

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS, Inc.
Petitioner,

v.

PERSONALIS, Inc.
Patent Owner.

IPR2024-00170
Patent 11,584,968 B2

Before ULRIKE W. JENKS, ROBERT A. POLLOCK, and
TIMOTHY G. MAJORS, *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

A. Background

Foresight Diagnostics Inc. (“Petitioner,” “Foresight”) filed a Petition for an *inter partes* review of claims 1–13 of U.S. Patent No. 11,584,968 B2 (“the ’968 patent,” Ex. 1001). Paper 1 (“Pet.”). Personalis, Inc. (“Patent Owner,” “Personalis”) timely filed a Preliminary Response. Paper 6 (“Prelim. Resp.”). With our authorization, Petitioner filed a Reply to the Preliminary Response (Paper 7, “Reply”); Patent Owner filed a corresponding Sur-reply (Paper 9, “Sur-reply”).

B. Summary of the Institution Decision

For the reasons provided below, we determine Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). Because Petitioner has demonstrated a reasonable likelihood that at least one claim of the ’968 patent is unpatentable, we institute an *inter partes* review of all challenged claims on each of the grounds raised in the Petition. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018); *see also* Guidance on the Impact of *SAS* on AIA Trial Proceedings (April 26, 2018) (available at <https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial>) (“Guidance”).

C. Real Parties-in-Interest

Petitioner identifies itself, Foresight Diagnostics Inc., as the real party-in-interest. Pet. 5. Patent Owner also identifies only itself, Personalis, Inc., as the real party-in-interest in this proceeding. Paper 4, 1.

D. Related Matters

In addition to the '968 patent at issue here, Petitioner concurrently challenges claims of Personalis's U.S. Patent Nos. 11,384,394 ("the '394 patent") in IPR2023-00224 ("the 00224 IPR"); 11,408,033 ("the '033 patent") in IPR2023-00317 ("the 00317 IPR"); 11,299,783 ("the '783 patent") in IPR2023-00545 ("the 00545 IPR"); and 10,450,611 ("the '611 patent") in IPR2023-00546 ("the 00546 IPR"). *See* Pet 6; Paper 4, 1. Although the '394, '033, '783, and '611 patents do not share benefit of priority with the '968 patent, they all address related subject matter.

As we understand the posture of the related district court proceedings, the '968, '394, '033, '783, and '611 patents are at issue in *Personalis, Inc. v. Foresight Diagnostics, Inc.*, C.A. No. 1:22-cv-01913 (D. Colo.) ("case 1") and/or *Personalis, Inc. v. Foresight Diagnostics Inc.*, No. 1:23-cv-01623-CNS-NRN (District of Colorado) ("Case 2"), collectively. *See* Pet. 1, 3–4; Paper 4, 1. According to Petitioner, "Case 1 in the District of Colorado is currently stayed pending the above referenced IPR proceedings. Foresight has moved to consolidate Case 1 and Case 2, and to extend the stay to Case 2. Ex1121. That motion is pending." Pet. 6.

E. Asserted Challenges to Patentability

Petitioner challenges the patentability of claims 1–13 on the following bases: (Pet. 15):

Ground	Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1	1–4, 7, 9–12	§ 102	Chan ¹

¹ Chan *et al.*, "Cancer Genome Scanning in Plasma: Detection of Tumor-Associated Copy Number Aberrations, Single-Nucleotide Variants, and

Ground	Claims Challenged	35 U.S.C. §	Reference(s)/Basis
2	1–13	§ 103	Chan
3	1–13	§ 103	Ley ²
4	1, 8–9, 11–13	§ 102	Okosun-II ³
5	1–13	§ 103	Okosun-II

In support of its patentability challenge, Petitioner relies on, *inter alia*, the Declaration of John Quackenbush, Ph.D. Ex. 1100. Patent Owner relies on, *inter alia*, the Declaration of Henry Morrice Furneaux, Ph.D. Ex. 2199.

In addition to Petitioner’s reliance on Okosun-II in Grounds 4 and 5, Petitioner notes that “Dr. Quackenbush has also mapped the findings of Okosun-I to the claims to the extent Personalis attempts to invoke any prior art exception under 35 U.S.C § 102(b)(1).” Pet. 15 (citing Ex. 1100 ¶ 236); Ex. 1101 (Okosun-I).⁴ Because Patent Owner does not presently contest the prior art status of Okosun-II, we need not address Okosun-I at this time.

Tumoral Heterogeneity by Massively Parallel Sequencing,” 59(1) *Clin. Chem.* 211–224 (2013). Ex. 1008.

² Ley *et al.*, “DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome,” 456 *Nature* 66–72 (2008). Ex. 1012 (primary article); Ex. 1042 (Suppl. Information).

³ Okosun, *et al.*, “Integrated genomic analysis identifies recurrent mutations and evolution patterns driving the initiation and progression of follicular lymphoma,” 46(2) *Nature Genetics* 176–181 (Online Methods attached) (2014). Ex. 1102 (primary article); Ex. 1113 ((Suppl. Information).

⁴ Okosun, *et al.*, “Whole Genome Sequencing in Sequential Biopsies Reveals the Genetic Evolution of Follicular Lymphoma to Transformed Follicular Lymphoma,” 120(21) *Blood* 145 (2012). Ex. 1101.

F. The '968 Patent and Related Background

1) Priority

The '968 patent, titled “Methods for Using Mosaicism in Nucleic Acids Sampled Distal to Their Origin,” issued to John West from U.S. Application 17/494,513, filed October 5, 2021, via a series of continuation and division applications first filed on October 30, 2015, and further claims benefit of priority to U.S. Provisional Application No. 62/072,936, filed on October 30, 2014. Ex. 1001, code (12), (21), (22), (54), and (60).⁵

2) Specification

The '968 patent discloses “methods for generating a mutation map for a subject and using the mutation map to determine the source of a given nucleic acid sequence or portion thereof in the subject.” Ex. 1001, 1:50–53. According to the Specification, the disclosed methods can be used to detect and monitor diseases such as cancer in a subject by detecting genetic variations in a subject’s blood and/or other body tissue. *Id.* at 1:53–61, 3:32–56, 8:19–29, 9:29–57, 36:46–51, 45:31–42. In one aspect, the invention comprises:

- a) separating the blood sample into at least a first component that includes cell-free or surface-bound nucleic acid molecules and a second component that includes leukocytes;
- b) extracting nucleic acid molecules from the first and second components;
- c) independently sequencing extracted nucleic molecules from the first and second components; and

⁵ Whether the '968 patent is entitled to the benefit of the provisional application is not presently at issue in this proceeding. *But see* Pet. 2, n.2; Ex. 1100 ¶ 33; Prelim. Resp. 10.

d) comparing with a programmed computer processor nucleic acid sequences of nucleic acid molecules of the first and second components to identify differential mutations.

Id. at 2:4–14 (paragraphing added).

In some embodiments, the nucleic acid molecules “are extracted from the samples and are sequenced by whole genome sequencing (WGS) to identify differential mutations between the various tissue samples.” *Id.* at 52:51–53, 17:36–37. “In some embodiments, the sequencing comprises whole genome sequencing. In some embodiments, the sequencing comprises targeted genome sequencing. In some embodiments, the sequencing comprises untargeted genome sequencing. In some embodiments, the untargeted genome sequencing comprises whole genome sequencing.” *Id.* at 3:22–27, 4:31–32.

In some embodiments,

whole blood can be collected and centrifuged to separate the plasma which contains the cfDNA [(cell-free DNA)], the buffy coat which contains the white blood cells, and the red blood cells. Nucleic acids can be extracted from the plasma and the white blood cells and sequenced. In some cases, the cfDNA may contain distal nucleic acids that originated from a tumor. In these cases, tumor variants may be identified by identifying mosaic variants in the cfDNA that are not represented in the white blood cells (“normal”).

Id. at 13:22–40.

3) Challenged Claims

Petitioner challenges claims 1–13 of the ’968 patent, of which only claim 1 is independent. Claim 1 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 [a] 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.

Ex. 1001, 54:30–63 (paragraphing added).

4) Asserted Prior Art

Patent Owner does not dispute the prior art status of the asserted references in its Preliminary Response. *See* Prelim. Resp. 10-11, 17, 31–32.

a. Overview of Chan (Exhibit 1008)

According to Chan, “[t]umor-derived DNA can be found in the plasma of cancer patients. In this study, we explored the use of shotgun massively parallel sequencing (MPS) of plasma DNA from cancer patients to scan a cancer genome noninvasively.” Ex. 1008, 211. Chan explains that, “[t]he presence of tumor-derived DNA in the plasma of cancer patients offers exciting opportunities for the detection and monitoring of cancer.” *Id.* at 211. Chan states, however, that, “[m]ost of the previously published work on plasma DNA as a cancer marker has focused on the detection of specific and predetermined molecular targets known to be associated with cancer by means of such methods such as the PCR.” *Id.*; *see also id.* at 223 (noting that “solution-phase hybridization-based capture approaches have already been successfully used to enrich plasma DNA for noninvasive prenatal diagnosis” (citing Liao, Ex. 1009)). In contrast to this targeted approach, Chan employed a “nontargeted random—or shotgun—sequencing approach” “to obtain a noninvasive, genomewide view of cancer associated copy number variations and mutations in DNA in plasma.” *Id.* at 212.

Illustrating the shotgun MPS approach, Chen follows the proportions of cancer-associated chromosomal aberrations in the plasma of four hepatocellular carcinoma patients over time, before and after resection. *Id.* at 212, 217–219; *see also id.* at 211, 219–221 (MPS analysis on patient with synchronous breast and ovarian cancers). Chen concludes that shotgun MPS

would allow genomic aberrations harbored by tumor cells within a patient to be scanned at different levels of resolution,

ranging from a global view of cancer-associated copy number aberrations to point mutations carried by different clones of tumor cells. This approach would allow qualitative and quantitative aspects of such aberrations to be followed serially, as evidenced by the changes we observed in the pre- and postsurgery plasma samples.

Id. at 221.

b. Overview of Ley (Exhibits 1012, 1042)

Ley discloses the use of whole-genome sequencing to identify tumor-specific single nucleotide variants (SNVs) in a patient with acute myeloid leukemia. *See, e.g.*, Ex. 1012, Abstract, 67. According to Ley:

Whole-genome sequencing is now possible at a reasonable cost and timeframe to use this approach for the unbiased discovery of tumour-specific somatic mutations that alter the protein-coding genes. Here we present the results obtained from sequencing a typical acute myeloid leukaemia genome, and its matched normal counterpart obtained from the same patient's skin. We discovered ten genes with acquired mutations; two were previously described mutations that are thought to contribute to tumour progression, and eight were new mutations present in virtually all tumour cells at presentation and relapse.

Id. at Abstract. In particular, Ley “used massively parallel sequencing technology to sequence the genomic DNA of tumour and normal skin cells obtained from a patient with a typical presentation of French-American-British (FAB) subtype M1 acute myeloid leukaemia (AML) with normal cytogenetics.” *Id.* at 66.⁶

Using a commercially-available Illumina Genome Analyzer, Ley achieved about 82% and 90% diploid coverage of the tumor and normal skin cell genomes, respectively. *Id.* at 67. Ley also reports sequencing data

⁶ Ley explains that “[o]f the eight FAB subtypes of AML, M1 AML is one of the most common (~20% of all cases).” *Id.* at 67.

comprising “32.7-fold ‘haploid’ coverage (98 billion bases)” for the tumor genome, “and 13.9-fold coverage (41.8 billion bases) . . . for the normal skin sample.” *Id.* at 66. According to Ley:

After alignment to the human reference genome, sequence variants were discovered in the tumour genome and compared to the patient’s normal sequence, to the dbSNP database, and to variants recently reported for two other human genomes; revealing new single nucleotide and small insertion/deletion (indel) variants genome-wide. Somatic mutations were detected in genes not previously implicated in AML pathogenesis, demonstrating the need for unbiased whole-genome approaches to discover all mutations associated with cancer pathogenesis.

Id. at 67 (internal endnote numbers omitted). Ley further reports that “[f]or the purposes of this initial study, we restricted our downstream analysis to the coding sequences of annotated genes,” noting that these included alterations in eight protein-coding sequences including “previously described, recurrent somatic insertions in the *FLT3* and *NPM1* genes.” *Id.* at 66.

Using a panel of 10 tumor-specific mutations, Ley compared the initial sequencing data to that from the same patient after relapse:

To better define the percentage of tumour cells that contained each of the discovered somatic mutations, we amplified each mutation containing locus from non-amplified genomic DNA derived from the *de novo* and relapse tumour samples, and from the skin biopsy obtained at presentation. The resulting amplicons were sequenced using the Roche/454 FLX platform, and the frequency of reads containing the reference and variant alleles were defined (Fig. 3 and Table 3).

Id. at 69; *see also* Fig. 3 (comparing variant % of each mutation in normal skin, primary tumor, and relapse tumor samples).

c. Overview of Okosun II (Exhibits 1102, 1113)

Okosun-II characterizes recurrent mutations and evolution patterns driving the initiation and progression of follicular lymphoma (FL) to transformed follicular lymphoma (tFL) in ten patients beginning at the time of diagnosis. Ex. 1102. According to Okosun-II, “[f]ollicular lymphoma is an incurable malignancy, with transformation to an aggressive subtype representing a critical event during disease progression. *Id.* at Abstract (internal footnote omitted).

Okosun-II performed “whole-genome or whole-exome sequencing of sequential follicular lymphoma–transformed follicular lymphoma (FL-tFL) pairs and matched germline samples from 10 cases (Fig. 1a and Online Methods), with deep targeted sequencing of 28 genes in an extension cohort (Supplementary Fig. 1 and Supplementary Table 1).” *Id.* at 176 (bolding removed). In particular, “Ten individuals with follicular lymphoma were selected on the basis of the availability of sequential tumor lymph node biopsies (a sample with follicular lymphoma and a subsequent sample with histological transformation to DLBCL (transformed follicular lymphoma)) and matched germline samples consisting of remission bone marrows or peripheral blood specimens.” *Id.* at 182.

For the ten index cases (six whole-genome sequenced^[7] and four whole-exome sequenced), the sequencing yielded mean genomic and exonic coverage of 37× and 110×, respectively, with 96% of the targeted bases covered by >10-fold (Supplementary Table 2). In the 6 whole-genome sequenced cases, we detected approximately 10,000 somatic variants per tumor (Supplementary Table 3).

Ex. 1102, 176 (bolding omitted).

⁷ Identified as patients S1–S6 in Supplementary Table 1. Ex. 1113, 20.

Okosun-II Figure 1 is reproduced below.

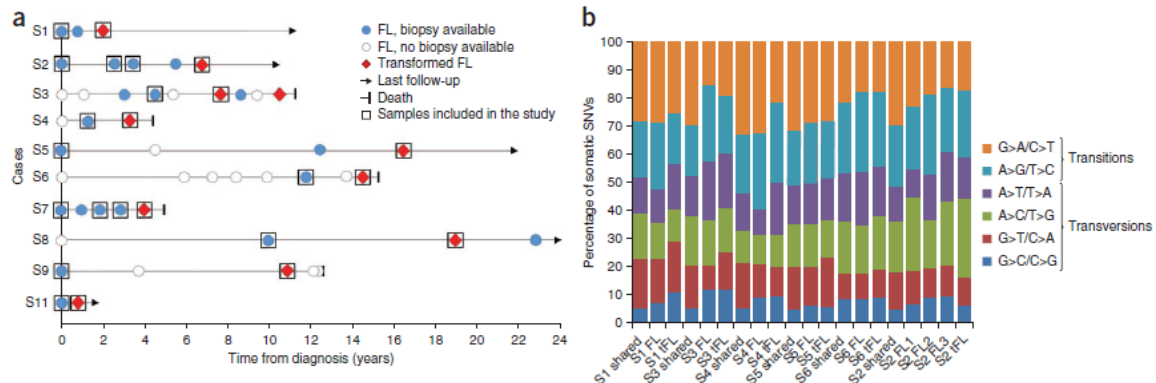
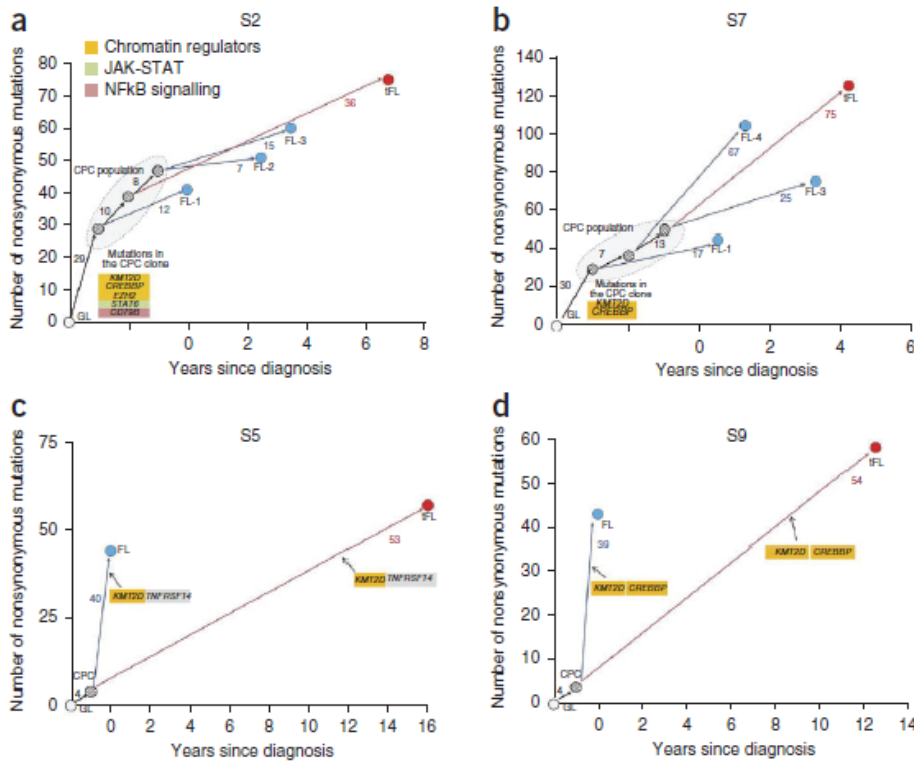


Figure 1 shows “[c]linical timelines and somatic mutation profiles for the discovery cases.” Ex. 1102, 177.⁸ Panel 1a of the figure indicates biopsy and disease timelines for the ten patients. *Id.* Panel 1b shows the distribution of nucleotide substitution patterns in identified somatic variants. “Somatic SNVs for each case were sorted into three categories: shared (variants present in both follicular lymphoma and transformed follicular lymphoma samples), follicular lymphoma specific and transformed follicular lymphoma specific.” *Id.*⁹

Figure 2 of Okosun-II is reproduced below.

⁸ Supplemental Figure 7 of Exhibit 1113 presents similar information.

⁹ Addressing Panel 1b, Dr. Quackenbush explains that the “mutations that are indicated as ‘shared’ were present in both the FL and tFL tumor samples but not in the germline samples, while mutations that are indicated as ‘FL’ were present in the FL sample but not in the germline (or subsequent tFL) samples.” Ex. 1100 ¶ 248.



Ex. 1102, 178, Fig. 2. Figure 2 shows “[p]atterns of evolution of follicular lymphoma to transformed follicular lymphoma for four cases,” where panels 2a and 2c are for (whole genome sequence) patients S2 and S5, respectively. *Id.* at legend. Okosun-II explains that,

[i]n each case, a phylogenetic tree was constructed using nonsynonymous mutations and is shown against the corresponding event timeline. All trees have shared mutations (trunk), which represent a common ancestral origin from a CPC, and unique branches, depicting the mutations present in that biopsy alone. The length of individual branches denotes the number of mutations separating the two disease events.

Id.

II. ANALYSIS

A. Legal Standards

“In an IPR, the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”)). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

Petitioner contends that claims 1–4, 7–13 are anticipated by Chan and/or Okosun II. Pet. 15. To show anticipation under 35 U.S.C. § 102, each and every claim element, arranged as in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359 (Fed. Cir. 2008). The prior art need not, however, use the same words as the claims to find anticipation. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009). In evaluating anticipation, it is permissible to take into account not only the literal teachings of the prior art reference, but also the inferences the skilled artisan would draw from it. *Eli Lilly and Co. v. Los Angeles Biomedical Res. Inst. At Harbor-UCLA Med. Ctr.*, 849 F.3d 1073, 1074–75 (Fed. Cir. 2017) (holding that the “dispositive question regarding anticipation is whether one skilled in the art would reasonably understand or infer from a prior art reference that every claim element is disclosed in that reference”). As such, “a reference can anticipate a claim even if it does not expressly spell out all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would at once envisage

the claimed arrangement or combination.” *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (internal quotation and alteration marks omitted).

Petitioner also contends that each claim of the ’968 patent is unpatentable as obvious under § 103 in view of Chan, Ley, or Okosun-II. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), reaffirmed the framework for determining obviousness set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). The *KSR* Court summarized the four factual inquiries set forth in *Graham* (383 U.S. at 17–18) that are applied in determining whether a claim is unpatentable as obvious under 35 U.S.C. § 103 as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and (4) considering objective evidence indicating obviousness or non-obviousness, if present.¹⁰ *KSR*, 550 U.S. at 406.

“[W]hen a patent ‘simply arranges old elements with each performing the same function it had been known to perform’ and yields no more than one would expect from such an arrangement, the combination is obvious.” *Id.* at 417 (quoting *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282 (1976)). But in analyzing the obviousness of a combination of prior art elements, it can also be important to identify a reason that would have prompted one of skill in the art “to combine . . . known elements in the fashion claimed by the patent at issue.” *Id.* at 418.

“[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences

¹⁰ Patent Owner does not raise objective indicia in the Preliminary Response.

which one skilled in the art would reasonably be expected to draw therefrom.” *In re Preda*, 401 F.2d 825, 826 (CCPA 1968). Moreover, a precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *KSR*, 550 U.S. at 418. Rather, “any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.” *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that “a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (quotations and citations omitted).

B. Level of Ordinary Skill in the Art

In determining the level of skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *See Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *see also Orthopedic Equip. Co. v. U.S.*, 702 F.2d 1005, 1011 (Fed. Cir. 1983).

Relying on the testimony of Dr. Quackenbush, Petitioner asserts that a person of ordinary skill in the art (“POSA”) would have had:

- 1) 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) . . .

- 2) 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
- 3) 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 . . . [and]
- 4) 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.

Pet. 8-9 (citing Ex. 1100 ¶ 36) (numbering added).

According to Patent Owner, Petitioner's proposed definition "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." Prelim. Resp. 10. Patent Owner does not offer a competing definition in the Preliminary Response, but notes that we adopted the above definition in the 00224, 00317, 00545, and 00546 IPRs.

Insofar as the prior art of record appears to support Petitioner's definition, we apply our earlier definition here as Petitioner urges. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) ("the prior art itself [may] reflect[] an appropriate level" as evidence of the ordinary level of skill in the art) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)). Patent Owner is, nevertheless, welcome to provide argument and evidence for an alternative definition at trial.

C. Claim Construction

We interpret a claim “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b).” 37 C.F.R. § 42.100(b) (2020). Under this standard, we construe the claim “in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” *Id.* Furthermore, we need only construe claim language that is in controversy, and only to the extent necessary to resolve the controversy. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017).

Petitioner contends that the preamble and step (d) of claim 1, and limitations of claims 8 and 12 are not entitled to patentable weight, and proposes definitions for the “mosaic variants” and “capture probe” limitations of claims 1 and 13, respectively. Pet. 20–25. The parties also dispute the meaning of “whole genome sequencing” (WGS), particularly as applied to Chan. *See, e.g.*, Prelim. Resp. 11–22.

We address these terms below and, as appropriate, discuss aspects of the asserted prior art to the extent they shed light on the nature of the controversy at this preliminary stage as to the disputed claim phrases. To the extent Patent Owner does not presently respond to Petitioner’s arguments we address these issues in the interest of clarity. The following constructions are provisional and either party is welcome to further address the meaning of these terms at trial.

1) Preamble¹¹

The preamble of claim 1 recites, “[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.” According to Petitioner, this language “is not entitled to patentable weight because it merely recites an intended use of the structurally complete series of method steps recited in the body of the claim.” Pet. 20 (citing *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997)).

“In general, a preamble limits the invention if it recites essential structure or steps, or if it is necessary to give life, meaning, and vitality to the claim.” *Catalina Mktg. Int’l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (quotation marks omitted). On its face, the preamble of claim 1 includes a “wherein” clause requiring that the biological sample be obtained “from a non-fetal source.” Because Petitioner does not explain how this limitation is either understood from the body of the claim, or severable from the remainder of the preamble, we do not find Petitioner’s argument persuasive. See *Cochlear Bone Anchored Sols. AB v. Oticon Med. AB*, 958 F.3d 1348, 1355 (Fed. Cir. 2020) (“A conclusion that some preamble language is limiting does not imply that other preamble language, or the entire preamble, is limiting.”). Absent further argument and evidence, and solely for the purpose of this Decision, we construe the preamble as limiting.

Insofar as the entire preamble may be limiting, Petitioner contends that we should construe “screening” in the preamble phrase “a subject being

¹¹ Petitioner makes several arguments with respect to the preamble, to which Patent Owner does not presently respond. See Pet. 20. We address these points in the interest of clarity.

screened for cancer” as encompassing the monitoring of disease in a subject previously diagnosed with cancer. *See id.* (citing Ex. 1100 ¶ 100; Ex. 1001, 1:19–23). In support, Petitioner relies on Dr. Quackenbush’s testimony that “[t]he ‘968 patent notes that a subject ‘being screened for a cancer’ includes patients who have already been diagnosed with cancer. Ex. 1001 at 1:19-23 ([I]t 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.’).” Ex. 1100 ¶ 100.

Considering the preliminary record before us, we provisionally agree with Petitioner that “a subject being screened for cancer” includes patients who have already been diagnosed with cancer.

2) “report[s],” “predict[ions],” and “recommendation[s]”

According to Petitioner, the following language from claims 1, 12, and 8, is directed to printed matter that is not entitled to patentable weight:

providing a report . . . wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a cancer in said patient (claim element 1(d));

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

providing a recommendation for a therapeutic intervention based on an identification of said mosaic variants” (dependent claim 8).

Pet. 23–24 (citing, e.g., *Praxair Distrib., Inc. v. Mallinckrodt Hosp. Prod. IP Ltd.*, 890 F.3d 1024, 1031 (Fed. Cir. 2018)).

Patent Owner does not presently respond to these contentions. Considering the plain language of the claims, however, we provisionally agree with Petitioner that

these claim elements merely recite conveying information, such as a prediction, diagnosis, and/or prognosis of disease status, outcome, or stage, or a therapy recommendation, which is based on an actor’s mental analysis of the ‘identification of mosaic variants.’ The conveyance of such information has no functional relationship to the substrate on which it is conveyed, so it is not entitled to patentable weight.

Id. at 24 (citing *In re Ngai*, 367 F.3d 1336, 1339 (Fed. Cir. 2004)). As such, we provisionally construe claim element 1(d), and the language of dependent claims 8 and 12 as non-limiting.

3) “mosaic variants”

Relying on the testimony of Dr. Quackenbush, and Patent Owner’s First Amended Complaint from district court Case 2, Petitioner contends that we should construe “‘mosaic variants’ to encompass any somatic mutation present in a cancer nucleic acid sample (i.e., either causal or non-causal somatic mutations, or both) that is not present in a normal nucleic acid.” Pet. 21–23 (citing, e.g., Ex. 1101 ¶¶101–103; Ex. 1107 ¶ 43–44 (“somatic cancer-causing variations are a type of mosaic variant”)). Patent Owner does not presently oppose this construction, which is further supported by the Specification’s teaching that “specific mosaic variants can be used as biomarkers . . . even if they are not causal for [a] medical condition.” Ex. 1001, 12:15–17. Likewise, the language of claim 5 specifies that the “mosaic variants” of claim 1 are “causal or predisposing for a cancer,”

which admits of a class of mosaic variants comprising *non*-causal somatic mutations. *See* Pet. 22–23; *see also, id.* (citing Ex. 1108, 18, 34, 137).

We are, however, confused as to why Petitioner’s proposed construction defines the nucleic acid sample as “*cancer* nucleic acid sample” or, indeed, what is meant by that qualifier. Absent further explanation, we omit the word “cancer” as unhelpful, and provisionally define “mosaic variant[]” to mean any somatic mutation present in a nucleic acid sample that is not a part of the patient’s normal DNA.

4) “whole genome sequencing”

Claim step 1(a) requires that “said first set of sequence reads and said second set of sequence reads are generated using whole genome sequencing.” According to Patent Owner, we should construe “whole genome sequencing” as “a non-targeted approach to sequencing all or almost all of a genome,” as we did in the IPR2023-00224 Institution Decision. Prelim. Resp. 14–17 (citing *e.g.*, Ex. 2199 ¶¶ 35–43, 47). In support, Patent Owner argues that “the ‘968 patent contains a nearly identical intrinsic record” as that at issue in the 00224 IPR and, thus, “compels the same construction.” *Id.* at 14.

As with the ’394 patent at issue in the 00224 IPR, the instant Specification provides little guidance regarding *how much* of the genome must be sequenced under Patent Owner’s construction. *See* generally 00224 IPR, Paper 11 at 19–23. As discussed in detail on pages 15–16 of the Preliminary Response, however, the instant Specification does make a clear distinction between “untargeted sequencing (e.g., whole genome sequencing)” as compared to targeted sequencing approaches such as “whole exome sequencing,” or “deep sequencing over a fraction of the genome.”

See e.g., Ex. 1001, 17:36–49, 25:64–34, 27:16–19, 43–46; *cf.* 00224 IPR, Paper 11 at 22 (“tak[ing] particular note of the [’394] Specification’s distinction between whole genome sequencing and targeted sequencing of the exome or other sub-genomic regions (e.g., Ex. 1001, 5:38–59, 24:35–58), as well as the Specification’s acknowledgement that whole genome sequencing may encompass “low mean coverage regions” and “zero mean coverage regions,” (*id.* at 24:59–62, 28:33–42)”). As we read the Specification, the phrase “sequencing all or almost all of a genome,” speaks more to the untargeted nature of the process rather than to an end result of the sequencing effort. In this respect, the instant Specification’s references to “high coverage whole genome sequencing,” “low coverage whole genome sequencing,” and “low” and “zero mean coverage regions from WGS,” indicate that whole genome sequencing does not mean that all or almost all of the nucleotide bases in a genome must be determined, but that “all or almost all” of the genome is available for sequencing.¹² *See e.g., id.* at 25:64–67, 26:6–14, 27:16–19, 28:57–60; 32:37–45; *see also* 00224 IPR, Paper 11 at 19–23 (preliminarily determining that Leary disclosed whole genome sequencing despite evidence that the authors sequenced only about half of the genome).

With the above explanation, we provisionally construe “whole genome sequencing as “a non-targeted approach to sequencing all or almost all of a genome.” We leave for later, and to the extent necessary, any

¹² Consistent with Owner’s argument that “WGS has taken on many different flavors of meaning,” we presently understand the Specification’s recognition of “high” and “low” coverage whole genome sequencing as species of the generic term. *See* Prelim Resp. 12–13 (citing Ex. 2018, 155:15–20, 161:21–162:1, 156:20–157:22).

determination of the lower limit (if any) one of ordinary skill would attach to the number sequencing reads, extent of genomic coverage, or nucleotide bases that must be determined to qualify as whole genome sequencing, and whether any particular experimental approach would have been understood to comprise whole genome sequencing.

In a related matter, Patent Owner contends that we should deny the Petition because Foresight failed to construe “whole genome sequencing” as required under Rule 42.104(b)(3)–(4) and, at best, merely equates Chan’s shotgun massively parallel sequencing (MPS) with WGS, asserts that the plain meaning should apply only in the Reply, and “bur[ies] a contingent claim construction theory of WGS in Dr. Quackenbush’s declaration.” Prelim. Resp. 2–3, 11–14; Sur-reply 1–3 (citing Pet. 29; Reply 2–3 (citing Ex. 1100 ¶ 120)).

On balance, we find insufficient cause to deny the Petition as Patent Owner requests. We note, in particular, Patent Owner’s assertion that “the ‘968 patent contains a nearly identical intrinsic record” as that at issue in the 00224 IPR and, thus, “compels the same construction.” Prelim. Resp. 14. Having so agreed with Patent Owner, we apply that same construction here, and view Petitioner’s relative silence on the matter as an indication that it does not contest our earlier construction made in the related 00224 IPR. Moreover, the only reference that Patent Owner argues at this stage lacks a disclosure of WGS is Chan, yet Dr. Quackenbush has analyzed that reference under Patent Owner’s preferred construction—the text of which we provisionally adopted in the 00224 IPR, and provisionally adopt here. *See* Ex. 1100 ¶ 120.

5) “capture probes”

Depending from claim 1, claim 13 requires that the “mosaic variants . . . are identified using capture probes in said first additional sample of step (c).” According to Petitioner and Dr. Quackenbush, one of ordinary skill in the art reading the ’968 Specification would have understood “capture probes” to encompass at least PCR primers and solution-based hybridization baits (e.g., biotinylated oligonucleotide baits)—a construction we provisionally adopted in the 00224 and 00317 IPRs. *See, e.g.*, Pet. 24–25; Ex. 1100 ¶¶ 104–107; 00224 IPR, Paper 11 at 23–29. This presently unopposed construction is supported by the ’968 Specification, which broadly provides that “capture probes may comprise one or more nucleotides,” and “may comprise a nucleic acid binding site that hybridizes to one or more genomic regions.” *See generally*, Ex. 1001, 35:29–36:31.

In view of the above, we provisionally construe “capture probes” as used in claim 13, to encompass at least PCR primers and solution-based hybridization baits (e.g., biotinylated oligonucleotide baits).

D. Ground 1: Anticipation by Chan

As to Ground 1, Petitioner challenges claims 1–4, 7, 9–12 as anticipated by Chan. Pet. 15. Petitioner provides an element-by-element comparison of the claims to the cited art. *Id.* at 26–35.

We focus first on the issues raised in the Patent Owner Preliminary Response. With respect to the remaining elements of the claims challenged under Ground 1, Petitioner presents reasoned arguments for unpatentability over Chan supported by the testimony of Dr. Quackenbush, which Patent Owner does not presently contest. *See generally* Pet. 31–35; Ex. 1020 ¶¶ 125–152; *see generally* Prelim. Resp.

Patent Owner’s arguments relate to claim step 1(a) which, in relevant part, is directed to “obtaining a first set of sequence reads and a second set of sequence reads . . . generated using whole genome sequencing . . . wherein [said second set of sequence reads corresponds to a second set of nucleic acid molecules, and]. . . said second set of nucleic acid molecules is extracted from leukocytes.” In particular, Patent Owner contends that Chan fails to disclose “whole genome sequencing” or “nucleic acid molecules . . . extracted from leukocytes,” as well as aspects of Elements 1(b) and 1(c), which relate to those terms. We address Patent Owner’s arguments below.

1) “whole genome sequencing”

Petitioner and Dr. Quackenbush contend that Chan’s application of shotgun MPS to sequence plasma DNA from cancer patients constitutes whole genome sequencing. *See generally*, Pet. 26–29; Ex. 1008 ¶¶ 112–120; *see e.g.*, Ex. 1008 ¶ 113 (“Chan discloses step 1(a) by performing WGS on matched (i) tumor tissue from hepatocellular carcinoma (HCC); and (ii) buffy coat DNA, which is the fraction of a centrifuged blood sample that contains leukocytes.”). Relying on the testimony of Dr. Furneaux, Patent Owner presents two arguments for why Chan does not disclose whole genome sequencing. Prelim. Resp. 17–22; Ex. 2199 ¶¶ 48–60.

Patent Owner first argues that “Foresight wrongly equates Chan’s MPS with WGS.” Prelim. Resp. 17. According to Patent Owner, MPS—also known as next generation sequencing (NGS)—“can be used for a host of different types of applications that are not WGS,” including targeted sequencing approaches such as whole exome sequencing, the sequencing of specific genes or exons, and even non-genomic applications such as transcriptome and small RNA sequencing. *Id.* at 18–19 (citing Pet. 10;

Ex. 2199 ¶ 50; Ex. 2192, 169, 173; Ex. 2193, 437; Ex. 1014, 527; Ex. 1013, 1135). Although we agree with Patent Owner that many of the possible applications of MPS are outside the scope of whole genome sequencing, Patent Owner’s argument is unavailing because Chan does *not* disclose MPS generally. Rather, Chan discloses a specific application of MPS (“shotgun MPS”), and its use in sequencing genomic DNA. *See* Ex. 1008, 211 (“In this study, we explored the use of shotgun massively parallel sequencing (MPS) of plasma DNA from cancer patients to scan a cancer genome noninvasively.”).

Patent Owner further argues that “a ‘shotgun’ type of MPS does not transform Chan’s MPS into WGS” because the term merely conveys that “the DNA to be sequenced has been randomly broken into smaller fragments.” Patent Owner further contends, for example, that because Chan’s “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,” Chan did not “sequence all or almost all of the genome” as it interprets whole genome sequencing. Prelim. Resp. 21–22 (citing e.g., Ex. 2199 ¶¶ 55–60; Ex. 1008, 215, 218, Figs. 1, 4).

Patent Owner’s argument, however, is based on an understanding of “whole genome sequencing” at odds with our provisional interpretation of the term, and our present understanding of the Specification’s teaching that whole genome sequencing may comprise “one or more low mean coverage regions” and “zero mean coverage regions.” *See* Ex. 1001, 28:57–60; 32:37–45 (similar).

Considering our provisional understanding of the term “whole genome sequencing,” for the purpose of institution, we find sufficient

Dr. Quackenbush's testimony that Chan discloses whole genome sequencing. As explained by Dr. Quackenbush, using "[s]equencing libraries of the genomic DNA samples . . . constructed with the Paired-End Sample Preparation Kit (Illumina),' which involved shearing genomic DNA into 200-bp fragments," Chan generated sequence reads using MPS by sequencing tumor DNA and buffy coat DNA to "mean depths of 29.5 fold . . . and 43-fold . . . haploid genome coverage, respectively." Ex. 1100 ¶¶ 118–119 (citing Ex. 1008, 212, 218). According to Dr. Quackenbush, "[t]his was non-targeted whole-genome sequencing to 'explore[] the *genomewide* detection of tumor-derived SNVs in the plasma of the 4 HCC patients.'" *Id.* ¶ 118 (citing Ex. 1008, 218).

Further applying a construction of "whole genome sequencing," defined as "a non-targeted approach to sequencing all or almost all of a genome," Dr. Quackenbush states:

Chan's approach is "non-targeted" because the sequencing libraries are prepared from randomly sheared genomic DNA, and thus reads are intended to be generated from all DNA in a sample, as opposed to targeted sequencing of chosen or selected DNA loci (e.g., the exome only). Second, Chan's approach sequences all or almost all of the genome, specifically noting "haploid genome coverage" of 29.5-fold (tumor DNA) and 43-fold (buffy coat DNA). Thus, on average, each base of the haploid genome was sequenced 29.5 times in the tumor sample, and 43 times in the buffy coat sample, confirming that Chan's nontargeted sequencing approach sequenced all or almost all of the genome.

Ex. 1100 ¶ 120. Although the record is incomplete as to whether, or to what extent, one of ordinary skill in the art would assign a lower limit to the number of sequencing reads, extent of genomic coverage, or nucleotide bases that must be determined to qualify as whole genome sequencing, we

find the testimony and evidence with respect to Chan sufficient for purposes of institution. As such, we find that Petitioner has established sufficiently at this stage that Chan discloses whole genome sequencing.

2) “nucleic acid molecules . . . extracted from leukocytes”

Claim element 1(a)(ii) recites that “said second set of nucleic acid molecules is extracted from leukocytes in a blood sample.” According to Petitioner, Chan discloses this step by “performing WGS on . . . buffy coat DNA, which is the fraction of a centrifuged blood sample that contains leukocytes.” Pet. 27 (citing e.g., Ex. 1008, 211; Ex. 1100 ¶ 113).

Patent Owner contends that Petitioner’s reliance on Chan fails because “buffy coat contains several types of nucleated non-leukocyte cells from which genomic DNA can be extracted” and, thus, “Foresight has not proven that Chan’s extraction of DNA from buffy coat samples necessarily involves extraction of nucleic acid molecules from leukocytes.” Prelim. Resp. 23–25 (citing e.g., Ex. 2199 ¶¶ 63–64).

Dr. Quackenbush provides testimony and evidence that one of ordinary skill in the art would have understood that buffy coat is a leukocyte-enriched fraction of whole blood. *See* Ex. 1100 ¶ 103, n.6 (citing Ex. 1109, 29); *see also* Ex. 2198, 1012 (describing buffy coat from peripheral blood as “leukocyte concentrates”). And nowhere do we find in Chan any suggestion that leukocytes are somehow *removed* from the buffy coat prior to nucleic acid extraction. To the contrary, for the POSA looking to extract from the buffy coat DNA for sequencing, we find it unlikely on the present record that the POSA would interpret Chan’s method as excluding the abundant DNA available in buffy coat leukocytes. As such, we fail to see the logic in Patent Owner’s contention. Moreover, we read

Example 4 of the Specification as teaching the extraction of leukocyte DNA from buffy coat—*exactly as described in Chan*. According to the '968 Specification:

A blood sample is taken from a patient during a routine visit to the clinic. The blood sample is centrifuged to separate the blood into plasma, buffy coat, and red blood cells. The plasma contains cfDNA and the buffy coat contains leukocytes (i.e., some of which may be leukemia cells). Nucleic acids are extracted from both the plasma and the leukocytes, the nucleic acids are sequenced, and variants are detected in the samples.

Ex. 1001, 53:59–66; *see also id.* at 13:22–40 (disclosing the extraction of “white blood cell[]” DNA from buffy coat), 14:50–52 (“blood-specific mosaic variants may be identified by sequencing DNA from the thin layer formed by centrifugation of blood (e.g., ‘Buffy Coat’)”); Ex. 3002 (explaining that white blood cells are synonymous with leukocytes).¹³

In view of the above, Petitioner has sufficiently shown that Chan discloses “nucleic acid molecules . . . extracted from leukocytes,” as required by claim element 1(a)(ii).

3) Elements 1(b) and 1(c)

Patent Owner’s arguments with respect to elements 1(b) and 1(c) also derive from its contentions that Chan fails to disclose “whole genome sequencing” or “nucleic acid molecules . . . extracted from leukocytes.” Element 1(b) involves “using said first set of sequence reads and said second set of sequence reads to identify mosaic variants.” Element 1(c) similarly relates to “identifying . . . mosaic variants.” According to Patent Owner,

¹³ “Leukocyte,” National Cancer Institute Dictionary of Cancer Terms, available at <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/leukocyte>. Ex. 3002.

Petitioner's proofs with respect to Elements 1(b) and 1(c) are deficient because Chan fails to disclose the use of whole genome sequencing or the extraction from leukocytes limitations of claim step 1(a). But, as discussed in Sections II.D.1 and II.D.2 above, Petitioner has shown sufficiently that Chan discloses these limitations. As such, Patent Owner's arguments with respect to Elements 1(b) and 1(c) are unavailing on the current record.

4) Conclusion as to Ground 1

Considering the record presently before us, and in light of our constructions based on the current record, Petitioner has the better position with respect to arguments discussed above. Having further considered the arguments and evidence at this preliminary stage, we determine that Petitioner has demonstrated a reasonable likelihood that claims 1–4, 7, 9–12 are anticipated by Chan.

E. Ground 2: Obviousness in View of Chan

As to Ground 2, Petitioner challenges claims 1–13 as obvious in view of Chan. Pet. 15, 35–38. As noted by Patent Owner, Petitioner rests on its Ground 1 anticipation proofs with respect to the independent claim. As Petitioner has shown sufficiently for the purpose of institution that Chan discloses all elements of claim 1, we need not presently address Patent Owner's arguments regarding obviousness for this claim. And whereas Petitioner provides argument and evidence under Ground 2 with respect to dependent claims 2, 5–6, 8, and 13, Patent Owner does not address these arguments with specificity in the Preliminary Response. Accordingly, we leave our discussion of the merits of Ground 2 for a more complete record developed through trial.

F. Ground 3: Obviousness in View of Ley

As to Ground 3, Petitioner challenges claims 1–13 as obvious in view of Ley. Pet. 15, 38–59; Ex. 1100 ¶ 167. Petitioner provides an element-by-element comparison of the claims to the cited art. Pet. 43–59. In short, Petitioner contends that Ley teaches every element of independent claim 1 except that, rather than comparing sequences from a “tissue sample of said subject” to that of a reference sequence “extracted from leukocytes,” as required by claim 1, Ley compares a reference sample derived from a skin biopsy to genomic sequences from leukemia cells in a patient’s blood. *See* Pet. 39 (citing Ex. 1101 ¶ 169). As explained by Dr. Quackenbush, instead of cells from a patient’s blood, Ley used a skin tissue biopsy as a suboptimal source of germline DNA in leukemia patients to reduce the contamination of leukemia DNA in the reference sample. Ex. 1101 ¶ 169.

According to the Petition, outside the context of a leukemia patient, one of ordinary skill in the art would have considered it an obvious “design choice” to apply Ley’s method to identifying mosaic variants in solid tumors (i.e., the claimed “tissue sample”), and obtain the reference sequence from the subject’s normal blood leukocytes. *See id.* As support, for the idea of application-dependent “design choice,” Petitioner points to Example 4 of the ’968 patent, which discloses a method of “Detecting Variants in Leukemia by Tumor Versus Normal Analysis” wherein normal genomic sequence from plasma cfDNA is compared to DNA extracted from buffy coat leukocytes (“some of which may be leukemia cells”) from a patient suspected of harboring leukemia. *Id.*; *see* Ex. 1001, 53:53–54:27.

Petitioner further argues that, in addition to Ley, numerous reports represented by Meyerson (Ex. 1031),¹⁴ Chapman (Ex. 1103),¹⁵ Lee (Ex. 1104),¹⁶ and Ding (Ex. 1105)¹⁷ “implemented the same general concept of (i) WGS of matched tumor/normal DNA to identify tumor-specific variants of interest and (ii) monitoring tumor-specific variants in the patient to screen their cancer.” Pet. 39–43 (citing Ex. 1100 ¶¶ 170–176). Meyerson, for example, states:

Complete 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 — including nucleotide substitutions, structural rearrangements, and copy number alterations — using a single approach

Ex. 1031, 687 (citing, e.g., Ley (Ex. 1101); Lee (Ex. 1104); Ding (Ex. 1105)).

Similarly, Chapman states:

A powerful way to understand the molecular basis of cancer is to sequence either the entire genome or the protein-coding exome, comparing tumour to normal from the same patient to identify the acquired somatic mutations. Recent reports have described the sequencing of whole genomes from a single patient [citing, e.g., Lee (Ex. 1104) and Ding (Ex. 1105)]. Although informative, we hypothesized that a larger number of

¹⁴ Meyerson, et al., “Advances in understanding cancer genomes through second-generation sequencing,” 471 *Nature Reviews* 467–472 (2010). Ex. 1031.

¹⁵ Chapman, *et al.*, “Initial genome sequencing and analysis of multiple myeloma,” 471 *Nature* 467–472 (2011). Ex. 1103.

¹⁶ Lee, *et al.*, “The mutation spectrum revealed by paired genome sequences from a lung cancer patient,” 465 *Nature* 473–477 (2012). Ex. 1104.

¹⁷ Ding *et al.*, “Genome remodelling in a basal-like breast cancer metastasis and xenograft,” 464 *Nature* 999–1005 (2010). Ex. 1105.

cases would permit the identification of biologically relevant patterns that would not otherwise be evident.

Ex. 1103, 467.

We focus below on the issues raised in the Patent Owner Preliminary Response. With respect to the remaining elements of the claims challenged under Ground 3, Petitioner presents reasoned arguments for unpatentability over Ley supported by the testimony of Dr. Quackenbush, which Patent Owner does not presently contest. *See generally* Pet. 38–59; Ex. 1100 ¶¶ 197–236; *see generally* Prelim. Resp.

2) Claim Elements 1(a)(i)-(2)

Claim 1 involves identifying mosaic variants in a tissue sample based on sequence reads from a first and second set of nucleic acid molecules, wherein

- (i) said first set of nucleic acid molecules is extracted from [a] tissue sample of said subject, and
- (ii) said second set of nucleic acid molecules is extracted from leukocytes from a blood sample.

According to Patent Owner, one of ordinary skill in the art would not have been motivated to modify Ley’s approach to use (1) a solid “tissue sample” as the tumor sample and, (2) leukocytes as the normal (i.e. reference) sample. Prelim. Resp. 37. We address these arguments in turn.

a. “*nucleic acid molecules . . . extracted from [a] tissue sample*”

Patent Owner appears to argue, first, that Ley teaches away from extracting a first sample from “[a] typical tumor sample contain[ing] a mixture of tumor and normal cells” in light of Meyerson’s statement that mixed “samples create ‘particular challenges for the detection and diagnosis

of cancer genome alterations.” *Id.* at 37–38 (citing Ex. 1031, 685–686; Ex. 2199 ¶ 86).¹⁸ Patent Owner argues that Ley’s method “‘**required** high sample purity’ in the tumor sample to ‘eliminate the need to further purify malignant cells’” and, therefore, Ley selected for its studies “typical acute myeloid leukemia (AML)” samples having a blast count of greater than 80%. *Id.* at 38 (citing Ex. 1042, 1 (Supplementary Methods); Ex. 2199 ¶¶ 87–88).

We note, however, that the passage in Ley relied on by Patent Owner states that “***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.” Ex. 1042, 1 (emphasis added). Ley’s “require[ment for] high sample purity” is, thus, arguably directed to preparatory flow cytometry of the M1 AML sample. The evidence of record does not suggest that morphologic flow cytometry would be used with a solid tumor sample, nor that one of ordinary skill in the art sampling a solid tumor tissue would necessarily eschew purification steps.

Moreover, neither Patent Owner nor Dr. Furneaux discuss the understanding of one of ordinary skill in the art as to, for example, (1) the homogeneity of a various, or even “typical” solid tumor sample as compared to Ley’s M1 AML samples,¹⁹ (2) the availability of techniques to separate

¹⁸ Meyerson, however, then teaches that “[s]econd-generation sequencing can solve such problems,” which teaching is unaddressed by Patent Owner. Ex. 1031, 685.

¹⁹ Patent Owner appears to conflate Ding’s statement that a “wide range of mutant allele frequencies suggests considerable genetic heterogeneity in the cellular population at the primary site,” with a contamination of normal cells in a tumor sample. *See* Prelim. Resp. 44; Ex. 1105, 1004. Ding, however, refers to the accumulation of genetic variants in sub-lines of a patient’s

malignant from normal cells in a solid tissue sample or, (3) the level of purity required in the tumor sample to identify mosaic variants using Ley's overall method. With respect to the latter, we note Ley's teachings that some mosaic variants were present and detectable in only a fraction of AML cells, indicating the sample was far from "pure" with respect to these alleles. *See e.g.*, Ex. 1012, 69 ("the *FLT3* internal tandem duplication (ITD) allele was only detected in 35.1% of the 454 reads at diagnosis and 31.3% at relapse, suggesting that the mutation was not present in all tumour cells at diagnosis or relapse"). Moreover, Ley's technique was sufficiently sensitive to detect traces of contaminating tumor variants in the reference skin biopsy. *See id.* at Fig. 3. Commenting on this observation, Ley states that,

variant alleles also were detected at frequencies of ~5–13% in the skin sample. In retrospect, it is clear that the skin sample contained contaminating leukaemic cells, because the patient's white blood cell count at presentation was 105,000 per microlitre, with 85% blasts. This information was used to inform the Decision Tree analysis described above: we allowed high-quality tumour variants to move forward in the discovery pipeline if they were detected at a low frequency (two or fewer reads) in the skin sample, as defined by a binomial test.

Id. at 69.

In view of the above, Patent Owner's concerns for sample purity are not supported on the current record, and we determine Petitioner has shown sufficiently that one of ordinary skill in the art would have been motivated to modify Ley such that a "first set of nucleic acid molecules is extracted from [a] tissue sample," as required by claim element 1(a)(1).

primary tumor as illustrated in the Circos plots of Figure 4. *See, e.g.*, Ex. 1105, Fig. 4.

b. “*nucleic acid molecules is extracted from leukocytes*”

Patent Owner further argues that one of ordinary skill in the art would not have been motivated to substitute reference DNA derived from a skin biopsy with reference DNA extracted from leukocytes as required by claim element 1(a)(2). *See* Prelim. Resp. 39–44. “Tellingly,” Patent Owner asserts, “none of [Meyerson, Chapman, Lee, or Ding,] teaches to use *leukocytes* as the normal sample.” *Id.* at 39. We do not find Patent Owner’s argument availing on the present record.

Petitioner points to, for example, Ding as teaching the identification of mosaic variants using whole genome sequencing and comparing breast cancer tumor sequences with (normal) reference data from the patient’s peripheral blood. *See* Pet. 41–43; Ex. 1100 ¶¶ 174–175; Ex. 1105; *see also* Ex. 1103, 467 (identifying Ding as disclosing “sequencing of whole genomes from a single patient”). Patent Owner contends, however, that “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),” because peripheral blood also contains cfDNA, and “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).” Prelim. Resp. 42–43 (citing Ex. 2199 ¶ 99).

For the reasons discussed in the Petition and, as discussed in Section II.D.2, above, we do not find Patent Owner’s argument availing on the present record. *See, e.g.,* Pet. 41–43, n.7; Ex. 1100 ¶ 176–176. We note, for example, Dr. Quackenbush’s testimony that:

A POSA would have known that the peripheral blood comprises leukocytes. Ex. 1109 (Qiagen Protocol) at 29 (stating that “[a] 200 µl sample of whole human bloods” contains a concentration of $\sim 5 \times 10^6$ leukocytes/ml). Moreover, a POSA would have found it obvious to extract DNA from buffy coat, which is “a leukocyte-enriched fraction of whole blood,” to obtain DNA for a sequencing experiment because “[p]reparing a buffy-coat fraction from whole blood is simple and yields approximately 5-10 times more DNA than an equivalent volume of whole blood.” *Id.*

Ex. 1100 ¶ 175. In short, the present record supports that it would have been obvious to extract reference DNA from the leukocyte-enriched buffy coat fraction of whole blood because it contains more DNA than an equivalent volume of whole blood and, presumably, less soluble materials referenced by Patent Owner such as cfDNA, “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).” *See* Prelim. Resp. 42–43.

In view of the above, Petitioner has shown sufficiently that one of ordinary skill in the art would have been motivated to modify Ley such that a “second set of nucleic acid molecules is extracted from leukocytes from a blood sample,” as required by claim element 1(a)(ii).

3) “identifying said mosaic variants”

Element 1(c) recites, in part, “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.” According to Patent Owner, we should read this in the context of element 1(b), which

“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.***”

Prelim. Resp. 45. Taken together, Patent Owner contends “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).” *Id.*

So construed, Patent Owner contends that Ley fails to teach or suggest element 1(c) because the skin biopsies Ley references in its Figure 3 and Table 3 in connection with the testing of relapse samples were contaminated with tumor cells. *Id.* at 45–46 (citing Ex. 2199 ¶¶ 104–105; Ex. 1012, 69, Fig.3, Tab. 3; Pet. 49–51). Thus, Patent Owner contends, “the mosaic variants in Ley’s relapse tumor sample were also present in the normal skin sample” in contravention of element 1(c)’s requirement that “said tissue sample . . . is obtained from a source that is different than said tissue sample.” *See id.* at 46 (citing Ex. 2199 ¶¶ 104–105). We do not find Patent Owner’s argument availing on the present record.

As we understand Ley’s Figure 3, the values represented by yellow bars were obtained from skin samples. In contrast, the “primary tumour” and “relapse tumour” values are from samples obtained from a neutrophil-enriched fraction of blood (buffy coat). Because skin is different than buffy coat, Ley’s skin samples are obtained, *prima facie*, from a source that is different than the tumor samples. Patent Owner is, nevertheless, welcome to

formally address at trial the construction of “obtained from a source that is different than said tissue sample.”²⁰

Further, even were Patent Owner to prevail on its implicit construction, this would be unlikely to impact our obviousness analysis insofar as we understand that Ley only detected a low level of variant alleles in the skin because the patient’s blood contained a high level of circulating leukocytes. *See* Ex. 1012, 69 (“In retrospect, it is clear that the skin sample contained contaminating leukaemic cells, because the patient’s white blood cell count at presentation was 105,000 per microlitre, with 85% blasts.”). That this finding was unexpected implies that one of ordinary skill in the art would prefer a reference sample uncontaminated with tumor cells, to the extent one was available for a particular application. Moreover, the ’968 patent appears to recognize that a single sample may comprise sources of both normal and variant cells or DNAs. *See, e.g.*, Ex. 1001, 13:28–29 (“In some cases, the normal analysis and the tumor analysis are performed on a single blood sample.”), 14:57–15:6 (discussing methods of “subtracting out the blood-specific signal from other signals”).

4) Conclusion as to Ground 3

Considering the record presently before us, and in light of our constructions based on the current record, Petitioner has the better position with respect to arguments discussed above. Having further considered the

²⁰ If either party intends to further argue claim construction at trial, they should do so in a clearly designated section of their briefing so as to expressly identify such arguments. *See, e.g.*, 37 C.F.R. § 42.104(b)(3) (content of petition); *see also* Board’s Consolidated Trial Practice Guide (CTPG), 84 Fed. Reg. 64,280, at 46, 48–45 (Nov. 2019) (available at <https://www.uspto.gov/TrialPracticeGuideConsolidated>). Claim construction arguments should not be relegated to patentability arguments on the facts.

arguments and evidence at this preliminary stage, we determine that Petitioner has demonstrated a reasonable likelihood that claims 1–13 would have been obvious in view of Ley.

G. Ground 4: Anticipation by Okosun-II

As to Ground 4, Petitioner challenges claims 1 and 8–13 as anticipated by Okosun-II. Pet. 15. Petitioner provides an element-by-element comparison of the claims to the cited art. *Id.* at 60–67.

We focus first on the issues raised in the Patent Owner Preliminary Response. In particular, Patent Owner contends that Okosun-II fails to disclose “whole genome sequencing” of “nucleic acid molecules . . . extracted from leukocytes,” and “identifying mosaic variants” in elements 1(b) and 1(c) of the challenged independent claim. With respect to the remaining elements of the claims challenged under Ground 4, Petitioner presents reasoned arguments for unpatentability over Okosun-II supported by the testimony of Dr. Quackenbush, which Patent Owner does not presently contest. *See generally* Pet. 64–67; Ex. 1020 ¶¶ 253–270; Prelim. Resp.

- 1) “*whole genome sequencing*” wherein the “*nucleic acid molecules [are] extracted from leukocytes*”

Petitioner and Dr. Quackenbush contend that Okosun-II discloses whole genome sequencing “of sequential follicular lymphoma-transformed follicular lymphoma (FL-tFL) pairs and matched germline samples,” where “the germline DNA sample may be obtained from ‘peripheral blood specimens,’” which contain leukocytes. *See* Pet. 61 (citing Ex. 1100 ¶¶ 243–245; Ex. 1102, 176–177). Patent Owner contends that these elements are not present in Okosun-II. Prelim. Resp. 50–55.

Patent Owner first asserts that “Okosun-II’s peripheral blood specimens fail[] to inherently disclose extraction of nucleic acid molecules from leukocytes because peripheral blood consists of a complex mixture of cells, cell fragments, hormones, enzymes” etc. *Id.* at 51. As discussed above, we find it sufficient that the source of the sequenced DNA (*e.g.*, the buffy coat used by Ley) contain leukocytes and, moreover, is *enriched* in leukocytes as compared to whole blood. *See* Section II.1.b, above.

Pointing to Okosun-II’s statement that “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,” Patent Owner next contends that the reference “does not describe which of the FL-tFL samples were subjected to WGS versus which samples were subjected to whole-exome sequencing (WES).” Prelim. Resp. 53. Okosun-II’s Supplementary Table 1 discloses that patients S1–S6 were “Genome Sequencing Cases,” and patients S7–9 and S11 were “Exome Sequencing Cases.” Ex. 1113, 20–21.

Noting Okosun-II’s teaching that “matched germline samples consist[ed] of remission bone marrows or peripheral blood specimens,” Patent Owner further contends Okosun-II does not specify which of the lymphoma samples were matched with peripheral blood specimens and that it is “possible that **none** of Okosun-II’s FL-tFL samples were sequenced via WGS **and** matched with germline from peripheral blood specimens.” Prelim. Resp. 53–54 (citing Ex. 1102, 183). We do not find Patent Owner’s argument availing because Okosun-II teaches that the FL-tFL samples are matched with “remission bone marrows **or** peripheral blood specimens.” *Id.* at 53 (emphasis added). And, a “finding of anticipation ‘does not require the

actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure.” *Arbutus Biopharma Corp. v. ModernaTX, Inc.*, 65 F.4th 656, 662 (Fed. Cir. 2023) (citing *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003)). Patent Owner does not argue that whole genome sequencing of peripheral blood to create a reference sequence was not enabled as of the time of the invention.

Further, even if all six of Okosun’s genome sequenced cases were matched with reference DNA extracted from bone marrow, one of ordinary skill in the art would have recognized bone marrow as a source of leukocytes (i.e., white blood cells). *See* Ex. 3003, Abstract (“Bone marrow contains a complex mixture of vascular cells, white blood cells present at much greater concentrations than in blood, and a small number of progenitor cells and stem cells.”), 6 (Tab. 1) (comparing WBC concentrations of whole blood and bone marrow aspirate), 7 (“Blood and bone marrow are not fundamentally different solutions, but rather a continuation of the same biological system.”).²¹ As such, we understand all six of the whole genome-sequenced matched pairs to employ nucleic acid molecules extracted from leucocytes as the reference sequence.

In view of the above, Petitioner has shown sufficiently that Okosun-II discloses “whole genome sequencing” wherein the “nucleic acid molecules [are] extracted from leucocytes,” as required by claim element 1(a).

²¹ King, et al., “Role of White Blood Cells in Blood- and Bone Marrow-Based Autologous Therapies,” *Biomed. Res. Int.*, published online 2018 Jul 10. doi: 10.1155/2018/6510842.

2) Element 1(b)

Element 1(b) recites “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,” where “said second set of sequence reads” is defined as in element 1(a) as having been obtained from “nucleic acid molecules [] extracted from leukocytes.” Patent Owner, thus, contends that Okosun-II fails to disclose the element 1(b) because it “does not anticipate generating the second set of sequencing reads using WGS on nucleic acids extracted from leukocytes.” Prelim. Resp. 54. As explained above, however, Petitioner has shown sufficiently that Okosun-II discloses “whole genome sequencing” wherein the “nucleic acid molecules [are] extracted from leukocytes,” as required by claim element 1(a).

3) Element 1(c)

Element 1(c) recites, in part, “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.” Patent Owner contends that this limitation is not satisfied because Petitioner relies on Okosun-II’s FL and tFL biopsies for both the “tissue sample” of element 1(a)(i), and for the “*additional sample . . . obtained from a source that is different than said tissue sample*” of element 1(c). Prelim. Resp. 55. In particular, Patent Owner argues that the two sources cannot be different because all of the biopsies are taken from follicular tissue. *Id.*

We do not find Patent Owner’s position availing on the present record. At a minimum, Okosun-II’s Figure 1a shows that sequential biopsies

from patients S1–S6 were taken from follicular lymphomas (FL) and, later, from transformed follicular lymphomas (tFL). Ex. 1102, 177, Fig. 1a. On the present record, we view those two tissue types as evidence that the later sampled tFL samples were “obtained from a source that is different than” the FL samples. Further, as illustrated in the phylogenetic trees of Okosun-II’s Figure 2, a patient’s follicular lymphoma undergoes clonal evolution such that the “source” of successive FL or tFL samples from the same patient may be understood to be different at later times.

Considering the above, Petitioner has shown sufficiently that Okosun-II discloses element 1(c) of the independent claim. We will further address this issue on a more complete record.

4) Conclusion as to Ground 4

Considering the record presently before us, and in light of our constructions based on the current record, Petitioner has the better position with respect to arguments discussed above. Having further considered the arguments and evidence at this preliminary stage, we determine that Petitioner has demonstrated a reasonable likelihood that claims 1 and 8–13 are anticipated by Okosun-II.

H. Ground 5: Obviousness in View of Okosun-II

As to Ground 5, Petitioner challenges claims 1–13 as obvious in view of Okosun-II. Pet. 15, 68–76. Petitioner expressly incorporates its anticipation proofs into its obviousness analysis. *Id.* at 68. As Petitioner has shown sufficiently that Okosun-II discloses all elements of claim 1, we need not presently address Patent Owner’s arguments regarding obviousness for the independent claim. And whereas Petitioner provides argument and evidence under Ground 5 with respect to dependent claims 2–13, Patent

Owner does not address these arguments with specificity in the Preliminary Response. Accordingly, we leave our discussion of the merits of Ground 5 for a more complete record developed through trial.

III. CONCLUSION

After considering the evidence and arguments presented in the current record, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least one of the challenged claims of the '968 patent is unpatentable. We therefore institute trial on all challenged claims under the grounds raised in the Petition. *See PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (indicating that a decision whether to institute an *inter partes* review “require[s] a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition.”); Guidance, 2–3. At this stage of the proceeding, we have not made a final determination with respect to the patentability of any of the challenged claims.

Any argument not raised in a timely Patent Owner Response to the Petition, or as permitted in another manner during trial, shall be deemed waived even if asserted in the Preliminary Response. In addition, nothing in this Decision authorizes Petitioner to supplement information advanced in the Petition in a manner not permitted by the Board’s Rules.

IV. ORDER

ORDERED, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–13 of the '968 Patent is instituted with respect to the grounds set forth in the Petition; and

FURTHER ORDERED, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), that the *inter partes* review of the '968 Patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

IPR2024-00170
Patent 11,584,968 B2

PETITIONER:

Andrew Krause
IRELL & MANELLA LLP
akrause@irell.com

Amir Naini
NAINI P.C.
amir@nainipc.com

PATENT OWNER:

Nathanael Luman
KNOBBE, MARTENS, OLSON, & BEAR, LLP
Nate.luman@knobbe.com

Derek Walter
WEIL, GOTSHAL & MANGES LLP
Derek.walter@weil.com