69. Quackenbush ¶195.

Ley's Figure 3 summarizes this data, and shows the frequency of mosaic variants ("ten somatic mutations") in each of the primary tumor, relapse tumor, and skin samples. This shows that Ley identified the presence of the mosaic variants (green bars) specific to the tumor sample in the subsequently obtained relapse tumor sample. Quackenbush ¶196.

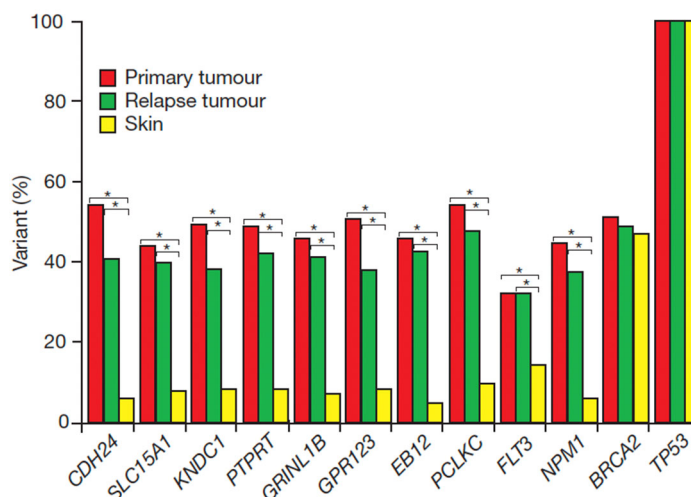


Figure 3 | Summary of Roche/454 FLX readcount data obtained for ten somatic mutations and two validated SNPs in the primary tumour, relapse tumour and skin specimens. The readcount data for the variant alleles in the primary tumour sample and relapse tumour sample are statistically different from that of the skin sample for all mutations ($P < 0.000001$ for all mutations, Fisher's exact test, denoted by a single asterisk in all cases). Note that the normal skin sample was contaminated with leukaemic cells containing the somatic mutations. The patient's white blood cell count was 105,000 (85% blasts) when the skin punch biopsy was obtained.

d) Step 1(d)

To the extent step 1(d) is limiting, Ley further discloses generating a report based on the identification of the frequencies of the mosaic variants occurring in the primary and relapse tumor samples. Specifically, Ley's Figure 3 reports sequence information regarding the relative abundance of particular somatic and germline mutations that were observed in samples taken at (i) primary onset, and (ii) relapse. Ex. 1012.69. These abundances are compared to the frequency of the same polymorphic alleles present in the skin sample, which represents a control. This report comprises predicting, diagnosing, and/or prognosing the status of the cancer at least insofar as it prognoses a status – the variant fraction of the identified mosaic

variants – of cancer cells in the patient. For example, a POSA would have understood that if the second sample did not show the presence of the tumor-associated mosaic variants (and thus appeared similar to the germline sample), that such a result might be consistent with remission or an improved condition. Quackenbush ¶197.

4. Claim 2

As explained above, including step 1(c), Ley in view of the knowledge of a POSA renders obvious analyzing various biological samples in cancer patients by (i) performing whole genome sequencing on paired tumor tissue and a source of germline DNA, such as a blood sample containing leukocytes; (ii) identifying tumor-specific mosaic variants (such as SNVs and indels present in tumor DNA but not in germline DNA) in the first-obtained tumor sample; and (iii) identifying those tumor-specific mosaic variants in additional patient samples, such as later-arising tumor samples (e.g., relapse or metastasized tumor samples), including to determine the patient's ongoing disease burden, disease status, and/or response to treatment. Quackenbush ¶¶199-200.

A POSA would have known that circulating cell-free DNA, such as that present in the blood plasma, was useful as a biomarker for multiple types of cancer. When paired with knowledge of tumor-associated SNVs and/or indels (or other mutations identified through an initial WGS step), a POSA would have been motivated to detect such tumor-specific mosaic variants in additional blood samples

taken over time to serially monitor the status of the patient's cancer. Numerous studies within the knowledge of a POSA, including Chan, Dawson, Leary, and McBride, demonstrated this approach. Quackenbush ¶201.

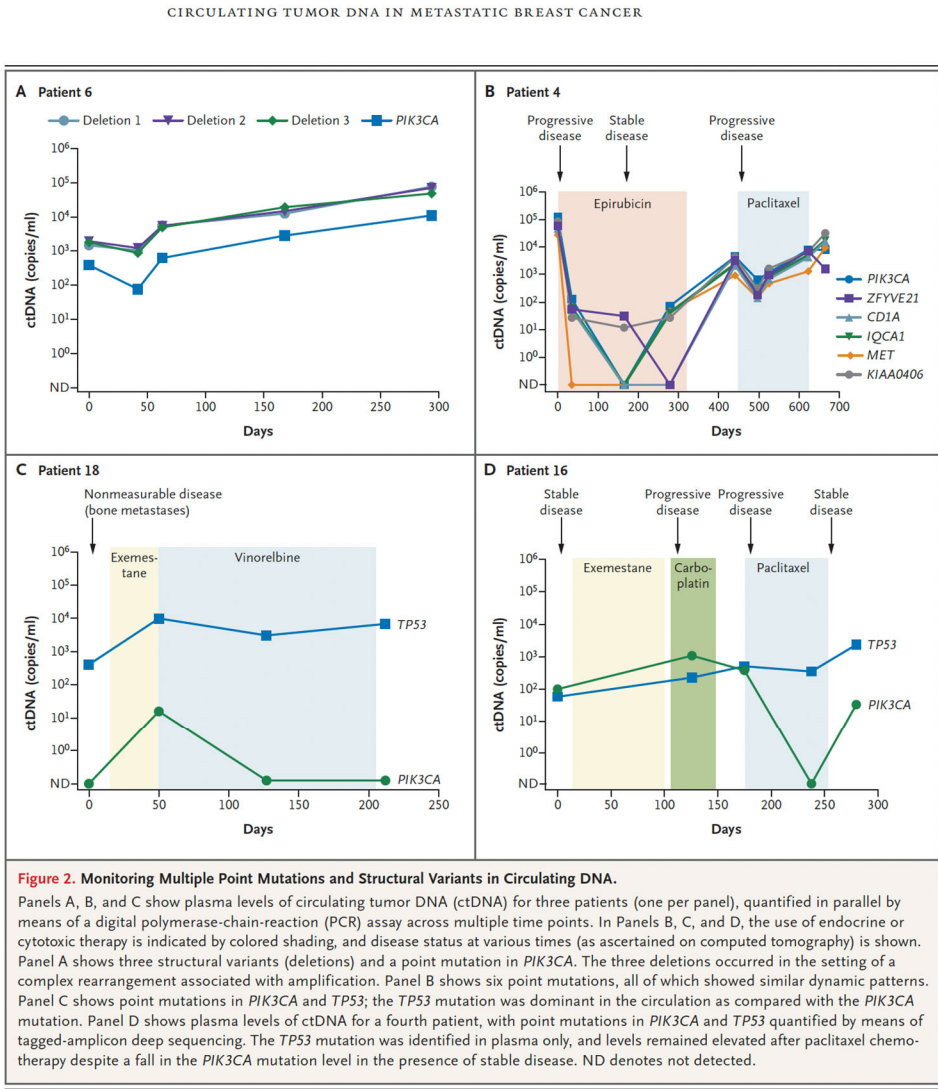
Chan: As discussed above in Grounds 1 and 2, Chan disclosed serially monitoring mosaic variants in cell-free DNA in plasma circulation after identifying them in paired tumor/normal whole genome sequencing. Chan further renders obvious the use of capture probes, such as solution-based hybridization capture probes for the targeted detection of mosaic variants of interest. Ex1008. Quackenbush ¶202.

Dawson: Dawson discloses a study evaluating “circulating cell-free DNA carrying tumor-specific alterations (circulating tumor DNA)” as a “circulating biomarker[] in breast cancer.” Ex1070.1199. One aspect of Dawson's investigation was to use “whole-genome sequencing to identify somatic genomic alterations and design[] personalized assays to quantify circulating tumor DNA in serially collected plasma specimens.” *Id.* Dawson reported that “[c]irculating tumor DNA was successfully detected in 29 of the 30 women (97%) in whom somatic genomic alterations,” i.e., mosaic variants identified in the tumor but not in the germline, “were identified,” concluding that “circulating tumor DNA is an informative, inherently specific, and highly sensitive biomarker of metastatic breast cancer.” *Id.* Quackenbush ¶203.

The patients being screened for cancer in Dawson “were women with metastatic breast cancer currently undergoing active treatment,” of which “30 had genomic alterations suitable for monitoring.” *Id.*, 1200. Such monitoring involved the analysis of “[s]erial blood samples (30 ml each)...at intervals of 3 or more weeks.” *Id.* For the “identification of somatic genomic alterations,” Dawson explains that “[s]equencing was performed on DNA from breast-cancer specimens and matched normal tissue specimens, with the use of one or both of two methods,” one of which was “paired-end whole-genome sequencing.” Dawson’s supplementary appendix, consistent with the discussion above, confirms that leukocytes are an appropriate source of matched normal DNA. Ex1117.6. Using WGS, Dawson “identified somatic structural variants in 8 patients,” and “[i]n 3 patients, both mutations and structural variants were identified, enabling us to compare and contrast the use of point mutations and structural variants for serial monitoring of circulating tumor DNA.” Ex1070.1201-1202, Fig. 1. Moreover, Dawson used WGS in one patient “to identify multiple somatic mutations, enabling us to monitor multiple mutations in parallel in circulating tumor DNA.” *Id.* Thus, Dawson’s WGS was used to identify mosaic variants, including point mutations (SNPs) and structural variants. Quackenbush ¶204.

After identifying mosaic mutations in the tumor sample, Dawson then analyzed serial blood samples to identify such mosaic variants, in the plasma using

two different techniques to interrogate the cell free circulating tumor DNA: digital PCR and TAm-Seq. *Id.*1202-1203. Figure 2 in Dawson constitutes a report that shows the plasma levels of the tumor-specific mosaic variants in four different patients, including reports on their disease status and response to therapeutic intervention. *Id.*, 1203. Quackenbush ¶205.



Leary and McBride: These studies demonstrated the use of the same concept, by using WGS to identify structural variants, and to subsequently use those identified markers as targets for serial monitoring of tumor DNA in the blood plasma of patients with solid tumors. *See* Ex1002.5 (explaining that the identified mosaic variants (“can be used to detect tumor DNA in the presence of large quantities of normal DNA and in patient plasma.”); Ex1015.8 (“Tumor-specific genetic variants,” i.e., mosaic variants, “unequivocally identify cancer cells.”). Quackenbush ¶206.

When applying the collective teachings of Ley and the many successor studies that applied its core approach of determining tumor-specific variants (i.e., mosaic variants) via matched-normal WGS, followed by targeted serial monitoring, a POSA therefore would have been motivated to identify mosaic variants that were identified by WGS of a tumor sample in serial plasma samples taken over time. There are multiple reasons for this, including to monitor disease burden, analyze the patient’s response to therapy or other medical intervention, and to predict impending relapse.⁸ A POSA would have reasonably expected success in performing such monitoring in view of the multiple successful reports that did so, using untargeted shotgun approaches (Chan), targeted approaches using solution phase hybridization capture

⁸ *See, e.g.,* Exs. 1002, 1008, 1015, 1070.

probes (Chan and cited references), and PCR-based capture techniques (Dawson, Leary, and McBride). Quackenbush ¶¶207-208.

5. Claim 3

As explained with respect to claim 2, above, the use of serial plasma samples as a source of cell-free tumor DNA comprising mosaic variants is rendered obvious by Ley in view of the knowledge of a POSA. Quackenbush ¶¶209-211.

6. Claim 4

As explained above with respect to claims 1 and 2, Ley discloses identifying mosaic variants to the tumor tissue sample in the form of tumor specific single nucleotide variants (aka single nucleotide polymorphisms). Ley also discloses the analysis of at least inDels. Quackenbush ¶¶212-214.

7. Claims 5 and 6

At a minimum, the mosaic variants identified in Ley and other references reflecting the knowledge of a POSA necessarily constitute either causal or non-causal mutations. Ley further explains that a POSA would have found it obvious to determine whether detected mosaic variants are “passenger” mutations or alternatively mutations “truly important for pathogenesis (that is, disease ‘drivers’ versus passengers).” Ex1012.70. Moreover, as noted above, Chan explained that a POSA would have wanted to identify both passenger mutations and driver mutations. The passenger mutations “provide[] a numerical advantage that has the

potential for more sensitive, precise, and representative detection of tumor DNA in plasma,” aiding tumor burden assessments, and also would have aided “selective analyses of driver mutations may allow more readily the identification of medically actionable targets.” Ex1008.222. Quackenbush ¶¶215-219.

8. Claim 8

To the extent claim 8 is limiting, the teachings of Ley in view of the knowledge of a POSA render obvious providing a recommendation for a therapeutic intervention based on an identification of said mosaic variants specific to said tissue sample of said subject. For example, in Dawson’s Figure 2, Dawson monitored the mosaic variants specific to the tissue sample over time in serial plasma samples, noting the relationship between disease status and the administration of different therapies. Quackenbush ¶¶220-222.

9. Claim 9

Ley, as well as subsequent references within a POSA’s knowledge, e.g., Ding, use biopsies as tissue samples. Quackenbush ¶¶223-225.

10. Claim 11

As explained above, the mosaic variants identified in Ley comprise at least single nucleotide variants or polymorphisms and indels. Quackenbush ¶¶226-228.

11. Claim 12

To the extent limiting, the teachings of Ley in view of the knowledge of a POSA render obvious providing a recommendation for a therapeutic intervention based on an identification of said mosaic variants specific to said tissue sample of said subject. For example, Dawson monitored the mosaic variants specific to the tissue sample over time in serial plasma samples, noting the relationship between disease status and the administration of different therapies, thus disclosing at least claim options (i); (ii); (iii); (vii) and combinations thereof. Ex1070 (Figure 2). Quackenbush ¶¶228-230.

12. Claims 7, 10, and 13

As explained above with respect to claim 2, a POSA would have found it obvious to identify tumor-specific mosaic variants in serially obtained blood samples using techniques that identify said mosaic variants using capture probes, including PCR-based (as in Ley, Dawson, Leary, and McBride) and solution phase capture probes (as in Chan). Such methods further constitute enriching the extracted nucleic acid molecules of the serially obtained additional samples. Quackenbush ¶¶232-236.

D. Ground 4: Okosun-II anticipates claims 1, and 8-13.

1. Claim 1

Okosun-II anticipates claim 1. Quackenbush ¶¶238-254.

To the extent limiting, Okosun discloses the preamble. Specifically, Okosun-II performs serial WGS assays of follicular lymphoma (“FL”) biopsies and paired germline DNA. Ex1102.176. Quackenbush ¶¶238-239.

a) Step 1(a)

Step 1(a) requires performing WGS on nucleic acid molecules extracted from (i) a tissue sample from the subject; and (ii) leukocytes from a blood sample. Okosun-II discloses step 1(a) by performing WGS on matched (i) tumor tissue from FL lymph node biopsies; and (ii) paired germline sample. *See, e.g.*, Ex1102.176; *id.*, 182 (“**Case samples.** Ten individuals with follicular lymphoma were selected on the basis of the availability of sequential tumor lymph node biopsies . . . and matched germline samples consisting of remission bone marrows or peripheral blood specimens.”). Quackenbush ¶241.

With respect to step 1(a)([1]), Okosun-II obtained sequence reads by sequencing a first set of nucleic acid molecules derived from the FL tumor, and a second set of nucleic acid molecules derived from the paired germline sample. Ex1102.176. Quackenbush ¶242.

With respect to step 1(a)([2]), Okosun-II's sequence reads necessarily correspond to the sample from which they were obtained. Quackenbush ¶243.

With respect to step 1(a)([3]), Okosun-II discloses that the first and second sets of sequence reads are generated using WGS: “[W]e conducted whole-genome or whole-exome sequencing of sequential follicular lymphoma-transformed follicular lymphoma (FL-tFL) pairs and matched germline samples from 10 cases.” Ex1102.176. Quackenbush ¶244.

With respect to step 1(a)([4]), Okosun-II discloses that the first set of nucleic acid molecules is extracted from a lymph node biopsy. Ex1102.176-177, Fig. 1; *see also id.*, 182. Okosun-II further discloses that the germline DNA sample may be obtained from “peripheral blood specimens.” *Id.*, 182 Such blood specimens contain leukocytes. Quackenbush ¶245.

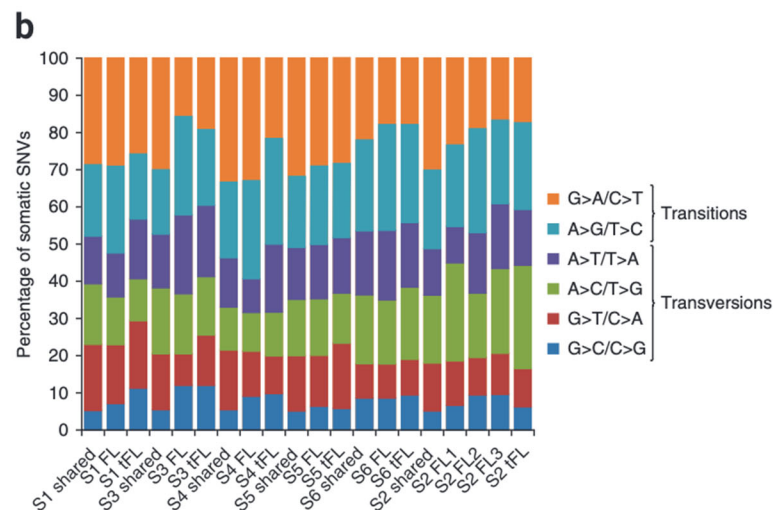
b) Step 1(b)

Okosun-II discloses identifying variants that were present in the FL genome (i.e., the genome of the FL lymph node biopsy) that were mutated as compared to the germline, thereby identifying mosaic variants specific to the FL tissue biopsy. For example, when describing its analysis of the generated WGS data (“**Whole-genome sequencing read mapping and somatic mutation detection**”), Okosun-II discloses implementing an “algorithm to identify somatic SNVs and indels for matched tumor-germline samples.” Ex1102.182. Quackenbush ¶246.

Okosun-II also describes additional filtration of mosaic variants for further analysis, noting that “[o]nly somatic calls originating from homozygous reference alleles in normal samples were considered.” Ex1102.182. Subsequently, “[a]ll somatic SNVs and short indels retained after filtering were annotated,” and “allele frequencies for individual variants in both germline and tumour samples were determined by read count.” *Id.* Quackenbush ¶247.

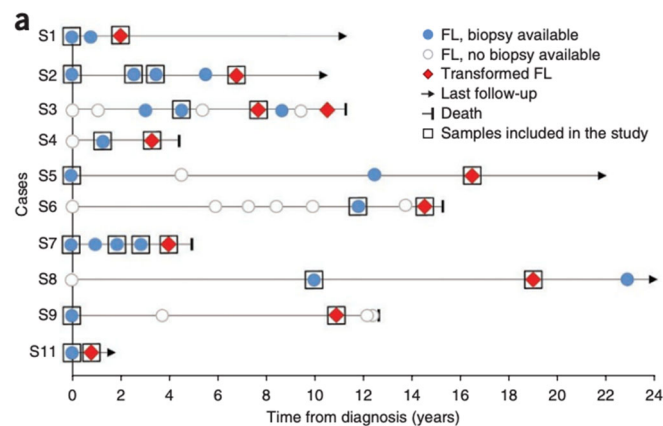
Figure 1b shows the distribution of base substitution patterns in the identified mosaic variants. “Somatic SNVs for each case were sorted into three categories: shared (variants present in both follicular and transformed follicular lymphoma samples), follicular lymphoma specific and transformed follicular lymphoma specific.” Ex1102.177 (Figure 1b). Thus, mutations that are indicated as “shared” were present in both the FL and tFL tumor samples but not in the germline samples, while mutations that are indicated as “FL” were present in the FL sample but not in the germline (or subsequent tFL) samples.⁹ Quackenbush ¶248-249.

⁹ Patients S1-S6 were the patients whose tumors were subjected to WGS. Ex. 1113 (Supplementary Information) at 20 (Supplementary Table 1).



c) Step 1(c)

Okosun-II identifies mosaic variants specific to the FL tissue sample in a first additional sample that is obtained from a different source at a different time point. Specifically, Okosun-II performs serial biopsies on FL patients for additional FL samples, which include instances of continued FL (blue circle), as well as tFL (red diamond). Samples that were analyzed in the study are boxed. Ex. 1102.177 (Fig. 1a). Quackenbush ¶250.



In patients S1-S6, Okosun-II discloses analyzing a transformed FL sample that was obtained after one or more FL samples was taken. *Id.* Okosun-II identifies the previously identified tumor-specific mosaic variants in the tFL samples, including in Figure 1b, where it identifies “shared” variants that were “variants present in both follicular lymphoma and transformed follicular lymphoma samples.” Ex1102.177 (Fig. 1b). Quackenbush ¶251.

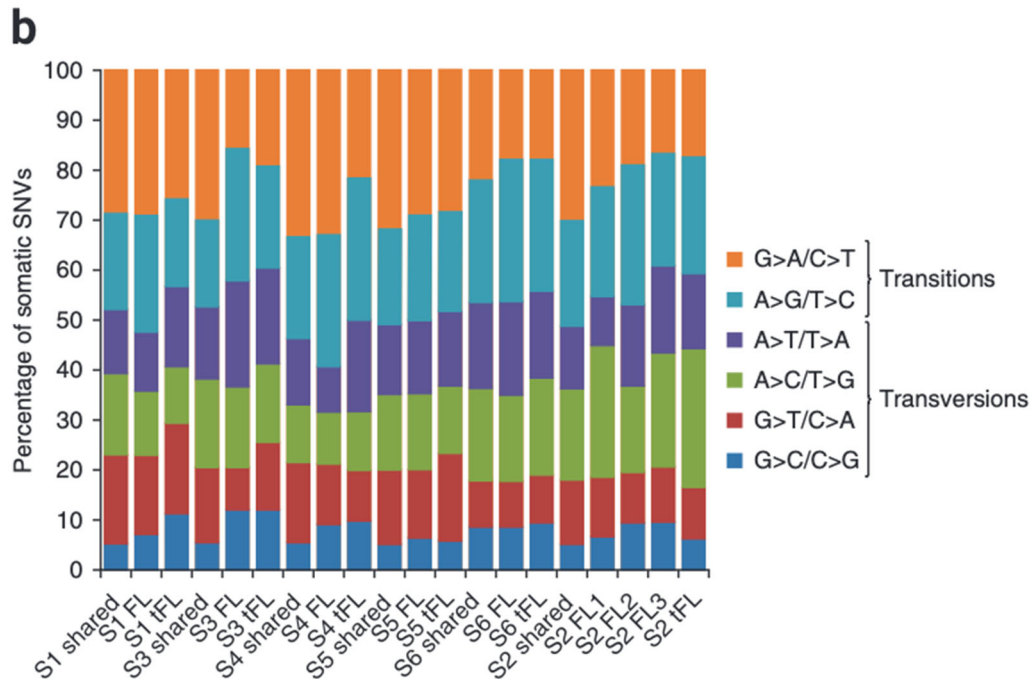
Through this analysis, Okosun-II “identified recurrent mutations,” i.e., tumor specific mosaic variants, “in linker histone, JAK-STAT signaling, NF-kB signaling and B cell developmental genes.” Ex1102.176. These results “suggest[ed] that personalizing therapies to target key genetic alterations in the CPC,” or “common progenitor clone,” “represents an attractive therapeutic strategy.” *Id.* In this analysis, Okosun-II describes the creation of developmental maps to track the evolution of mosaic variants in the follicular lymphoma samples to their transformation. *Id.*, 177. Quackenbush ¶252.

d) Step 1(d)

To the extent limiting, Okosun-II discloses step 1(d) because it provides a report based on an identification of the shared mosaic variants – i.e., the mosaic variants specific to the FL sample that were subsequently identified in the tFL sample. Ex1102.177 (Figure 1b). This report, at a minimum, diagnoses and/or prognoses the status of a cancer – namely and types (e.g. transitions and/or

transversions) and the frequencies of mosaic mutations present in the tFL sample.

Quackenbush ¶253-254.



2. Claim 8

To the extent limiting, Okosun-II discloses claim 8 because it discloses that certain of the mosaic variants it detected affect the NF-kB signaling pathway. Ex1102.178-179. Okosun-II provides a recommendation for a therapeutic intervention in cases where such mosaic variants are detected: “A number of emerging therapeutic agents target the NF-kB signaling cascade, and such treatments may be beneficial to a preselected subset of patients with follicular lymphoma harboring mutations in this pathway” *Id.*, 179. Okosun-II further recommends

“adopting a stratified approach targeting the specific early genetic lesions identified” via its methods. *Id.*, 180. Quackenbush ¶¶255-257.

3. Claim 9

As discussed above, Okosun-II utilized FL biopsies as its tissue samples. *See, e.g.*, Ex1102.177. Quackenbush ¶¶258-260

4. Claim 11

The mosaic variants identified in Okosun-II include at least SNVs (i.e., SNPs and indels: “We verified 235 single-nucleotide variants (SNVs) and 48 indels out of 293 variants, corresponding to 118 genes.” Ex1102.177. Okosun-II also discloses that “[i]nterrogation of the six whole-genome sequenced cases identified copy number alterations (CNAs), previously unreported structural variants, fusion transcripts and recurrent mutations in noncoding regions.” *Id.* Quackenbush ¶¶261-263.

5. Claim 12

To the extent limiting, Okosun-II discloses claim 12 because it provides a report based on an identification of the shared mosaic variants – i.e., the mosaic variants specific to the FL sample that were subsequently identified in the tFL sample. Ex1102.177 (Figure 1b). This report, at a minimum, diagnoses and/or prognoses the status, identity, and/or stage of a cancer, including based on the types

(e.g. transitions and/or transversions) and the frequencies of mosaic mutations present in the tFL sample. Quackenbush ¶¶264-266.

6. Claim 13

Okusun-II discloses identifying the tumor-specific mosaic variants identified in the initial whole-genome sequencing assay in a first additional sample using capture probes. Specifically, Okusun-II conducted “deep targeted resequencing of 28 genes in an extension cohort.” Ex. 1102.176. To do so, Okusun-II used “targeted resequencing” with capture probes to specifically identify the tumor-specific mosaic variants in additional samples. *Id.*, 177. Specifically, to perform its targeted resequencing, Okusun-II used “the Access Array platform (Fluidigm),” which as Dr. Quackenbush explains utilized PCR primers as capture probes in order to enrich the mosaic variants of interest for the resequencing experiment. Quackenbush ¶¶267-270.

E. Ground 5: Okosun-II renders claims 1-13 obvious.

As noted above, Okosun-II anticipates claim 1, which is incorporated by reference here. Quackenbush ¶271. Okosun-II in view of the knowledge of a POSA would have further rendered claims 1-13 obvious, as explained below. Quackenbush ¶¶272-301.

1. Claim 1

Even had Okosun-II's use of peripheral blood as a source of germline DNA not anticipated the claimed use of leukocytes, a POSA would have found it obvious to do so. A POSA would have known that whole peripheral blood comprises leukocytes. Ex1109. Meyerson further notes that "[t]he samples generally used for germline genome analysis [are] peripheral blood mononuclear cells." Ex1031.686. Peripheral blood mononuclear cells, by Patent Owner's own admission, constitute leukocytes. Ex1119 (contending that Foresight's use of PBMCs in its methods satisfies the "leukocyte" limitation). Moreover, a POSA would have found it obvious to extract DNA from buffy coat because "[p]reparing a buffy-coat fraction from whole blood is simple and yields approximately 5-10 times more DNA than an equivalent volume of whole blood." Ex1109.9. Thus, the selection of a blood sample containing leukocytes as a source of germline DNA – whether whole blood, PBMCs, or buffy coat – would have been a routine and predictable experimental design

choice based on Okosun-II's use of peripheral blood as a germline DNA sample. Quackenbush ¶272.

2. Claim 2

As explained with respect to step 1(c) above, Okosun-II discloses identifying tumor-specific mosaic variants serially to monitor the course of a given patient's disease over time. *See, e.g.*, Ex1102.177 (Fig. 1); *id.*, 178 (Fig. 2). To do so, Okosun-II discloses obtaining biopsies of the patient's tumor at each time tested. *See* Fig. 1. Patient 2, for example, underwent surgery to resect lymph node biopsies at least 5 times, and all patients studied were biopsied at least 2 times. *Id.* Quackenbush ¶¶273-274.

Personalis and its expert, Dr. Furneaux, admitted in co-pending proceedings that a POSA would have been motivated to avoid serial biopsies of the same patient. For example, Dr. Furneaux testified that “[a] POSA would have been dissuaded from obtaining a second tumor sample...because it would have involved an invasive procedure.” Ex1114 ¶136. Dr. Furneaux confirmed that a POSA would have been motivated to monitor tumor-specific mosaic variants using non-invasive methods. *Id.* (“***Noninvasive access to malignant DNA is particularly attractive for solid tumors***, which cannot be repeatedly sampled without invasive procedures.”). Thus, though Okosun-II successfully performed its methods by “repeatedly samp[ling] with[] invasive procedures,” a POSA would have been motivated to obviate such

repeated invasive procedures by gaining noninvasive access to the FL tumor (which is a solid tumor) DNA. Quackenbush ¶275.

To that end, a POSA would have known that circulating tumor DNA in the plasma was a useful tool for noninvasively tracking tumor-associated mutations in blood samples taken over time. Moreover, those in the art would have known that as in other solid cancers, FL tumors released circulating tumor DNA into the blood. *See* Ex1111.1412. Quackenbush ¶276.

Thus, a POSA would have found it obvious to apply, and reasonably would have expected success in applying, any one of the various known techniques for detecting tumor-specific variants in cfDNA from plasma, including those used in Chan, Dawson, Leary and McBride. Utilizing such techniques, and with knowledge of the sequences of the mosaic variants of interest based on its initial WGS assay, a POSA would have found it obvious to utilize capture probes or plasma shotgun sequencing to noninvasively perform serial monitoring of the identified mosaic variants, as explained with respect to Ground 3, claim 2, which is incorporated by reference here. Quackenbush ¶277.

Moreover, Diehn-530 further evidences the knowledge of a POSA and discloses “[m]ethods for creating a selector of mutated genomic regions and for using the selector set to analyze genetic alterations in a cell-free nucleic acid sample.... The methods can be used to measure tumor-derived nucleic acids in a

blood sample from a subject and thus to monitor the progression of disease in the subject. The methods can also be used for cancer screening, cancer diagnosis, cancer prognosis, and cancer therapy designation.” Ex1112 (Abstract). Quackenbush ¶278.

Diehn-530 explains that its methods “are provided for the highly sensitive analysis of circulating tumor DNA (ctDNA), e.g. DNA sequences present in the blood of an individual that are derived from tumor cells,” and that for its methods, “[t]umors of particular interest are solid tumors, including...lymphomas.” *Id.*, [0012]. In Table 10, Diehn-530 provides an exemplary selector (capture probe) set “comprising one or more genomic regions...useful for follicular lymphoma (FL)” ctDNA analysis. *Id.*, [0530]. Quackenbush ¶279.

Diehn-530 further explains methods for making “personalized selector” sets based on the identification of tumor-specific mosaic variants in paired versus normal whole-genome sequencing, as in Okosun-II. *Id.*, [880]. Capture probes are then created. *Id.* This personalized selector, i.e., a capture probe set, can be “applied for capture of the fragments of interest” in the cfDNA, “allowing the tracking and quantitation of those mutations originally discovered in the primary tumor within the corresponding cfDNA.” *Id.* In addition to the use of biotinylated oligonucleotide baits, Diehn-530 further explains that PCR-based capture probes may be used. *Id.* (“an alternative to affinity based hybrid capture of ctDNA/cfDNA,

amplicons specific to the corresponding region could be interrogated by PCR[.]”).

Quackenbush ¶280.

Accordingly, Okosun-II in view of knowledge of a POSA renders claim 2 obvious. Quackenbush ¶281.

3. Claim 3

As explained with respect to claim 2, above, the use of serial plasma samples as a source of cell-free tumor DNA comprising mosaic variants is rendered obvious by Okosun-II in view of the knowledge of a POSA. Quackenbush ¶¶282-283.

4. Claim 4

As explained above with respect to claims 1 and 2, Okosun-II discloses identifying mosaic variants to the tumor tissue sample in the form of tumor specific single nucleotide variants, which are also known as single nucleotide polymorphisms. *See, e.g.*, Ex1102.177. Quackenbush ¶¶285-287.

5. Claims 5 and 6

At a minimum, the mosaic variants identified in Okosun-II and other references reflecting the knowledge of a POSA necessarily constitute either causal or non-causal mutations. For example, Okosun-II states that “[l]ongitudinal analyses identified early driver mutations in chromatin regulator genes . . . whereas mutations in EBF1 and regulators of NF-kB signaling . . . were gained at transformation.” Ex1102.176; *see also id.* at 179 (“Mutations present in nearly all tumor cells (clonal)

would suggest early events and therefore represent initiating ‘driver’ genes.”). Thus, Okosun-II identified cancer-causing mosaic variants. Okosun’s analysis identifying driver genes also resulted in the ruling out of other mosaic variants as non-causal of cancer. Ex. 1102.177. Quackenbush ¶¶288-292.

6. Claims 7, 10, and 13

Okosun-II renders claims 7, 10, and 13 obvious. Quackenbush ¶¶293-301.

a) Obviousness Based on Serial Monitoring of ctDNA in Plasma

As explained above with respect to claim 2, a POSA would have found it obvious to identify tumor-specific mosaic variants in serially obtained blood samples using techniques that identify said mosaic variants using capture probes, including PCR-based capture probes and solution phase hybridization bait capture probes. Such methods further constitute enriching the extracted nucleic acid molecules of the serially obtained additional samples. Quackenbush ¶297.

b) Obviousness Based on Use of Whole Exome Sequencing for Additional Samples

In addition, Okosun-II renders obvious the use of capture probes to identify tumor-specific mosaic variants in an additional sample using whole exome sequencing (“WES”). Specifically, Okosun-II explained that it “performed whole-genome or whole-exome sequencing on 10 follicular lymphoma-transformed follicular lymphoma pairs followed by deep sequencing of 28 genes in an extension

cohort.” Ex1102.176. Okosun’s findings and results would have motivated a POSA to perform less sequencing than WGS on additional serial samples in some applications. For example, Okosun demonstrated the success of WES in parallel with its WGS experiment, and such WES would have represented a reliable and predictable way to reduce the amount of sequencing required in subsequent samples after identifying mutations of interest via initial WGS. The performance of such WES involves the use of capture probes. Quackenbush ¶298.

For example, Okosun-II explains that after identifying mosaic variants using the WGS and WES data generated in its ten index cases, they “focus[ed] on protein-altering changes” and “protein altering variants” affecting the identified mosaic genes. *Id.*, 176-177. When focused specifically on tumor-specific mosaic variants that effect protein-encoding genes, a POSA would have been motivated to target sequencing to protein-encoding genes, and applying WES to subsequent samples would have represented an obvious upper bound on such sequencing. Sequencing and analyzing “protein-altering changes” in subsequent samples using WES, as compared to WGS, would have been an economical approach to monitoring the mosaic variants identified in the initial WGS over time. A POSA would have reasonably expected success in doing so, given that Okosun-II reported successfully analyzing samples using both methods. This confirms that the choice of WES or

WGS in its workflow involves only the predictable substitution of one known method for another. Quackenbush ¶299.

Okosun-II further establishes that its WES involved the use of capture probes. The whole exome sequencing “[c]apture libraries were constructed from 3 µg of tumor and germline DNA using the Agilent SureSelect XT Human All Exon V4 kit.” It is well known in the art that the Agilent SureSelect product constituted a type of capture probes. *See* Ex1115, ¶93. Quackenbush ¶300.

F. There is no evidence of secondary considerations.

In the Case 1 IPRs, Personalis argued that each Petition’s alleged “failure to consider...secondary considerations of nonobviousness [] dooms [the] Petition.” *See, e.g.,* Ex1122.60; Ex1123.45. Here, as in the Case 1 IPRs, Foresight is unaware of any evidence of secondary considerations supporting the patentability of the ’968 patent.

In each of the Case 1 IPRs, Personalis contends that “Personalis’ assay has received widespread industry attention and praise due in part to its sensitivity relative to other methods.” *See, e.g.,* Ex1124.101 (“Personalis’ assay can detect tumor in DNA in blood plasma at levels of about one part per million (or 0.0001%).”). Neither the Case 1 patents nor the ’968 patent claim any particular “sensitivity,” nor do the pertinent specifications even discuss it. *See* Ex1001; Quackenbush ¶302. Thus, Personalis is not entitled to a presumption of nexus because the assay that is

allegedly praiseworthy “is not coextensive with the patented invention.” *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019). Nor can it prove that “the evidence of secondary considerations is the ‘direct result of the unique characteristics of the claimed invention.’” *Id.* at 1374.

G. The Board should not exercise its discretion under Section 325(d).

This Petition bases its grounds of challenge on three different primary references: Chan, Ley, and Okosun-II. Since Okosun-II was not cited at all during prosecution, and Chan and Ley were merely cited in an IDS, the Board should reach the merits. *See also* Ex1125.24511 (under USPTO proposed rulemaking, “The mere citation of a reference on an [IDS] during prosecution of the challenged patent, or in search results would not be considered sufficient to be deemed ‘previously addressed’ for purposes of 35 U.S.C. §325(d).”). Moreover, discretionary denial is inappropriate on the sole basis that Okosun-II invalidates all challenged claims (and anticipates the majority). *See Yita LLC v. MacNeil IP LLC*, IPR2023-00172, Paper No. 12 at 47 (P.T.A.B. June 13, 2023) (when reference not previously presented, “the first prong of the *Advanced Bionics* framework is not satisfied and we need not consider the second prong.”).

Nevertheless, discretionary denial based on Personalis’s citation of Chan and Ley in an IDS is also inappropriate. Even accepting that Chan and Ley were “previously presented,” “the Office erred in a manner material to the patentability of

the challenged claims” by not applying rejections based on the Grounds advanced in the Petition. *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8–9 (P.T.A.B. Feb. 13, 2020) (precedential). Chan and Ley were just two of the hundreds of references cited on the face of the patent. The Examiner did not cite them in rejections, and Personalis cannot contend that the claims were expressly distinguished over them.

Personalis contends that it “intentionally delayed issuance after the claims were first allowed” so that it could submit Ley and Chan, which Petitioner had cited against Personalis in the Case 1 IPRs. Ex1126.9. Not quite so. Foresight provided advance copies of its IPR against the ’394 patent (citing Ley and Chan), to Personalis on November 23, 2022, and filed the IPR on November 30, 2022. The initial Notice of Allowance for the ’968 patent was not mailed until weeks later, on December 15, 2022. Only after that allowance did Personalis then submit Ley and Chan, among many other references. *See* Ex1108.57-70; *id.*, 51-56. A new Notice of Allowance, which merely mentioned that this IDS was “considered,” issued on January 9, 2023. *Id.*, 48.

Further, the December 16, 2022 IDS did not include Foresight’s petitions and accompanying declarations, which provided additional information that would have informed the Examiner’s analysis, such as the mapping of the references to Personalis’s (albeit different) claims and Dr. Quackenbush’s explanation of a

POSA's understanding of the references. *Id.*, 51-56. Where, as here, references were “not extensively evaluated during examination and [were] not the basis for a rejection,” and the Petition “present[s] a sufficient showing that the Examiner overlooked disclosures” that invalidate the claims, “the Office erred in a manner material to [] patentability.” *Apple Inc. v. Telefonaktiebolaget LM Ericsson*, IPR2022-00457, Paper No. 7 at 8 (P.T.A.B. Sept. 21, 2022).

XII. CONCLUSION

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

Dated: November 22, 2023

Respectfully submitted,

/Andrew E. Krause/

Andrew E. Krause (Reg. No. 76,276)

Alan Heinrich (*pro hac vice* to be requested)

Jordan Nafekh (*pro hac vice* to be requested)

IRELL & MANELLA LLP

1800 Avenue of the Stars, Suite 900

Los Angeles, California 90067

Telephone: (310) 277-1010

Facsimile: (310) 203-7199

Amir Naini (Reg. No. 45,770)

NAINI P.C.

2632 Wilshire Blvd., Suite 268

Santa Monica, California 90403

Telephone: (310) 592-3030

Facsimile: (310) 453-9008

Attorneys for Petitioner,

Foresight Diagnostics Inc.

CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

I hereby certify, pursuant to 37 C.F.R. § 42.24, that the petition contains 13,772 words, excluding the words in the table of contents, exhibit list, claim listing, mandatory notices under § 42.8, this certificate of word count, and the certificate of service. The word count is based on the word count of the Microsoft Word program used to prepare the petition.

Dated: November 22, 2023

Respectfully submitted,

/Andrew E. Krause/

Andrew E. Krause

CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. sections 42.6 and 42.105, that a complete copy of the Petition for *Inter Partes* Review of U.S. Patent No. 11,584,968 and EX1001-1003, 1005-1008, 1010, 1012-1015, 1021, 1023-1024, 1027-1029, 1070, 1077, 1100-1126 are being served via Express Mail on November 22, 2023, the same day as the filing of the above-identified documents in the United States Patent and Trademark Office/Patent Trial and Appeal Board, upon the patent prosecution counsel of record for the Patent Owner:

182685 - ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614
UNITED STATES

Courtesy copies were also sent via ShareSite to Patent Owner's counsel of record in the related district court litigation at the following addresses:

edward.reines@weil.com
derek.walter@weil.com
nate.ngerebara@weil.com

/Susan M. Langworthy/
Susan M. Langworthy