

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS INC.,
Petitioner,

v.

PERSONALIS, INC.
Patent Owner.

Case IPR2024-00170
U.S. Patent No. 11,584,968

**PATENT OWNER'S PRELIMINARY RESPONSE TO PETITION FOR
INTER PARTES REVIEW OF U.S. PATENT NO. 11,584,968**

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37 C.F.R. § 42.104	3, 13, 22, 29, 36

EXHIBIT LIST

Exhibit No.	Description
2001	The Scientist Staff, “2022 Top 10 Innovations,” Dec. 12, 2022, available at https://www.the-scientist.com/features/2022-top-10-innovations-70792
2002-2009	RESERVED
2010	<i>Curriculum Vitae</i> of Dr. Henry Morrice Furneaux
2011-2017	RESERVED
2018	Transcript of the deposition of John Quackenbush, Ph.D., taken on September 21, 2023 in the related matter of <i>Foresight Diagnostics Inc. v. Personalis, Inc.</i> , IPR2023-00224 and IPR2023-00317.
2019-2188	RESERVED
2189	Institution Decision in the related matter of <i>Foresight Diagnostics Inc. v. Personalis, Inc.</i> , IPR2023-00224, Paper 11.
2190	Foresight’s Corrected Reply to Patent Owner’s Response in the related matter of <i>Foresight Diagnostics Inc. v. Personalis, Inc.</i> , IPR2023-00224, Paper 35.
2191	“Low-coverage Whole Genome Sequencing,” available at https://www.cd-genomics.com/resource-lcwgs.html
2192	Nguyen et al., “Automation of molecular-based analyses: a primer on massively parallel sequencing,” Clin Biochem Rev 35:169-176 (2014)

Exhibit No.	Description
2193	Jessri et al., “Harnessing massively parallel sequencing in personalized head and neck oncology,” J. Dent Res 93:437-444 (2013)
2194	Forsheew, et al., “Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA,” Science Translational Medicine (2012); EX1030 in the related matter of Foresight Diagnostics Inc. v. Personalis, Inc., IPR2023-00224.
2195	Zvaifler et al., “Mesenchymal precursor cells in the blood of normal individuals,” Arthritis Res 2:477-488 (2000)
2196	Solovey et al., “Circulating activated endothelial cells in sickle cell anemia,” The New England Journal of Medicine, 1584-1590, 1997
2197	Schmid et al., “Circulating Endothelial Progenitor Cells,” Chapter 8 in Methods in Molecular Biology, Angiogenesis Protocols, 2nd ed., 467:139-155
2198	Efrati et al., "The morphology of buffy coat in normal human adults," Blood 16:1012-1019 (1960)
2199	Declaration of Dr. Henry Morrice Furneaux
2200	Spiro et al., “Follicular lymphoma: a survey of 75 cases with special reference to the syndrome resembling chronic lymphocytic leukaemia,” British Journal of Cancer 31, Suppl. II, 60-72 (1975)

Patent Owner Personalis Inc. (“Personalis”) submits this Preliminary Response to the Petition filed by Foresight Diagnostic Inc. (“Foresight”) regarding U.S. 11,584,968 (“the ’968 patent”).

I. INTRODUCTION

Personalis is an undisputed leader in developing innovative assays for screening patients for cancer. Personalis has been developing innovative assays in this field since its founding in 2011—nearly a decade before Foresight was founded in 2020. Seeking to compete in the marketplace, Foresight has adopted the innovations developed by Personalis. EX1119.

This proceeding marks the fifth petition filed by Foresight in its invalidity campaign against the patents rightfully issued by the U.S. Patent & Trademark Office to Personalis. Across these proceedings, Foresight has taken the unreasonable position that every single one of over 100 challenged claims from five different patents are all unpatentable. Moreover, Foresight is planning to file IPR petitions on yet two more patents that collectively contain over 60 additional claims. Foresight apparently believes that the Office is incapable of examining and issuing patentable claims to Personalis.

Here, the ’968 patent claims recite a novel and nonobvious process for analyzing a biological sample obtained from a subject being screened for a cancer by using whole genome sequencing (WGS) of the cancer patient’s tumor tissue DNA

and matching normal leukocyte DNA from a blood sample to identify mosaic variants such as single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms, or other variants present only in the patient's tumor tissue and then looking for those variants from an additional blood or other sample obtained from a source different than the tumor tissue sample in order to predict, diagnose, and/or prognose a status or outcome of a cancer in that patient. Personalis' NeXT Personal[®] detection and monitoring assay practices the '968 patent and has been hailed by *The Scientist* magazine as the top scientific innovation in 2022. EX2001 1-2.

Through this proceeding, Foresight seeks to avoid liability for infringing the claimed invention via five Grounds based on three references: (1) alleged anticipation by the Chan reference, (2) alleged obviousness based on Chan, (3) alleged obviousness based on Ley, (4) alleged anticipation by Okosun-II, and (5) alleged obviousness based on Okosun-II. Foresight fails to raise a reasonable likelihood of unpatentability based on any of these challenges.

First, Foresight fails to proffer any construction of the WGS recited by the claims. WGS has been—and remains—a central dispute between the parties dating back to the first IPR petition filed by Foresight against Personalis. The parties submitted competing definitions of WGS in that proceeding, and the Board has preliminarily adopted Personalis's construction. Foresight's expert, Dr. Quackenbush, conceded that WGS has taken on different meanings in different

contexts. Construction of this term is therefore required. There is no excuse for Foresight's failure to inform the Board and Personalis how it believes WGS should be construed in this case. Foresight was required to construe this term in its Petition under Rule §42.104(b)(3)-(4). Its failure to do so compels denial of the Petition.

Second, Foresight's challenges based on Chan require this reference to teach multiple claim limitations *inherently* rather than expressly. For example, Foresight alleges that Chan's massively parallel sequencing (MPS) inherently teaches WGS. But there is no indication that Chan's MPS constitutes WGS. Foresight also alleges that Chan's buffy coat sample inherently teaches the use of the claimed leukocytes. But there are several types of non-leukocyte cells in the buffy coat. Foresight fails to establish that Chan's disclosures necessarily teach the claimed limitations, and its inherency positions therefore fail.

Third, Foresight fails to present any obviousness theory regarding independent claim 1 based on Chan. Its obviousness challenge based on Chan therefore fails.

Fourth, Foresight's challenge based on Ley fails to teach multiple claim limitations. For example, Foresight's challenge requires a person of ordinary skill in the art (POSA) to reverse the *tumor blood* sample and *normal tissue* sample used by Ley to arrive at the *tumor tissue* and *normal blood* samples required by the claimed invention. Ley, however, explains that its method involved carefully

selecting a leukemia patient precisely because the tumor blood sample in the patient provides the type of highly pure tumor sample **required** for Ley's approach. Foresight fails to establish a motivation for a POSA to go against Ley's teachings to instead use a **tumor tissue** sample that would be contaminated with non-tumor cells. In fact, Foresight's own exhibits teach that such contamination creates undesirable challenges for detecting and diagnosing cancer that a POSA would have avoided.

Fifth, Foresight's challenges based on Okosun-II fail to teach or suggest multiple claim limitations. For example, Foresight alleges that Okosun-II's peripheral blood sample inherently teaches the use of the claimed leukocytes. But there are several non-leukocyte sources of DNA in peripheral blood, and Foresight does not prove that a POSA would have used the claimed leukocytes in view of Okosun-II's teachings. This is particularly true because Okosun-II's study was designed to identify and monitor progression of follicular lymphoma. There was no motivation to use the claimed leukocytes in Okosun-II's study because follicular lymphoma patients that enter, or present with, leukemic phase follicular lymphoma would have cancerous lymphocytes contaminating the normal leukocyte population in the peripheral blood. As another example, Foresight relies on Okosun-II's follicular lymphoma tissue biopsies to allegedly meet the claimed invention. The claimed invention, however, requires the tissue tumor sample to be obtained from a **different** source than the additional sample. Okosun-II's tissue biopsies are taken

from the *same* follicular tissue source, and therefore fail to meet the claimed invention.

Numerous additional deficiencies with each of Foresight's challenges are detailed throughout this Preliminary Response. Foresight has not raised a reasonable likelihood of establishing that the challenged claims were anticipated or obvious at the time of the invention. The Board should not institute review.

II. OVERVIEW OF THE '968 PATENT

The '968 patent relates to "methods for using mosaicism in nucleic acids sampled distal to their origin," and such methods are useful for "improving detection and monitoring of human diseases." EX1001 Title, Abstract. Claim 1 is the only independent claim challenged by the Petition and it recites:

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.

EX1001 Claim 1.

The specification explains that diseases may “occur in locations of the body which are difficult to access without surgery or similarly invasive procedures.”

EX1001 1:18-20. Detecting such diseases becomes difficult due to the invasive nature of the procedures, 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.” *Id.* 1:20-24.

The claimed invention is directed to “[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.” *Id.* 54:30-33. The claimed method provides an innovative solution to detecting and monitoring cancer in a subject. *Id.* 1:60-61, 8:19-29, 36:46-51.

The claimed method requires obtaining a first set of sequence reads and a second set of sequence reads by sequencing nucleic acid molecules using whole genome sequencing, such that the first set of nucleic acid molecules is extracted from a tissue sample of the subject and the second set of nucleic acid molecules is extracted from leukocytes from a blood sample. *Id.* 54:34-47. The specification provides embodiments where “the method comprises identifying variants in nucleic acid molecules of the first component with respect to nucleic acid molecules of the second component. In some embodiments, the nucleic acid molecules of the second component are extracted by disrupting the leukocytes.” *Id.* 2:33-38. The specification describes tissue sample sources of nucleic acids. *See e.g., id.* 44:54-45:4, 45:31-42. The specification explains, for example, that “[n]ucleic acids are extracted from the samples and are sequenced by whole genome sequencing (WGS) to identify differential mutations between the various tissue samples.” *Id.* 52:51-53; *see e.g., id.* 3:22-24 (“In some embodiments, the sequencing comprises whole genome sequencing.”); 4:31-32, 17:36-37.

The claimed method uses the first set of sequence reads and second set of sequence reads to identify mosaic variants specific to the tissue sample of the first set of sequence reads that is not present in the second set of sequence reads. *Id.* 54:48-52. The term variant “generally refer[s] to a nucleic acid molecule comprising a polymorphism.” *Id.* 6:46-49. The specification explains, for example, that “the methods may comprise identifying mosaic mutations specific to at least one particular subset of patient's cells.” *Id.* 13:42-50.

The claimed method requires identifying mosaic variants specific to the tissue sample in an additional sample of the subject that is obtained from a different sample source and at a different time point than the previously obtained tissue sample. *Id.* 54:53-58. The identification of mosaic variants in an additional sample from the subject from a different sample source and different time point allows the detection and monitoring of cancer in the subject. *See e.g., id.* 1:60-61, 8:19-29, 36:46-51. The specification describes appropriate sample sources for the identification of mosaic variants in the claimed method. *See e.g., id.* 13:22-26, 44:54-45:2, 45:31-35.

Finally, the claimed method provides a report based on the identification of the mosaic variants of the tissue sample from the additional sample taken from the subject where the report may provide predicting, diagnosing, and/or prognosing a status or outcome of a cancer in the subject. *Id.* 54:59-63. The report may include

“a determination of the state of health of the subject” and “providing a therapeutic intervention based on a determination of the state of health of the subject.” See *e.g.*, *id.* 11:21-27; see also *e.g.*, *id.* 2:17-24, 4:28-30.

III. THE LEVEL OF ORDINARY SKILL IN THE ART

Foresight proposes an expansive definition for a POSA. Specifically, Foresight contends that as of October 2014 a POSA:

Would 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.

Petition 8-9 (citing EX1100 ¶36).

Over Personalis’s objection, the Board adopted Foresight’s definition of the POSA in the related matters of *Foresight Diagnostics Inc. v. Personalis, Inc.*,

IPR2023-00224, IPR2023-00317, IPR2023-00545, and IPR2023-00546. Here, Foresight’s challenges fail to establish a reasonable likelihood of prevailing under its proposed level of ordinary skill. Foresight’s definition, however, attempts to imbue the POSA with an array of different skills and competencies that do not accurately reflect the state of the field at the time of the October 2014 priority date. Therefore, Personalis reserves the right to offer a competing definition in this proceeding in the unlikely event that the Board institutes trial. Personalis further reserves the right to offer a competing definition in other forums.

IV. GROUND 1: LACK OF ANTICIPATION BY CHAN

“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. Inc. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Chan fails to anticipate claim 1 because it does not teach at least four distinct requirements of the claim. Specifically, Chan fails to teach:

- “whole genome sequencing” as required by limitation 1(a);
- the “second set of nucleic acid molecules is extracted from *leukocytes*”¹
as required by limitation 1(a)(ii);

¹ All emphases supplied unless otherwise noted.

- “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” as required by limitation 1(b); and
- “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” as required by limitation 1(c).

A. Limitation 1(a): whole genome sequencing

Limitation 1(a) requires, *inter alia*, “said first set of sequence reads and said second set of sequence reads are generated using ***whole genome sequencing***.”

Foresight’s petition fails to demonstrate that Chan teaches the claimed “whole genome sequencing” for several reasons discussed below.

1. Foresight failed to construe “whole genome sequencing”

Foresight fails to proffer any construction of “whole genome sequencing” (WGS), even though it is well aware that determining whether the prior art teaches WGS has been—and remains—a central dispute between the parties. For example, in the related matter of *Foresight Diagnostics Inc. v. Personalis, Inc.*, IPR2023-00224, the Board evaluated the relevant intrinsic record in its Institution Decision

and correctly determined that WGS means “a non-targeted approach to sequencing all or almost all of a genome.” IPR2023-00224, Paper 11 at 19-23 (PTAB June 2023) (EX2189). In that proceeding, Personalis disputes whether Chan discloses WGS under this correct construction. EX1116 77-78. Foresight was aware of this dispute for nearly two months before it filed the present petition.

Further, in IPR2023-00224 Foresight disagreed with the Board’s construction of WGS and instead asserted that the plain meaning of WGS is “a non-targeted approach to generating sequence reads and mapping those reads back to a reference genome (rather than a genome subset).” IPR2023-00224, Paper 35 at 1-5 (EX2190). Given the competing definition of WGS presented by Foresight in the related matter, it was incumbent upon Foresight to explain how WGS should be construed in the context of the ’968 patent.

Construction of “whole genome sequencing” is required because the term has taken on different meanings in different contexts. For example, Foresight’s expert in IPR2023-00224 is Dr. Quackenbush, who is the same expert used by Foresight in this proceeding. He testified that the term WGS has taken on many different flavors of meaning as follows:

Q. Now, we've talked a lot about whole-genome sequencing. When did you first become familiar with whole-genome sequencing?

A. So it's hard to answer that question because the term has taken on many different flavors of meaning.

EX2018 155:15-20. He further testified that “[w]hole-genome sequencing is a concept that has existed for a long time, and it’s had a variety of different definitions,” *id.* 161:21-162:1, and that the term has been used “in different ways by different individuals in different contexts.” *Id.* 156:20-157:22. There is no excuse for Foresight’s failure to construe WGS in this proceeding in view of Dr. Quackenbush’s explanation that WGS has different meanings in different contexts and the competing definitions of WGS presented by the parties in the related matter.

The rules require Foresight to establish “[h]ow the challenged claim is to be construed,” and “[h]ow the construed claim is unpatentable.” 37 C.F.R. §42.104(b)(3)-(4). The Petition does not satisfy the rules and should be denied for at least this reason. *See Hologic, Inc. v. Enzo Life Sciences, Inc.*, IPR2018-00019, Paper 17 at 6-9 (PTAB 2018) (denying institution because “[t]he Petition does not satisfy 37 C.F.R. 42.104(b).”); *Jiawei Tech. Ltd. v. Simon Nicholas Richmond*, IPR2014-00937, Paper 22 at 7-8 (PTAB 2014) (denying institution because petitioner did not “explain how the challenged claims are to be construed” and, therefore, “has not demonstrated a reasonable likelihood of success”); *DJI Europe B.V. v. Textron Innovations Inc.*, IPR2023-01107, Paper 14 at 6-9 (PTAB 2024) (denying institution where “Petitioner chose not to provide a claim interpretation.... in the face of claim language that is admittedly subject to some range of interpretations”).

Foresight cannot bypass claim construction because the first step of a validity determination “involves the proper interpretation of the claims,” and only thereafter does it proceed to the second step of “determining whether the limitations of the claims as properly interpreted are met by the prior art.” *TI Group Automotive Sys., Inc. v. VDO N.Am., LLC*, 375 F.3d 1126, 1139 (Fed. Cir. 2004). Foresight’s failure to construe WGS compels denial of the Petition. Denial is required because, “[u]nlike district court litigation—where parties have greater freedom to revise and develop their arguments over time and in response to newly discovered material—the expedited nature of IPRs bring with it an obligation for petitioners to make their case in their petition to institute.” *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016).

2. The proper construction of “whole genome sequencing”

As mentioned above, the Board previously construed “whole genome sequencing” to mean “a non-targeted approach to sequencing all or almost all of a genome” in the related matter of IPR2023-00224. *See* EX2189 19-23. The Board based its construction on the intrinsic record of the relevant patent. *Id.* Here, the ‘968 patent contains a nearly identical intrinsic record that compels the same construction. Just as in the previous proceeding, the same construction is supported here by the plain language of the term and the specification.

As to the claim language, “whole genome sequencing” uses the word “whole” to modify “genome” to indicate that the entirety—not a part or subset—of the genome must be sequenced. The plain language of the claim term confirms that the Board’s previous construction of WGS is correct.

The specification supports the Board’s construction. The specification consistently distinguishes methods that sequence the “whole genome” from “targeted genome sequencing” that sequence only a portion of the genome, such as the “exome.” EX1001 3:22-29 (“In some embodiments, the sequencing comprises whole genome sequencing. In some embodiments, the sequencing comprises targeted genome sequencing.”), 4:31-38 (same), 17:36-64 (comparing “whole genome sequencing” and sequencing “over an entire exome (e.g., whole exome sequencing)”), 25:46-52 (“combin[ing] whole exome sequencing and a whole genome sequencing reactions may increase the sensitivity or specificity in detecting one or more copy number variations or diagnosing a specific condition when compared to the sensitivity or specificity of whole exome sequencing alone”), 26:46-53 (same). The “exome” is the part of the genome containing the exons (*see e.g., id.*, 30:19-22), and the specification consistently refers to “whole genome sequencing” as a separate category of sequencing than “exome sequencing.” *Id.* 15:34-37 (referring to “exome **or** whole genome sequencing”), 17:67-18:1 (“In some cases, sequencing specific genomic regions may comprise using exome

sequencing.”). The specification also distinguishes “whole genome sequencing” from “other methods” that sequence only a portion of the genome, such as “deep sequencing over a fraction of the genome.” *Id.* 17:36-49.

The specification further differentiates “whole genome sequencing” from methods that sequence sub-genomic regions.² For example, the specification explains that “genomic regions” can be selected based on various traits, and “may comprise an entire genome or a portion thereof.” *Id.* 28:40-41. Alternatively, “genomic regions” may comprise “an entire exome or a portion thereof,” “one or more sets of genes,” or “one or more sets of regulatory elements.” *Id.* 28:41-48. The specification further acknowledges that whole genome sequencing may encompass “low mean coverage regions” and “zero mean coverage regions.” *Id.* 28:57-60, 32:37-46.

² The specification additionally refers to “low coverage whole genome sequencing,” which a POSA would understand constitutes its own category of sequencing rather than a subclass within WGS. *Compare* EX1001 25:64-67, 26:6-13 (describing “low coverage whole genome sequencing”) *with* 26:18-25 (describing “whole genome sequencing”); EX2191; EX2199 ¶¶44, 46.

Personalis's expert, Dr. Furneaux, has reviewed the intrinsic record and agrees that the Board's construction of WGS from IPR2023-00224 should also apply here. EX2199 ¶¶35-43, 47.

In view of the intrinsic evidence, whole genome sequencing should be construed as "a non-targeted approach to sequencing all or almost all of a genome." This construction stays true to the intrinsic evidence and is consistent with the Board's previous construction based on a substantively identical intrinsic record.

3. **Chan does not expressly or inherently teach "whole genome sequencing"**

Foresight does not assert that Chan ***expressly*** discloses the "whole genome sequencing" required by limitation 1(a). Petition 27-28. Indeed, Chan never refers to its method as using "whole genome sequencing" or as "a non-targeted approach to sequencing all or almost all of the genome." Instead, Foresight relies on Chan's "massively parallel sequencing" (MPS) to ***inherently*** teach the WGS required by limitation 1(a). *Id.* There is a "high standard" for Foresight to prove anticipation because inherency requires that the limitation at issue "necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *Par Pharm., Inc. v. TWI Pharms. Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014). Foresight has not met that high standard.

Foresight wrongly equates Chan's MPS with WGS. Petition 28. MPS is a broad term that refers to "hundreds of thousands to millions of DNA sequencing

reactions [being] performed simultaneously, or ‘in parallel’, with each sequencing step being coupled with detection.” EX2192 169. “MPS is also referred to as next-generation sequencing (NGS).” *Id.*; *see also* EX2193 437 (“Massively parallel sequencing, otherwise known as next generation sequencing (NGS)”); EX2199 ¶¶48-49. Even Foresight’s Petition and exhibits acknowledge that MPS is merely another name for NGS. *See* Petition 10 (“‘next generation sequencing’ (‘NGS’), sometimes also called ‘massively parallel sequencing’”); EX1014 527 (“next-generation sequencing (NGS) or massively parallel sequencing”); EX1013 1135 (entitled “Next-generation DNA sequencing” and abstract discussing “massively parallel DNA sequencing platforms”).

MPS can be used for a host of different types of applications that are not WGS. MPS can be used for sequencing whole exomes, targeted genes, targeted exons, confirmatory sequencing, reduced representation sequencing, transcriptome sequencing, metagenomic sequencing, small RNA sequencing, nuclease fragmentation, and chromatin immunoprecipitation-sequencing (ChIP-Seq). For example, Nguyen teaches that “MPS is being increasingly used in many areas of medicine” and explains that MPS can be used to sequence at least eight types of nucleic acid targets as follows:

Depending on the purpose, different nucleic acid targets may be sequenced:

- Whole genome
- Whole exome
- Targeted genes
- Transcriptome - RNA sequence including mRNA, tRNA
- Mitochondrial genome
- Metagenome-microbial DNA in biological samples
- Methylome – DNA sequence including cytosine methylation state
- Chromatin immunoprecipitation-Sequencing (ChIP-Seq): regions of DNA that bind to transcription factors, co-factors or chromatin proteins.

EX2192 173; EX2199 ¶50.

Foresight’s Ross reference teaches that MPS/NGS has several “major uses” that include “whole exome sequencing,” “whole genome sequencing,” “SNP detection,” “targeted exon sequencing,” “confirmatory sequencing,” and “targeted sequencing projects” as follows:

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Table 3
Commercial Next-Generation Sequencing Platforms*

	Basic Technique	Major Uses	Time Needed	Instrument Cost (\$, thousands)
Illumina	Flow cell-based, reversible dye termination, and 4-color optical imaging	Whole exome sequencing; whole genome sequencing; SNP detection	Intermediate, 4 d fragment; 9 d paired end	500-900
454 Pyrosequencing	Emulsion PCR with bead-based pyrosequencing and CCD light imaging	Targeted exon sequencing; confirmatory sequencing; SNP detection	Fast, <1 d	500-700
Helicos	Oligo-dT captured PolyA-tailed DNA fragments; flow cell 4-color dNTP optical imaging	Single molecule sequencing; whole genome sequencing	Slowest, 8 d	999
SOLiD	Sequential dinucleotide ligation; flow cell-based 4-color optical imaging	Whole exome sequencing; whole genome sequencing; SNP detection	Slow, 7 d fragment run; 14 d paired end	600-700
Ion Torrent	Semiconductor-based nonoptical detection; standard dNTP sequencing chemistry	Targeted sequencing projects not demanding deep sequencing	Fast, <1 d	50

CCD, charge-coupled device; dNTP, deoxynucleoside triphosphate; PCR, polymerase chain reaction; SNP, single nucleotide polymorphism.
* Adapted from Metzker.⁵⁵

EX1014 530; EX2199 ¶51.

Foresight’s Shendure reference teaches that MPS/NGS has at least eleven applications:

Table 2 Applications of next-generation sequencing		
Category	Examples of applications	Refs
Complete genome resequencing	Comprehensive polymorphism and mutation discovery in individual human genomes	44
Reduced representation sequencing	Large-scale polymorphism discovery	45
Targeted genomic resequencing	Targeted polymorphism and mutation discovery	46–52
Paired end sequencing	Discovery of inherited and acquired structural variation	53,54
Metagenomic sequencing	Discovery of infectious and commensal flora	55
Transcriptome sequencing	Quantification of gene expression and alternative splicing; transcript annotation; discovery of transcribed SNPs or somatic mutations	56–63
Small RNA sequencing	microRNA profiling	64
Sequencing of bisulfite-treated DNA	Determining patterns of cytosine methylation in genomic DNA	60,65,66
Chromatin immunoprecipitation–sequencing (ChIP-Seq)	Genome-wide mapping of protein-DNA interactions	67–70
Nuclease fragmentation and sequencing	Nucleosome positioning	69
Molecular barcoding	Multiplex sequencing of samples from multiple individuals	61,71

EX1013 1141; EX2199 ¶52.

Chan cites to Forshew (EX2194) when describing MPS as follows:

With the advent of massively parallel sequencing (MPS),⁸ several groups have incorporated this approach for developing new plasma DNA-based cancer markers.

EX1008 211. Citation 8 in Chan is the Forshew reference (EX2194). Forshew describes the “targeted deep sequencing” of certain genomic regions, which does not constitute WGS. EX2194 1; EX2199 ¶53.

Chan’s description of a “shotgun” type of MPS does not transform Chan’s MPS into WGS. “Shotgun” MPS merely refers to MPS in which the DNA to be sequenced has been randomly broken into smaller fragments. For example, Foresight’s Gnirke reference performed “[t]argeting genomic loci by massively parallel sequencing,” EX1005 182, using shotgun sequencing of the targeted loci, *id.* 183-184. Gnirke’s shotgun MPS is not WGS because it sequenced targeted loci. EX2199 ¶54. Foresight’s Meyerson reference teaches that “shotgun sequencing with incomplete coverage” provides a “lower-cost” alternative to WGS that is “sufficient to identify somatic rearrangements in the genome and copy number alterations.” EX1031 687.

Chan does not report that its shotgun MPS sequenced all or almost all of the genome. Chan’s note that it sequenced to a **depth** of “29.5-fold” or “43-fold” does not indicate that its MPS sequencing provided coverage across all or almost all of the genome. EX1008 218. Chan is devoid of any mention of the sequence coverage

achieved by its MPS. EX2199 ¶55. Further, Chan fails to provide the sequencing data for the buffy coat samples. The limited information provided by Chan demonstrates that its MPS is not WGS. Chan's Figures 1 and 4 are "Circos" plots resulting from the MPS sequencing data. EX1008 215 ("Fig. 1 shows Circos plots"). The Circos plots show that large portions of sequencing data are missing from at least chromosomes 1, 9, 13, 14, 15, 16, 19, 21, and 22—and all data from chromosomes x and y are missing. *Id.* Figs. 1, 4; EX2199 ¶¶55-60. From the available information in Chan's Circos plots, Dr. Furneaux determined that Chan did not sequence all or almost all of the genome. *Id.* The record is overwhelmingly clear that Chan's MPS cannot be equated with WGS. Thus, Chan's use of MPS does not expressly or inherently teach WGS.

4. Conclusion regarding WGS

Foresight failed to conduct the first step in a validity analysis, which is to construe WGS. The Petition must be denied for at least this reason. 37 C.F.R. §42.104(b)(3)-(4); *Hologic*, IPR2018-00019, Paper 17 at 6-9.

Foresight further failed to demonstrate that Chan's MPS constitutes WGS. MPS is not expressly or inherently WGS. Accordingly, Foresight failed to prove that Chan anticipates claim 1, and the Petition must be denied.

B. Limitation 1(a)(ii): nucleic acid molecules extracted from leukocytes

Limitation 1(a)(ii) requires that “said second set of nucleic acid molecules is extracted from *leukocytes* from a blood sample.”

Foresight does not allege that Chan *expressly* teaches extracting a set of nucleic acid molecules from leukocytes. Petition 27-29. Instead, Foresight alleges that Chan’s disclosure that “[g]enomic DNA was extracted from patients’ buffy coat samples” *inherently* teaches extracting nucleic acid molecules from leukocytes. *Id.*; EX1008 212. Foresight asserts that Chan’s buffy coat sample inherently meets the leukocytes required by limitation 1(a)(ii) merely because the buffy coat sample “contains leukocytes.” Petition 29. This assertion fails to prove anticipation because inherency requires that the limitation at issue “necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art.” *Par Pharm.*, 773 F.3d at 1196.

Foresight ignores that a patient’s buffy coat contains several types of nucleated non-leukocyte cells from which genomic DNA can be extracted. EX2199 ¶¶63-64. For example, a patient’s buffy coat contains at least the following four types of nucleated non-leukocyte cells: (1) endothelial cells, (2) endothelial progenitor cells, (3) mesenchymal precursor cells, and (4) megakaryocytes. Personalis’s expert, Dr. Furneaux, explains that the literature verifies the presence of these non-leukocyte cells in the buffy coat as follows:

- **Endothelial cells.** Solovey “used immunohistochemical examination of buffy-coat smears to enumerate circulating endothelial cells.” EX2196 1584. Solovey determined that the “[m]ean ($\pm$ SD) numbers of circulating endothelial cells in normal blood donors, patients with sickle cell trait, and patients with hemolytic anemias not due to hemoglobin S were 2.6 ± 1.6 , 3.0 ± 2.6 , and 2.0 ± 0.8 per milliliter of whole blood, respectively.” *Id.*
- **Endothelial progenitor cells.** Schmid describes a protocol that isolates endothelial progenitor cells from the buffy coat. EX2197 139, 146-148.
- **Mesenchymal precursor cells.** Zvaifler teaches that “BMPCs [blood-derived mesenchymal precursor cells] were elutriated by diluting the buffy coats” in more than 100 normal persons. EX2195 478. Zvaifler reports that “[m]ore than 100 consecutive buffy coats from normal individuals were processed.... In every case, the appropriate elutriation fractions had cells with the BMPC morphology.” *Id.* 479. Zvaifler explains that “it is likely that 500 ml of normal blood will have several thousand BMPCs.” *Id.* 482.

- **Megakaryocytes:** Efrati “examined buffy coats from peripheral blood of 55 normal adults,” EX2198 1012, and reported a mean value of 21.79 ± 17.27 megakaryocytes per ml of blood. *Id.* 1017, Table 2.

EX2199 ¶¶65-70.

Foresight has not proven that Chan’s extraction of DNA from buffy coat samples necessarily involves extraction of nucleic acid molecules from leukocytes because the buffy coat samples contain several types of nucleated non-leukocyte cells from which nucleic acid molecules might have been extracted. Foresight’s petition is based merely on “assumption[s] and its own contentions” about what type of cell Chan might have extracted nucleic acid molecules from, which fails to prove inherent anticipation. *Crown Operations Intern., Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1378 (Fed. Cir. 2002).

C. Limitation 1(b)

Limitation 1(b) requires “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.”

Chan fails to disclose the “first set of sequence reads” and “second set of sequence reads” required by limitation 1(b) for several reasons.

First, the “said” sets of first and second sequence reads required by limitation 1(b) refers back to the sequence reads generated by limitation 1(a). Chan does not anticipate generating the first and second sets of sequencing reads using WGS required by limitation 1(a). *Supra* Section IV.A. Therefore, Chan also necessarily fails to anticipate the first and second sets of sequencing reads required by limitation 1(b).

Second, Chan does not anticipate the second set of nucleic acid molecules that is extracted from leukocytes as required by limitation 1(a)(ii). *Supra* Section IV.B. Therefore, Chan also necessarily fails to anticipate using the second set of sequencing reads of limitation 1(b).

Third, the invention recited by claim 1 constitutes an integrated series of steps for analyzing a biological sample that captures the inventors’ innovative contribution to screening subjects for cancer. Foresight’s failure to prove that Chan anticipates limitation 1(a) has a cascading impact on its failure to prove unpatentability for the rest of claim 1, which highlights the many ways that Chan’s disclosure departs from the claimed invention. For at least these reasons, Foresight fails to demonstrate that Chan anticipates limitation 1(b).

D. Limitation 1(c)

Limitation 1(c) requires “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.” The “said” mosaic variants of limitation 1(c) refers back to the mosaic variants identified using the first and second set of sequence reads of limitation 1(b).

Chan does not anticipate identifying mosaic variants using the first and second sets of sequence reads of limitation 1(b) because Chan does not anticipate the WGS required by limitation 1(a), and also because Chan does not anticipate extracting nucleic molecules from leukocytes as required by limitation 1(a)(ii). Chan also necessarily fails to anticipate limitation 1(c) at least because Chan fails to anticipate limitations 1(b) and 1(a). Chan’s failure to anticipate multiple requirements of limitations 1(a) and 1(b) that provide antecedent basis for the identification of the mosaic variants recited by limitation 1(c) demonstrates just how divergent Chan’s disclosures are from the specific series of steps that comprise the invention recited by claim 1.

E. Conclusion regarding Ground 1

Foresight failed to construe “whole genome sequencing,” which provides an independent reason for denying the Petition. In addition, Foresight failed to prove that Chan anticipates at least four requirements of independent claim 1. Foresight therefore also fails to establish anticipation of any dependent claim. *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012) (“It is axiomatic that a

dependent claim cannot be broader than the claim from which it depends.”). Ground 1 therefore fails.

V. GROUND 2: NONOBVIOUSNESS OVER CHAN

A petition based on “obviousness requires a suggestion of all limitations in a claim.” *CFMT, Inc. v. YieldUp Int’l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003). Foresight fails to prove obviousness of claim 1 for several reasons discussed below.

A. Foresight fails to present an obviousness theory for claim 1

First, Ground 2 begins with Foresight’s obviousness position for dependent claim 2—*Foresight’s petition is completely silent as to how it believes claim 1 could possibly be obvious over Chan.* Petition 35. Foresight apparently has an incorrect belief that its anticipation challenge to claim 1 necessarily proves obviousness. Anticipation and obviousness, however, “are distinct and separate challenges to a patent’s validity.” *Duro-Last, Inc. v. Custom Seal, Inc.*, 321 F.3d 1098, 1107 (Fed. Cir. 2003); *TorPharm, Inc. v. Ranbaxy Pharms., Inc.*, 336 F.3d 1322, 1326 n3 (Fed. Cir. 2003) (“novelty and nonobviousness are separate concepts that are best kept analytically distinct”). Foresight’s lack of any analysis regarding how it believes Chan might render obvious claim 1 fails to prove obviousness because “there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). ***Ground 2 fails for this reason alone.***

Although Personalis is not required to further rebut Foresight's complete silence regarding the obviousness of claim 1 over Chan, Personalis provides the following substantive reasons why Chan fails to render obvious claim 1.

B. Limitation 1(a): whole genome sequencing

As discussed above, Foresight failed to proffer a construction of WGS, and Ground 2 fails for at least this reason. 37 C.F.R. §42.104(b)(3)-(4); *Jiawei*, IPR2014-00937, Paper 22 at 7-8 (PTAB 2014) (denying institution because petitioner did not “explain how the challenged claims are to be construed” and, therefore, “has not demonstrated a reasonable likelihood of success”).

Also as discussed above, Foresight relies on Chan's MPS as a supposed *inherent* disclosure of WGS. “The use of inherency in the context of obviousness must be carefully circumscribed because that which may be inherent is not necessarily known and that which is unknown cannot be obvious.” *Southwire Co. v. Cerro Wire LLC*, 870 F.3d 1306, 1310 (Fed. Cir. 2017). For inherency to supply a missing claim limitation in an obviousness analysis, “the limitation at issue necessarily must be present.” *Id.* 1311. Foresight did not prove that Chan's MPS inherently discloses WGS, and Ground 2 fails for at least this reason.

Foresight provides no reason why a POSA would modify Chan's MPS to use WGS. As discussed below, a POSA would not have been so motivated based on at

least (1) the large data burden imposed by WGS, and (2) the constraining expenses levied by WGS.

1. Data burden

Foresight's exhibits demonstrate that WGS was undesirable because it imposes a large data burden that is an order of magnitude larger than targeted approaches. For example, Foresight's Meyerson exhibit teaches that WGS requires "the 3 billion bases of the human genome [to be] covered at least 30-fold on average, requiring the generation of 90 billion bases of sequence data per sample." EX1031 688. The data burden is even higher for Chan's cancer samples "to account for the decreased purity and often increased ploidy of each sample." *Id.* WGS at 30-fold coverage requires "90 Gb of sequence," which is nearly two orders of magnitude higher than the "3 Gb of sequence" required for targeted approaches. *Id.* 690. Meyerson explains that "computational issues" caused by "the huge quantity of experimental data," *id.* 692, results in a "major challenge... to make biological sense of the mountains of genomic data." *Id.* 694; EX2199 ¶¶72-73.

Foresight's Mertes exhibit teaches that targeted exome sequencing, as opposed to WGS, provides "simpler data interpretation" that is a "crucial consideration as it is generally much more challenging to find the functional impact of variants in noncoding regions." EX1006 382. Foresight's Mamanova exhibit teaches that a POSA would pursue targeted methods because the demands "on

laboratory time and funding” required by WGS “would place a substantial burden on a research center’s informatics infrastructure.” EX1007 111; EX2199 ¶¶74-76.

Foresight provides no reason why a POSA would have been motivated to modify Chan’s MPS approach to use WGS in the face of its own exhibits teaching that WGS should be avoided. EX2199 ¶77. Foresight fails to prove obviousness for at least this reason.

2. Expenses incurred with WGS

Foresight’s exhibits demonstrate that WGS was undesirable because it is significantly more expensive than other prior art approaches. The difference in expense is not trivial. Chan itself concedes “the shotgun sequencing approach we have described is relatively expensive.” EX1008 223. Foresight’s Meyerson exhibit explains that “whole-genome sequencing provides the most comprehensive characterization of the cancer genome but, as it requires the greatest amount of sequencing, it is the most costly.” EX1031 687. Foresight’s Mertes exhibit teaches that targeted approaches allow “costs and efforts [to] be reduced significantly compared with whole-genome sequencing.” EX1006 374. Foresight’s Gnirke exhibit teaches that there is a “substantial economy in targeting” that “substantially lower[s] the sequencing costs of a project.” EX1005 182. A POSA faced with the real-world cost constraints imposed by WGS would not have been motivated to modify Chan’s MPS to be WGS. EX2199 ¶¶79-82.

3. **Foresight is not excused from addressing the data burden and cost limitations of WGS**

Foresight was well aware of the data burden and cost limitations associated with WGS and why a POSA would not have been motivated to modify prior art assays to become WGS based on these issues via Personalis's Patent Owner Response submitted October 6, 2023 in the related matter of IPR2023-00224. EX1116 10-14. Foresight had nearly two months before it filed the present petition to formulate a response on these issues, yet it failed to provide any explanation why a POSA would modify Chan's admittedly expensive MPS approach to instead use a an even more expensive and complicated WGS approach.

Foresight cannot prove obviousness by ignoring the real-world data burden and cost constraints associated with WGS that pervade its references. "[I]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests" to a POSA. *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986). Foresight cannot refuse to engage on these issues because "[t]he benefits, ***both lost and gained***, should be weighed against one another." *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019) (emphasis in original). Here, the inventors persisted against known disadvantages to combine WGS with the other aspects of claim 1, which provides significant evidence of nonobviousness that cannot be ignored.

Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 958 (Fed. Cir. 1997).

Foresight failed to prove that Chan renders obvious limitation 1(a).

C. Limitation 1(a)(ii): nucleic acid molecules extracted from leukocytes

As discussed above, Foresight fails to establish that Chan inherently teaches a “second set of nucleic acid molecules [that] is extracted from leukocytes” as required by limitation 1(a)(ii). *Supra* Section IV.B. Foresight provides no rationale why a POSA would have modified Chan’s method to extract nucleic acid molecules from leukocytes. Foresight’s incorrect anticipation-via-inherency position based on the buffy coat “contain[ing] leukocytes,” Petition 29, likewise fails to prove obviousness because “[t]he use of inherency in the context of obviousness must be carefully circumscribed because that which may be inherent is not necessarily known and that which is unknown cannot be obvious.” *Southwire*, 870 F.3d 1306 at 1310–11. Foresight failed to prove that Chan renders obvious limitation 1(a)(ii).

D. Limitation 1(b)

Limitation 1(b) requires “using said first set of sequence reads and said second set of sequence reads to identify mosaic variants...”

As discussed above, Chan fails to disclose the “first set of sequence reads” and the “second set of sequence reads” of limitation 1(b) for several reasons. *Supra* Section IV.C. Foresight provides no explanation why a POSA would have been motivated to modify Chan to arrive at limitation 1(b). Foresight fails to prove that

Chan renders obvious limitation 1(b) because a finding of a motivation to combine “must be supported by a reasoned explanation.” *In re NuVasive, Inc.*, 842 F.3d 1376, 1383 (Fed. Cir. 2016).

E. Limitation 1(c)

Limitation 1(c) requires identifying “said mosaic variants” in a first additional sample of the subject, wherein the mosaic variants were previously identified according to limitation 1(b).

As discussed above, Chan cannot possibly disclose limitation 1(c) because Chan fails to disclose limitation 1(a) and limitation 1(b). *Supra* Section IV.D. Foresight has not provided any explanation why a POSA would have been motivated to modify Chan to arrive at limitation 1(c). Foresight failed to prove that Chan renders obvious limitation 1(c). *In re NuVasive, Inc.*, 842 F.3d at 1383.

F. No motivation to modify Chan

A POSA would not have been motivated to modify Chan’s assay to (1) modify its MPS to become a “whole genome sequencing” method as required by limitation 1(a), (2) extract nucleic acid molecules from leukocytes as required by limitation 1(a)(ii), (3) use first and second sets of sequence reads generated via WGS to identify mosaic variants according to limitation 1(b), and (4) identify said mosaic variants in a first additional sample of the subject according to limitation 1(c). Foresight fails to provide a persuasive motivation for any one of these modifications, much less the

redesign of Chan’s disclosure that would be required to perform all of them in the manner recited by claim 1. Accordingly, Foresight failed to prove obviousness of independent claim 1 and all its dependent claims.

VI. GROUND 3: NONOBVIOUSNESS OVER LEY

Foresight fails to prove that Ley teaches or suggests at least the following requirements of claim 1:

- “whole genome sequencing” as required by limitation 1(a);
- “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” as required by limitation 1(a)(i)-(ii);
- “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” as required by limitation 1(c); and
- “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” as required by limitation 1(c).

A. Limitation 1(a): Foresight failed to construe WGS

“In an IPR, the petitioner bears the ultimate burden of persuasion on invalidity, which never shifts to the patent owner.” *Medtronic, Inc. v. Teleflex Innovations SARL*, 68 F.4th 1298, 1303 (Fed. Cir. 2023).

As discussed above, Foresight failed to construe WGS. It was incumbent upon Foresight to inform the Board and Personalis how it believes WGS should be interpreted and applied to Ley in this proceeding in view of Dr. Quackenbush’s testimony that the term has a variety of different definitions. EX2018 161:21-162:1, 155:15-20, 156:20-157:22. This is especially true here because the parties have submitted competing definitions of this term in the related matter of *Foresight Diagnostics Inc. v. Personalis, Inc.*, IPR2023-00224, Paper 35 at 1-5 (EX2190).

Foresight cannot bypass claim construction because the first step of a validity determination “involves the proper interpretation of the claims,” and only thereafter does it proceed to the second step of “determining whether the limitations of the claims as properly interpreted are met by the prior art.” *TI Group*, 375 F.3d at 1139 (Fed. Cir. 2004). The Petition must be denied because Foresight failed to prove “[h]ow the challenged claim is to be construed,” and “[h]ow the construed claim is unpatentable.” 37 C.F.R. §42.104(b)(3)-(4); *Hologic*, IPR2018-00019, Paper 17 at

6-9; *Jiawei*, IPR2014-00937, Paper 22 at 7-8; *DJI Europe*, IPR2023-01107, Paper 14 at 6-9 (PTAB 2024).

B. Limitation 1(a)(i)-(ii)

Limitation 1(a)(i)-(ii) recites “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.”

Foresight admits that Ley fails to teach limitation 1(a)(i)-(ii) because Ley “differs from the claim insofar as the tumor sample is blood (rather than tissue) in a leukemia.” Petition 39. A POSA would not have been motivated to modify Ley’s approach to instead use a “tissue sample” as the tumor sample and leukocytes as the normal sample for several reasons.

1. Ley counsels against Foresight’s proposed modification

A typical tumor tissue sample contains a mixture of tumor and normal cells. For example, Foresight’s Meyerson reference teaches that a tumor tissue sample “contains a mixture of malignant and non-malignant cells and, therefore, a mixture of cancer and normal genomes (and transcriptomes).” EX1031 686. Meyerson warns that such samples create “particular challenges for the detection and diagnosis of cancer genome alterations.” *Id.* 685. The normal (non-malignant) cells in a tumor tissue sample are problematic because they cause a high background level of normal cell signal that makes it difficult to establish the identity of a presence or absence of

genetic variants in the sample. Meyerson explains that this problem was not yet solved, and explains that this problem merely **might** be solved if there were large “data sets” of “sufficient statistical power to overcome experimental and biological noise.” *Id.* 686; EX2199 ¶86.

Ley’s method gets around this problem by selecting a patient having “a typical acute myeloid leukemia [AML],” such that the patient’s blood sample has a blast count of greater than 80% that provided a highly pure source of tumor DNA. EX1042 1 (“Rationale for selection [of] an AML genome for sequencing.... based on the following criteria.... 2. High sample purity. The morphologic and flow cytometric criteria for M1 AML required high sample purity (e.g. a blast count of >80%) to eliminate the need to further purify malignant cells.”). Ley teaches that its method “**required** high sample purity” in the tumor sample to “eliminate the need to further purify malignant cells.” *Id.* Ley warns that “contaminating normal cells would complicate our analysis.” *Id.* Thus, Ley selected a leukemia patient precisely because the patient’s high blast blood count provided a highly pure source of tumor DNA. *Id.*; EX2199 ¶¶87-88. Ley’s method stands in stark contrast to a typical tumor sample containing a mixture of tumor and normal cells that involves challenges for detection and diagnosis as conceded in Foresight’s own Meyerson exhibit. EX1031 686. Foresight’s obviousness theory requires a POSA to go against Ley’s express teachings to instead use a tumor tissue sample contaminated with normal cells,

which would defeat the very purpose of Ley’s rationale for selecting an AML patient with the highly pure source of tumor DNA required for Ley’s method. EX2199 ¶89. Here, “[a]n inference of nonobviousness is especially strong [because] the prior art’s teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements” of the prior art. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009).

2. **None of Foresight’s references provide the motivation to modify Ley**

Apparently recognizing the weakness of its obviousness theory, Foresight attempts to drown out Ley’s teachings against the proposed modification with four other references: Meyerson, Chapman, Lee, and Ding. Petition 39-46. Tellingly, none of these references teaches to use *leukocytes* as the normal sample. In fact, each of these references verify that a POSA would not have gone against Ley’s teachings to instead use leukocytes the normal sample.

a) **Meyerson**

Foresight states that Meyerson reported “[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,” and also “[t]he first of seven references Meyerson cites for this proposition is Ley.” Petition 40. The mere fact that Meyerson cites Ley as the first of seven references for this proposition has nothing to do with whether a POSA

would have been motivated to modify Ley's approach to instead use a tissue sample as the tumor sample **and leukocytes** as the normal sample to arrive at limitation 1(a)(i)-(ii). EX2199 ¶¶90-91. Foresight's reliance on Meyerson is a non sequitur.

b) Chapman

Foresight states that Chapman reported "the massively parallel sequencing of 38 tumor genomes and their comparison to matched normal DNAs" and cites Ley as an "exemplary recent report." Petition 40. Chapman's mere citation to Ley does not establish that a POSA would have been motivated to modify Ley's approach to instead use a tissue sample as the tumor sample and leukocytes as the normal sample to arrive at the claimed invention.

Chapman fails to teach extracting nucleic acids **from leukocytes** as required by limitation 1(a)(ii). EX2199 ¶¶92-93. Chapman therefore fails to establish obviousness of claim 1 because obviousness requires proof that all of the claim limitations are disclosed in the prior art. *Par Pharms., Inc. v. TWi Pharms, Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014) (for an obviousness determination "[w]e must first determine whether [the patent challenger] carried its burden to prove that all claimed limitations are disclosed in the prior art").

Also, Chapman teaches using **bone marrow aspirate** tumor samples from patients suffering from multiple myeloma. EX1103 471. Multiple myeloma is an uncommon bone marrow cancer that would not be regarded by a POSA as a

representative model for general oncological investigations. EX2199 ¶94. Studying multiple myeloma involves sampling bone marrow aspirate, which contains a complex mixture of cells. *Id.* Chapman’s study of this uncommon cancer and complex sample source entailed so many complexity issues that Chapman required sequencing **38 separate patients**. EX1103 471 (“Importantly, most of these discoveries could not have been made by sequencing only a single multiple myeloma genome—the complex patterns of pathway dysregulation required the analysis of multiple genomes.”); *id.* 467 (discussing sequencing of “38 tumour genomes and their comparison to matched normal DNAs”); EX2199 ¶94. Chapman’s approach that required 38 separate patients stands in stark contrast to Ley’s carefully selected leukemia patient that required a highly pure blood tumor sample and sequencing a single subject. EX1042 1; EX2199 ¶94.

Chapman’s sequencing of 38 separate patients only allowed a “preliminary” analysis, which caused the authors to caution the POSA that “[a]dditional multiple myeloma genomes will be required to establish the definitive genomic landscape of the disease and determine accurate estimates of mutation frequency in the disease.” EX1103 471; EX2199 ¶95. Foresight provides no explanation why a POSA would have altered Ley’s approach to instead use a tissue sample as the tumor sample and leukocytes as the normal sample in view of Chapman’s failure to teach leukocytes and the complexity issues raised by Chapman. Chapman demonstrates that using a

tissue sample as the tumor sample greatly increases complexity issues and requires performing the assay on at least 38 patients to provide just a preliminary analysis.

c) **Lee**

Foresight asserts that Lee “performed WGS on paired tumor and adjacent normal tissue of a lung cancer patient.” Petition 40-41. The adjacent normal tissue in Lee is ***lung tissue, which is not leukocytes***. EX1104 473; EX2199 ¶97. Lee fails to teach extracting nucleic acids ***from leukocytes*** as required by limitation 1(a)(ii). Lee therefore fails to establish obviousness of claim 1. *Par Pharms*, 773 F.3d 1186 at 1194.

d) **Ding**

Foresight asserts that Ding used “peripheral blood” as the normal sample for WGS. Petition 41-42. First, Ding does not use the term “whole genome sequencing.” Ding discloses MPS. *Id.* 41 (Ding describes “massively parallel DNA sequencing technologies”) (quoting EX1105 999). As discussed above, Foresight fails to establish that MPS constitutes the WGS required by limitation 1(a).

Second, Ding’s use of “peripheral blood” as the normal sample does not ***expressly*** disclose the use of ***leukocytes*** as required by limitation 1(a)(ii). Foresight’s footnoted and parenthetical statement that peripheral blood “comprises” or “contains” leukocytes, *see* Petition 42 n.7 & 46, fails to prove that Ding ***inherently*** discloses the use of leukocytes because it is basic biology that peripheral blood

consists of a complex mixture of cells, cell fragments, hormones, enzymes, and other proteins, electrolytes, amino acids, glucose and other carbohydrates, cholesterol, vitamins, fatty acids, glycerol, triglycerides, respiratory gases, water, and wastes (such as, lactic acid, creatinine, urea, bilirubin, ammonia). EX2199 ¶99. Peripheral blood contains many types of nucleated non-leukocyte cell types from which DNA can be extracted, including at least endothelial cells, endothelial progenitor cells, mesenchymal precursor cells, and megakaryocytes. *Supra* Section IV.B. In addition, Foresight admits that peripheral blood contains circulating extracellular DNA (“cell-free DNA” or “cfDNA”) from non-leukocyte sources of healthy and diseased cells. Petition 12-13 (admitting “there is always cfDNA being released into and circulating through the bloodstream”).

Foresight’s footnoted statement that the buffy coat contains leukocytes, *see* Petition 42 n.7, likewise fails to acknowledge that the buffy coat contains at least the following types of nucleated non-leukocyte cell types: endothelial cells, endothelial progenitor cells, mesenchymal precursor cells, and megakaryocytes. *Supra* Section IV.B. Moreover, Foresight provides no motivation why a POSA would have modified Ding to abandon its use of peripheral blood to instead use the buffy coat portion of centrifuged blood. Foresight’s footnoted statement and conclusory statement that it would have been “obvious to extract DNA from buffy coat,” *see* Petition 42 n.7 & 46, does not prove obviousness because assertions of obviousness

are not “sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

Further, Ding teaches using **breast cancer** and **brain metastasis** tumor samples. EX1105 Abstract. Ding teaches that there was considerable heterogeneity in the primary tumor. *Id.* 1004 (“The wide range of mutant allele frequencies suggests considerable genetic heterogeneity in the cellular population at the primary site.”). The heterogeneity complexities involved in analyzing these samples required the design of an unpublished “cnvHMM algorithm” to “align[] sequence reads” and “calculate[] the read depth contributed from the tumor cells alone.” *Id.* 1001; EX2199 ¶100. Foresight provides no explanation as to whether a POSA would have been able to develop or otherwise access such an algorithm required to use such tumor samples to arrive at the claimed invention with a reasonable expectation of success. In contrast to Ding’s approach, Ley selected a leukemia patient that provided a highly pure blood tumor sample to “eliminate the need to further purify malignant cells” because “contaminating normal cells would complicate our analysis.” EX1042 1; EX2199 ¶100. Thus, Ding emphasizes that using a tissue sample as the tumor sample would increase the complexity of analyzing the samples, which a POSA would find undesirable. Foresight fails to address any of these issues with Ding.

C. Limitation 1(c): said mosaic variants

Limitation 1(c) recites “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.”

The “said” mosaic variants specific to said tissue sample of limitation 1(c) refers back to the mosaic variants identified using the first and second sets of sequence reads of limitation 1(b). Limitation 1(b) requires using “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*.”

Reading these two limitations together, the “said” mosaic variants specific to said tissue sample in the first additional sample of limitation 1(c) must be “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*” as required by limitation 1(b).

For limitation 1(c), Foresight relies on the Ley’s “relapse tumor” sample data in Ley Figure 3 and Table 3. Petition 49-51. Foresight asserts that “Figure 3 summarizes [Ley’s] data, and shows the frequency of mosaic variants (‘ten somatic mutations’) in each of the primary tumor, relapse tumor, and skin samples.” *Id.* 50.

Foresight further asserts “[t]his shows that Ley identified the presence of mosaic variants (green bars) specific to the tumor sample in the subsequently obtained relapse tumor sample.” *Id.*

Foresight fails to account for Ley’s teaching that the normal skin samples used to generate Figure 3 and Table 3 were contaminated with tumor cells. Specifically, Ley expressly teaches that “***the normal skin sample was contaminated with leukaemic cells containing the somatic mutations.***” EX1012 69. Thus, the mosaic variants in Ley’s relapse tumor sample were also present in the normal skin sample. EX2199 ¶¶104-105. Indeed, the yellow bars in Ley’s Figure 3 shows the presence of each of the mosaic variants in the normal reference samples:

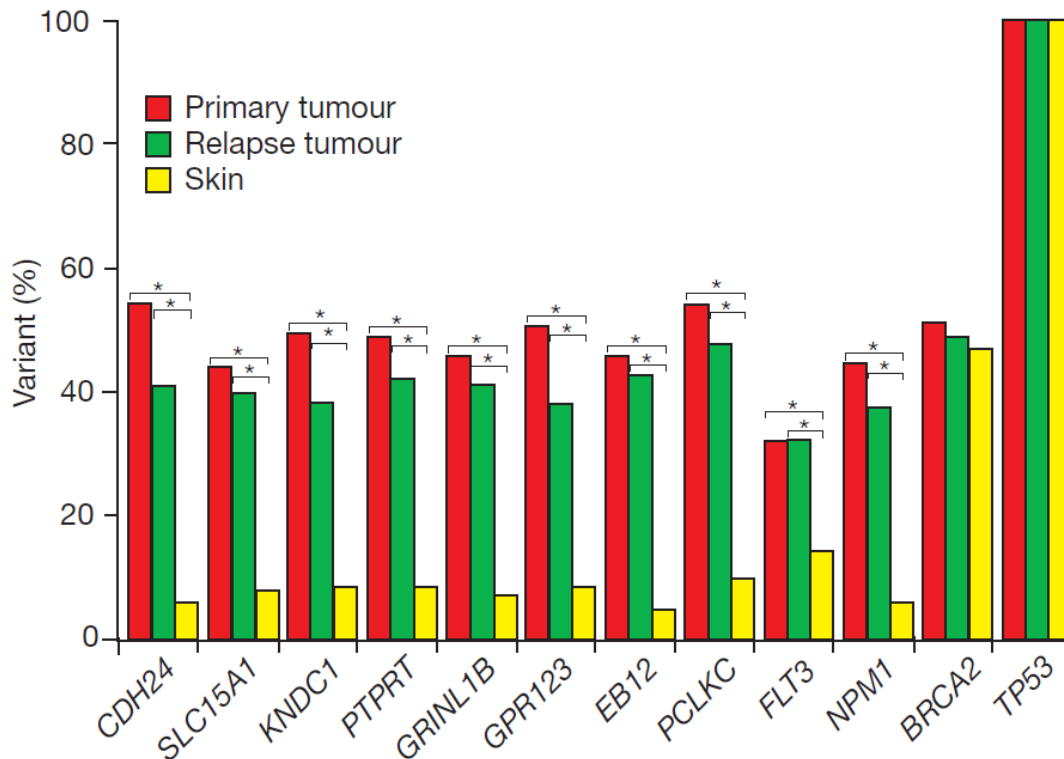


Figure 3 | Summary of Roche/454 FLX readcount data obtained for ten somatic mutations and two validated SNPs in the primary tumour, relapse tumour and skin specimens. The readcount data for the variant alleles in the primary tumour sample and relapse tumour sample are statistically different from that 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.

Because the data in Ley's Figure 3 and Table 3 shows that the mosaic variants **were** present in the normal skin sample, Ley fails to teach that the sequence reads for mosaic variants in the relapse tumor sample were not present in the sequence reads for the normal skin sample. EX2199 ¶105. Foresight therefore fails to prove that Ley teaches or suggests limitation 1(c).

D. Limitation 1(c): obtained from a different source

Limitation 1(c) requires “subsequent to (b), identifying said mosaic variants... 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...***”

Foresight relies on Ley’s “relapse tumor sample” to allegedly meet the first additional sample required by limitation 1(c). Foresight’s obviousness theory fails because it requires using a tumor sample as the tissue sample for limitation 1(a) and also using a relapse tumor sample from ***the same source*** for limitation 1(c). For example, Foresight’s obviousness theory relies on a POSA using a tumor sample as the tissue sample (such as a breast cancer tumor biopsy sample) to supposedly meet limitation 1(a). See Petition 45 (alleging “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***)”); *id.* 42 (alleging “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”). Foresight’s obviousness theory additionally relies on a relapse tumor sample “obtained from the patient’s relapsed disease” to meet limitation 1(c). Petition 49-51. The relapse tumor sample would be obtained from the same source as the original tumor sample because both samples would involve biopsies of the same source tissue. For example, the relapse tumor sample from Foresight’s exemplary breast cancer patient would be obtained from a

biopsy of the relapsed breast cancer tissue. The relapse breast cancer biopsy sample would be obtained from the same source as the original breast cancer tumor biopsy sample because both samples would involve biopsies of breast cancer tissue. Foresight's reliance on Ley's "relapse tumor sample" fails to meet the requirement of limitation 1(c) that the first additional sample must be ***obtained from a source that is different than said tissue sample*** of limitation 1(a). Foresight therefore fails to prove that Ley teaches or suggests limitation 1(c).

E. No motivation to modify Ley

A POSA would not have been motivated to modify Ley's assay to arrive at the claimed invention. Foresight failed to construe the term "whole genome sequencing" required by limitation 1(a). It failed to prove that a POSA would modify Ley's approach to instead use a "tissue sample" as the tumor sample and leukocytes as the normal sample to arrive at limitation 1(a)(i)-(ii). It failed to prove that Ley teaches or suggests sequence reads for mosaic variants in an additional sample that were not present in the second set of sequence reads to arrive at limitation 1(c). It failed to prove that Ley teaches or suggests obtaining a first additional sample from a source that is different than the tissue sample to arrive at limitation 1(c). Foresight fails to prove that a POSA would have made any one of these modifications, much less all of them to arrive at the specific method recited by

claim 1. Accordingly, Foresight's Ground 3 fails to prove obviousness of independent claim 1 and all its dependent claims.

VII. GROUND 4: LACK OF ANTICIPATION BY OKOSUN-II

Okosun-II fails to teach at least the following four requirements of claim 1:

- the “second set of nucleic acid molecules is extracted from *leukocytes*” as required by limitation 1(a)(ii);
- “using whole genome sequencing” to generate “said second set of sequence reads wherein said second set of nucleic acid molecules is extracted from leukocytes” as required by limitation 1(a);
- “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” as required by limitation 1(b); and
- “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” as required by limitation 1(c).

A. Limitation 1(a)(ii)

Limitation 1(a)(ii) requires that “said second set of nucleic acid molecules is extracted from leukocytes from a blood sample.”

Foresight does not allege that Okosun-II ***expressly*** teaches extracting a set of nucleic acid molecules from leukocytes. Foresight’s challenge is based on Okosun-II allegedly disclosing this limitation ***inherently***. Petition 61. Okosun-II teaches that “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.” EX1102 182. Foresight asserts that Okosun-II’s peripheral blood specimens inherently meets limitation 1(a)(ii) because the specimens “contain leukocytes.” Petition 61. This assertion fails to prove anticipation because inherency requires that the limitation at issue “necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art.” *Par Pharm.*, 773 F.3d at 1196.

Okosun-II’s peripheral blood specimens fails to inherently disclose extraction of nucleic acid molecules from leukocytes because peripheral blood consists of a complex mixture of cells, cell fragments, hormones, enzymes, and other proteins, electrolytes, amino acids, glucose and other carbohydrates, cholesterol, vitamins, fatty acids, glycerol, triglycerides, respiratory gases, water, and wastes (such as,

lactic acid, creatinine, urea, bilirubin, ammonia). EX2199 ¶108. Peripheral blood contains many types of nucleated non-leukocyte cell types from which DNA can be extracted, including at least endothelial cells, endothelial progenitor cells, mesenchymal precursor cells, and megakaryocytes. *Supra* Section IV.B. In addition, Foresight admits that peripheral blood contains circulating extracellular DNA (“cell-free DNA” or “cfDNA”) from non-leukocyte sources of healthy and diseased cells. Petition 12-13 (admitting “there is always cfDNA being released into and circulating through the bloodstream”). Foresight’s petition is merely based on “assumption[s] and its own contentions” about what type of cell Okosun-II might have extracted nucleic acid molecules from, which fails to prove inherent anticipation. *Crown Operations*, 289 F.3d 1367 at 1378.

B. Limitation 1(a): using WGS wherein nucleic acid molecules are extracted from leukocytes

Limitation 1(a) requires “*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*.”

As discussed above, Foresight failed to inform the Board and Personalis how it believes WGS should be interpreted and applied to Okosun-II in this proceeding in view of Dr. Quackenbush’s testimony that WGS has a variety of different definitions and the competing definitions of WGS submitted by the parties in the related matter of IPR2023-00224.

Foresight does not allege that Okosun-II **expressly** teaches using WGS to generate sequencing reads by sequencing nucleic acid molecules extracted from leukocytes. Foresight's challenge is based on Okosun-II allegedly disclosing limitation 1(a) **inherently**. Petition 60-61.

Okosun-II ambiguously states “we 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. Okosun-II does not describe which of the FL-tFL samples were subjected to WGS versus which samples were subjected to whole-exome sequencing (WES).

Also, Okosun-II ambiguously states that the “matched germline samples consist[ed] of remission bone marrows or peripheral blood specimens.” EX1102 183. Okosun-II does not describe which of the FL-tFL samples were paired with matched germline from peripheral blood specimens versus which samples were matched with remission bone marrow specimens.

Based on Okosun-II's ambiguous statements it is impossible to tell which (if any) of the FL-tFL samples that were sequenced via WGS might also have been matched with germline from peripheral blood specimens. It is entirely possible that **none** of Okosun-II's FL-tFL samples were sequenced via WGS **and** matched with germline from peripheral blood specimens. Foresight's anticipation challenge fails

because inherency cannot be established “by probabilities or possibilities.” *Par Pharm.*, 773 F.3d at 1196.

Regardless of these ambiguities, Okosun-II’s peripheral blood specimens do not inherently disclose extraction of nucleic acid molecules from leukocytes for reasons discussed above. *Supra* Section VII.A. For at least these reasons, Foresight fails to prove that Okosun-II inherently teaches limitation 1(a).

C. Limitation 1(b)

Limitation 1(b) requires “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.”

Okosun-II fails to disclose at least the “second set of sequence reads” required by limitation 1(b). The “said” set of second sequence reads required by limitation 1(b) refers back to the sequence reads of limitation 1(a). Okosun-II does not anticipate generating the second set of sequencing reads using WGS on nucleic acids extracted from leukocytes as required by limitation 1(a). Therefore, Okosun-II also necessarily fails to anticipate the second set of sequencing reads required by limitation 1(b).

D. Limitation 1(c)

Limitation 1(c) requires “identifying said mosaic variants... 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.***”

Foresight relies on Okosun-II’s follicular lymphoma (FL) and transformed follicular lymphoma (tFL) biopsies to allegedly meet the first additional sample required by limitation 1(c). Petition 63. Foresight also relies on Okosun-II’s FL and tFL biopsies to allegedly meet the tissue sample required by limitation 1(a). Petition 60-61. FL and tFL biopsies are taken from the same source (follicle tissue). EX2199 ¶118. Thus, Foresight relies on tissue samples from the ***same source*** (i.e., follicle tissue biopsies) to supposedly meet limitations 1(a) and 1(c). However, limitation 1(c) requires the first additional sample to be obtained from a ***source that is different*** than the tissue sample of limitation 1(a). Because Foresight’s anticipation theory requires using a follicle biopsy tissue sample for limitation 1(a) and using a follicle biopsy tissue sample for limitation 1(c), it necessarily fails to teach the requirement of limitation 1(c) that the first additional sample must be obtained from a source that is different than said tissue sample of limitation 1(a).

E. Conclusion regarding Ground 1

Foresight failed to prove that Okosun-II anticipates at least four requirements of independent claim 1. Foresight therefore additionally failed to establish anticipation of any dependent claim. Ground 4 therefore fails.

VIII. GROUND 5: OBVIOUSNESS OVER OKOSUN-II

Okosun-II fails to suggest at least the following three limitations of claim 1:

- “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” as required by limitation 1(c);
- the “second set of nucleic acid molecules is extracted from leukocytes” as required by limitation 1(a)(ii); and
- “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” as required by limitation 1(b).

A. Limitation 1(c)

Limitation 1(c) requires “identifying said mosaic variants... 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.”

As discussed above, Foresight relies on using Okosun-II’s follicle biopsy tissue sample for limitation 1(a) and using Okosun-II’s follicle biopsy tissue sample from the **same** source for limitation 1(c). *Supra* Section VII.D. Foresight therefore fails to establish that Okosun-II discloses the requirement of limitation 1(c) for the first additional sample to be obtained from a source that is **different** from said tissue sample of limitation 1(a).

Foresight provides no explanation why a POSA would have modified Okosun-II to arrive at limitation 1(c). On this basis alone, Foresight fails to prove obviousness. *Par Pharms.*, 773 F.3d 1186 at 1194.

A POSA would not have been motivated to use a non-follicle tissue sample in Okosun-II’s protocol to arrive at limitation 1(c) because the entire purpose of Okosun-II was to identify and monitor the “progression of follicular lymphoma” (FL). EX1102 title. Thus, modifications of Okosun-II to use non-follicle tissue samples would undermine the purpose of Okosun-II’s approach to test follicle tissue samples to identify and monitor the progression of follicular lymphoma. EX2199 ¶119. Here, “[a]n inference of nonobviousness is especially strong [because] the

prior art’s teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements” to allegedly arrive at the claimed invention. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009).

B. Limitation 1(a)(ii)

Limitation 1(a)(ii) recites that the “second set of nucleic acid molecules is extracted from leukocytes from a blood sample.”

Foresight alleges that it would have been obvious to use leukocytes in place of Okosun-II’s peripheral blood specimens based on Meyerson’s teaching that “samples generally used for germline genome analysis [are] peripheral blood mononuclear cells [PBMCs].” Petition 68.

A POSA would not have been motivated to modify Okosun-II’s method of sequencing based on Meyerson for several reasons. First, Meyerson does not exclusively teach using PBMCs for germline genome analysis. Meyerson also teaches that peripheral blood samples are appropriate. EX1031 686 (describing “peripheral blood samples that are used for germline genome analysis”); *id.* (describing nucleic acids “purified from peripheral blood”); EX2199 ¶112. Myerson’s peripheral blood samples are the same type of sample taught by Okosun-II to use in Okosun-II’s protocol.

Second, and more importantly, Meyerson’s statement about PBMCs “generally” being used for germline genome analysis provides no reason why a POSA would modify Okosun-II’s follicular lymphoma study to use PBMCs. Follicular lymphoma is a hematologic cancer. A significant percentage of follicular lymphoma patients evolve to (or in some cases present with) a leukemic phase in which the patients’ peripheral blood contains lymphocytes that are cancerous. EX2200 63 (“A characteristic form of lymphocyte, the ‘notched nucleus cell’ of Anday and Schmitz (1952), or the ‘haematogone’ of Rosenthal et al. (1952) was found in the peripheral blood in 8 of 17 cases [of follicular lymphoma] with lymphocytosis and accounted for the majority of lymphocytes in the cases in which the lymphocyte counts were considerably elevated, but the proportion was variable in those with only moderate lymphocytosis.”); EX2199 ¶113. A POSA would not have been motivated to use PBMCs as the normal sample for Okosun-II’s follicular lymphoma study because the PBMCs would be expected to be contaminated with cancerous lymphocyte cells for patients that enter or present with leukemic phase follicular lymphoma. EX2199 ¶¶113-114.

Third, the standard method for isolating PBMCs was a relatively labor-intensive density gradient centrifugation process involving the precise layering of peripheral blood over a density medium with careful pipetting of the floating cell layer after centrifugation. EX2199 ¶115; EX2195 478. The user must take

meticulous care throughout the process to keep from mixing layers before and after centrifugation, and in some cases the multistep process led to inconsistency between users and sample variability. EX2199 ¶115. In contrast, Okosun-II’s peripheral blood samples are obtained by a simple blood draw from the patient. Even if a POSA **could** have modified Okosun-II to use PBMCs instead of peripheral blood, Foresight provides no supposed advantages that might arise from such a modification within the specific context of Okosun-II’s protocol that **would** have motivated a POSA to further complicate Okosun-II’s already-working protocol with unnecessary processing steps required to isolate PBMCs from the peripheral blood samples. Foresight has not proven obviousness because “[a]n assertion that something **could** be done does not articulate a reason why something **would** be done” and “raises a specter of impermissible hindsight bias.” *Nautilus Hyosung Inc. v. Diebold, Inc.*, IPR2016-00633, Paper 9 at 21 (PTAB 2016). As discussed above, a POSA would not have been motivated to use PBMCs as the normal sample for Okosun-II’s follicular lymphoma study because the PBMCs would be expected to be contaminated with cancerous lymphocyte cells for patients that enter or present with leukemic phase follicular lymphoma. EX2199 ¶¶109, 113.

Fourth, Meyerson was published in 2010, which is five years before Okosun-II was published. Thus, Okosun-II was likely aware of the supposed general understanding described by Meyerson that PBMCs were “generally” used for

germline genome analysis. EX2199 ¶116. If Okosun-II had thought that complicating its protocol with the additional processing steps of peripheral blood required to isolate PBMCs and the potential contaminating effect of cancerous lymphocyte cells in the PBMCs would have been a beneficial improvement, then Okosun-II would have done so.

Fifth, Foresight alleges that “a POSA would have found it obvious to extract DNA from buffy coat” simply because the use of buffy coat was supposedly a “routine and predictable experimental design choice.” Petition 68-69. Something that is merely “a design choice does not make it obvious.” *Polaris Indus. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1069 n.4 (Fed. Cir. 2018). Foresight must “affirmatively demonstrate that a skilled artisan would have been motivated to” arrive at the invention. *Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1380-81 (Fed. Cir. 2018). Even if a POSA **could** have modified Okosun-II to use buffy coat instead of peripheral blood, Foresight provides no supposed disadvantages with the amount or quality of DNA extracted from peripheral blood within the specific context of Okosun-II’s protocol that **would** have motivated a POSA to alter Okosun-II’s already-working protocol to instead use buffy coat. Foresight fails to prove obviousness because “obviousness concerns whether a skilled artisan not only **could have made** but **would have been motivated to make** the combinations or modifications of prior art to arrive at the claimed invention.” *Belden Inc. v. Bertk-*

Tek LLC, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (emphases in original). Thus, Foresight fails to prove that a POSA would have arrived at limitation 1(a)(ii).

C. Limitation 1(b)

Limitation 1(b) requires “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.”

As discussed above Okosun-II fails to disclose at least the “second set of sequence reads” required by limitation 1(b). *Supra* Section VII.C. Foresight provides no explanation why a POSA would have been motivated to modify Okosun-II to arrive at limitation 1(b), and therefore fails to prove obviousness. *In re NuVasive, Inc.*, 842 F.3d at 1383.

D. No motivation to modify Okosun-II

A POSA would not have been motivated to modify Okosun-II’s protocol to (1) use a non-follicular tissue sample to obtain a first additional sample from a source that is different than Okosun-II’s original follicular tissue sample as required by limitation 1(c), (2) extract nucleic acid molecules from leukocytes as required by limitation 1(a)(ii), and (3) use a second set of sequence reads generated via WGS from nucleic acid molecules extracted from leukocytes to identify mosaic variants according to limitation 1(b). Foresight fails to provide a persuasive motivation for

any one of these modifications, much less the collective motivations that would be required to make all of them to arrive at the specific method recited by the claimed invention. Accordingly, Foresight failed to prove obviousness of independent claim 1 and all its dependent claims.

IX. CONCLUSION

Foresight's Petition for *Inter Parter Review* should be denied in its entirety.

Respectfully submitted,

KNOBBE MARTENS OLSON & BEAR, LLP

Dated: February 29, 2024

/Nathanael R. Luman/

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), Counsel for Patent Owner Personalis, Inc. hereby certifies that this document complies with the type-volume limitation of 37 C.F.R. § 42.24(b). This document contains approximately 13,021 words, including any statement of material facts to be admitted or denied in support, and excluding the table of contents, table of authorities, mandatory notices under § 42.8, exhibit list, certificate of service or word count, or appendix of exhibits or claim listing.

Dated: February 29, 2024

/Nathanael R. Luman/

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Lead Counsel for Personalis, Inc.

CERTIFICATE OF SERVICE

I hereby certify that, pursuant to 37 C.F.R. § 42.6(e) and with the agreement of counsel for Petitioner, a true and correct copy of **PATENT OWNER'S PRELIMINARY RESPONSE TO PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 11,584,968 AND EXHIBITS 2001, 2010, 2018, AND 2189-2200** are being served electronically on February 29, 2024, to the e-mail addresses shown below:

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