

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS, Inc.
Petitioner,

v.

PERSONALIS, Inc.
Patent Owner.

IPR2023-00545
Patent 11,299,783 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”) filed a Petition for an *inter partes* review of claims 1–9, 13–19, and 21–19 of U.S. Patent No. 11, 299,783 B2 (“the ’783 patent,” Ex. 1001). Paper 1 (“Pet.”). Personalis, Inc. (“Patent Owner”) timely filed a Preliminary Response. Paper 10 (“Prelim. Resp.”). With our authorization (*see* Exhibit 3001), Petitioner filed a Reply to the Preliminary Response (Paper 11, “Reply”); Patent Owner filed a corresponding Sur-reply (Paper 12, “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 ’783 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. 1. Patent Owner also identifies only itself, Personalis, Inc., as the real party-in-interest in this proceeding. Paper 9, 1.

D. Related Matters

In addition to the '783 patent at issue here, Petitioner concurrently challenges claims of related U.S. Patent Nos. 11, 450,611 B2 (“the '611 patent”) in IPR2023-00546. Patent Owner further identifies as “related proceedings,” Petitioner’s challenge of U.S. Patent Nos. 11,384,394 (“the '394 patent”) and 11,408,033 (“the '033 patent”) in IPR2023-00224 and IPR2023-00317, respectively. *See* Paper 9, 1. The '738, '611, '394, and '033, patents are at issue in *Personalis, Inc. v. Foresight Diagnostics, Inc.*, C.A. No. 1:22-cv-01913 (D. Colo.) (“the related litigation”). *See* Pet. 1–2; Paper 6, 1; Ex. 1010.

E. Asserted Challenges to Patentability

Petitioner challenges the patentability of claims 1–9, 13–19, and 21–19 on the following bases: (Pet. 14):

Ground	Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1	1, 2, 5–7, 9, 14, 15, 17–19, 21, 23–25, 27	§ 102	Ley ¹
2	1–9, 13–19, 21–29	§ 103	Ley
3	1–9, 13–19, 21–29	§ 103	Forsheew, ² Dawson ³

¹ Ley *et al.*, “DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome,” 456 *Nature* 66–72 (2008). Exs. 1012, 1042 (Supplementary Information).

² Tim Forsheew, et al., “Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA,” 4 *Science Translational Medicine* 136ra68 (2012). Ex. 1030.

³ Dawson, *et al.*, “Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer,” *New England Journal of Medicine* (2013). Ex. 1070.

In support of its patentability challenge, Petitioner relies on, *inter alia*, the Declaration of John Quackenbush, Ph.D. Ex. 1020.

F. The '783 Patent and Related Background

1) Priority

The '783 patent, titled Methods and Systems for Genetic Analysis, issued to West et al., from U.S. Application 17/235,776, filed April 20, 2021, via a series of continuation applications first filed on May 26, 2017, and a continuation-in-part application first filed on October 7, 2020, and further claims benefit of priority to U.S. provisional Application No. 61/342,674, filed on May 26, 2016. Ex. 1001, code (12), (21), (22), (54), and (60). In addressing the art of record, Petitioner and its expert, Dr. Quackenbush, presume the earliest possible priority date (May 27, 2016). *See, e.g.*, Pet. 54, 75; Ex. 1020 ¶ 32.

2) Abstract and Specification

The Abstract of the '783 patent broadly describes “systems and methods for sample processing and data analysis,” which can include “nucleic acid sample processing and subsequent sequencing.” Ex. 1001, code (57). According to the Abstract, the “sequence information may be analyzed with the aid of a computer processor, and the analyzed sequence information may be stored in an electronic storage location that may include a pool or collection of sequence information and analyzed sequence information generated from the nucleic acid sample.” *Id.*

The '783 Specification further discloses

a method for personalized genetic testing, comprising: (a) obtaining a personalized probe set for a subject, which personalized probe set comprises a plurality of nucleic acid probe molecules having the plurality of nucleic acid sequences

or complements thereof, wherein the plurality of nucleic acid probe molecules are configured to selectively enrich or amplify sequences comprising a set of genetic variants over other sequences in at least one biological sample of the subject, wherein the set of genetic variants are identified in sequence data for the at least one biological sample; (b) using the personalized probe set to selectively enrich or amplify sequences comprising the set of genetic variants over other sequences in at least an additional biological sample from the subject, to generate a sequencing library; (c) subjecting the sequencing library to sequencing to identify a presence or absence of at least a subset of the set of genetic variants in at least the additional biological sample from the subject, wherein a sequencing footprint of the sequencing of (c) is less than a sequencing footprint of the sequence data of (a); and (d) generating a report identifying a presence or absence of a health condition or disease of the subject in the additional biological sample based on the identified at least a subset of (c).

Id. at 10:59–11. Certain embodiments of the '783 patent are directed to the analysis of familial traits (*id.* at 62:34–65:6) and to tumor detection (*id.* at 56:7–68:41). With respect to the latter, the Specification discloses that, “[i]n some embodiments, the individual of (a) is a cancer patient, the first assay is sequencing of DNA derived from their tumor,” and “the genetic characteristics determined in (b) are one or more of (i) variations of the DNA sequence so determined, from a human reference sequence, or (ii) alleles which match the human reference sequence but which are known to be correlated with some type of cancer or other disease.” *Id.* at 20:33–40.

In some embodiments, the personalized probe set comprises . . . (i) at least one variable portion from a result of the sequence data of (a) and (ii) at least one fixed portion independent of the result of the sequence data of (a). In some embodiments, the at

least one fixed portion comprises one or more known tumor variants.

Id. at 11:57–64. In other embodiments, “the variable portion of the oligo-directed genomic content corresponds to genes whose expression is thought to vary more from sample to sample, and the fixed portion corresponds to genes with more consistent levels of expression.” *Id.* at 19:8–11.

Where the personalized assay is designed for a cancer application, the variable content may correspond to potential neoantigen-causing variants of the subject. The fixed portion may be selected from a group consisting of one or more of (i) cancer driver genes, (ii) genes involved in the pharmacogenomics of cancer drugs, (iii) genes involved in Mendelian immunological diseases, (iv) genes related to inherited forms of cancer, (v) genes associated with tumor escape from a targeted or immune cancer therapy, (vi) HLA typing, or (vii) variants common in the population and used by B-allele methods to detect structural variation.

Id. at 42:10–20.

In some embodiments directed to the analysis of familial traits, the

at least one variable portion corresponds to genetic variants responsible for Mendelian phenotype of a proband, and wherein the at least one fixed portion corresponds to one or more of (1) additional genetic content not related to the Mendelian condition of the proband, (2) pharmacogenomics, (3) genetic sample ID by a fixed panel of genetic variants or a fixed panel of phenotype-related genetic variants, and (4) genetic variants common in the population and used by B-allele methods to detect structural variation

Id. at 19:29–38.

3) Challenged Claims

Petitioner challenges claims 1–9, 13–19, 21–29, of which only claim 1 is independent and recites:

1. A method for personalized genetic testing, comprising:

- (a) obtaining a personalized probe set for a subject, which personalized probe set comprises a plurality of nucleic acid probe molecules having a plurality of nucleic acid sequences or complements thereof,
wherein said plurality of nucleic acid probe molecules are configured to selectively enrich or amplify sequences comprising a set of one or more genetic variants over other sequences in at least one biological sample of said subject,
wherein said set of genetic variants are identified in sequence data for said at least one biological sample,
further wherein said personalized probe set comprises nucleic acid probe molecules having oligonucleotide-directed genomic content comprising: (i) at least one variable portion from a result of said sequence data and (ii) at least one fixed portion independent of said result of said sequencing data
- (b) using said personalized probe set to selectively enrich or amplify sequences comprising said set of genetic variants over other sequences in at least an additional biological sample from said subject, to generate a sequencing library;
- (c) subjecting said sequencing library to sequencing to identify a presence or absence of at least a subset of said set of genetic variants in at least said additional biological sample from said subject, wherein a sequencing footprint of said sequencing of (c) is less than a sequencing footprint of said sequence data of (a); and
- (d) generating a report identifying (i) a presence or absence of a health condition or disease of the subject in said additional biological sample based on said identified at least a subset of (c) and (ii) genetic variants which inform a therapy choice or a change in therapy for the subject.

Id. at 72:19–53 (formatting added). Illustrative of the challenged dependent claims, claims 15 and 29, respectively recite:

15. The method of claim 1, wherein said additional biological sample is a blood sample comprising: (i) cfDNA, (ii) cfRNA, (iii) DNA or RNA from circulating tumor cells, or (iv) RNA or DNA from a tumor metastasis.^[4]

(*id.* at 73:33–37), and

29. The method of claim 1, wherein the report of (d) further comprises reporting biomedical information of said subject that is predictive, prognostic, or diagnostic of one or more biomedical features selected from the group consisting of a disease state, efficacy of a drug therapy, prediction of optimal drug dosage, a recommendation of one or more therapies, and a recommendation of a course of treatment of a disease.

(*id.* at 74:38–45).

G. Asserted Prior Art

Patent Owner does not dispute the prior art status of the asserted references. *See* Pet. 13; Prelim. Resp. 11

1) Overview of Ley (Exhibit 1012, Exhibit 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, the “study “establishes whole-genome sequencing as an unbiased method for discovering cancer-initiating mutations in previously unidentified genes that may respond to targeted therapies.” *Id.* at Abstract.

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

⁴ According to the '783 patent, cfDNA and cfRNA refer to cell-free DNA and cell-free RNA, respectively. *See id.* at 11:19–24.

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.

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 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.

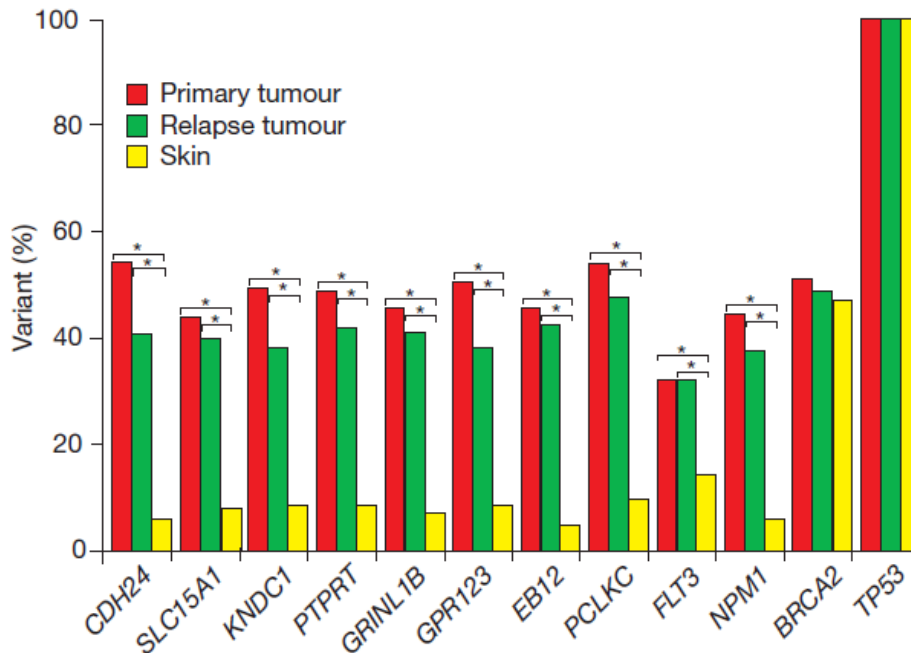
Id. at 67 (internal endnote numbers omitted). Ley further reports that “[f]or the purposes of this initial study, we restricted our downstream analysis to the coding sequences of annotated genes,” noting that these included alterations in eight protein-coding sequences including “previously

described, recurrent somatic insertions in the *FLT3* and *NPM1* genes.” *Id.* at 66.

Using a panel of 10 tumor-specific mutations, Ley compared the 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. Ley’s Figure 3, reproduced below, summarizes these results:



Id. at Fig. 3. Figure 3 compares the frequency of variant alleles for ten somatic variations and two validated SNPs (*BRCA2* and *TP53*) in normal skin, primary tumor, and relapse tumor samples from a single patient. As noted in the legend to Figure 3, asterisks indicate that “readcount data for the

variant alleles in the primary tumour sample and relapse tumor sample are statistically different from that of the skin sample for all mutations.” *Id.*

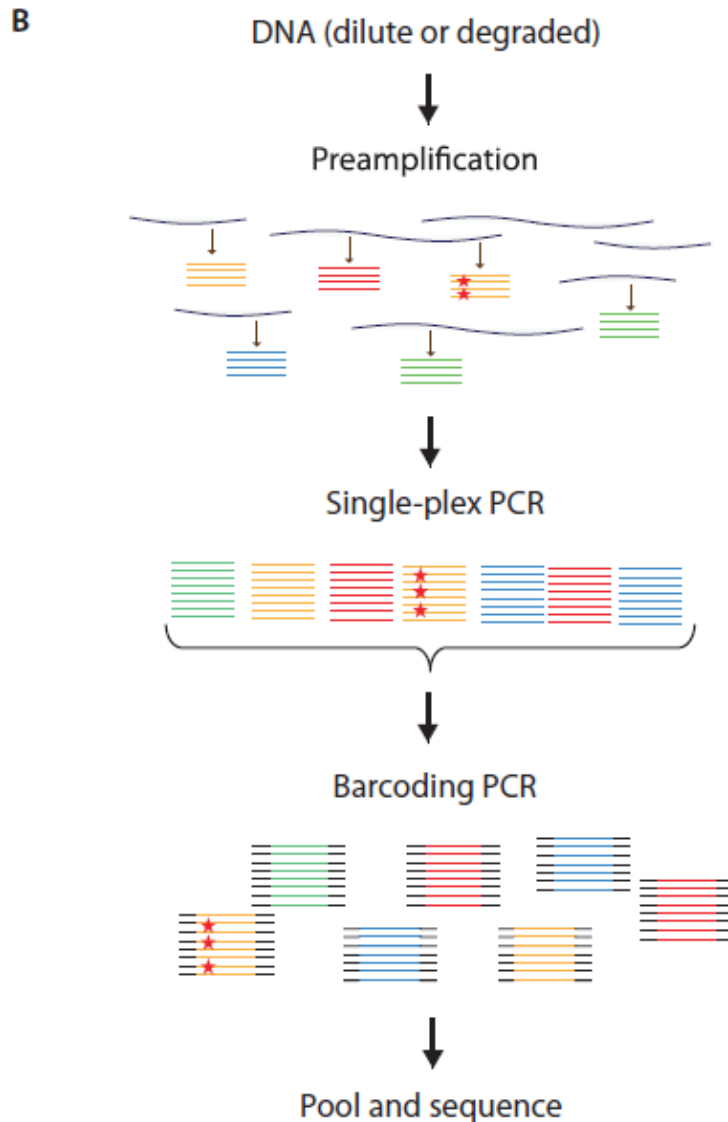
Ley derived the above patient data from an AML patient designated subject UPN 933124. *See e.g., id.* at 67, Tab. 1, Fig. 1. Ley presents a detailed case report, including treatment regimen, for subject UPN 933124 on page 2 of the accompanying Supplementary Information. Ex. 1042, 2.

2) Overview of Forshew (Exhibit 1030)

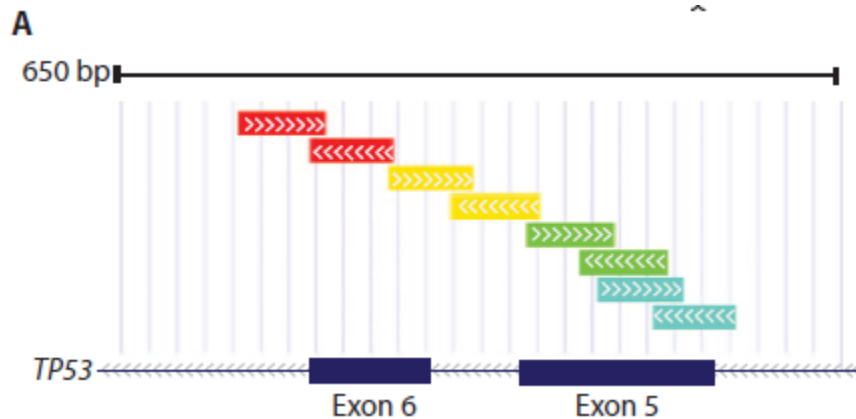
Forshew discloses the use of tagged-amplicon deep sequencing (TAm-Seq) for the detection and monitoring of cancer-associated alleles circulating in patient plasma samples. Ex. 1030, 1. According to Forshew, the Tam-Seq approach “allows amplification and deep sequencing of genomic regions spanning thousands of bases from as little as individual copies of fragmented DNA,” which “allowed us to monitor changes in tumor burden by sampling only patient plasma over time.” *Id.* at 1–2; *see also id.* at Figs. 4B–D (graphics illustrating monitoring frequency of mutant DNA in cancer patients over time).

To amplify and sequence fragmented cell-free DNA in patient plasma samples, Forshew used the Primer3 program⁵ to “design[] primers to generate amplicons that tile regions of interest in short segments of about 150 to 200 bases.” *Id.* at 2, Ex. 1032, 2. Forshew illustrates the generation of amplicons for a targeted genomic region in Figure 1B, reproduced below.

⁵ Dr. Quackenbush describes Primer3 as “a computer program used for designing PCR primers (also referred to as PCR probes).” Ex. 1020 ¶ 241 (citing <http://primer3.org>; Exhibit 1034 (Untergasser et al., “Primer3—new capabilities and interfaces,” 40(15) NAR e115 (2012))).



Ex. 1030, Fig. 1B. Figure 1B shows a multi-step PCR amplification process including the addition of barcodes and sequencing adaptors, wherein amplified, barcoded PCR products are pooled and sequenced. *See id.* at legend. Red stars in some amplicons indicate the presence of mutations. *Id.* Amplicon sequences are compared and aligned based on partial overlaps, as shown for a portion of the *TP53* gene in Figure 1A, reproduced below.

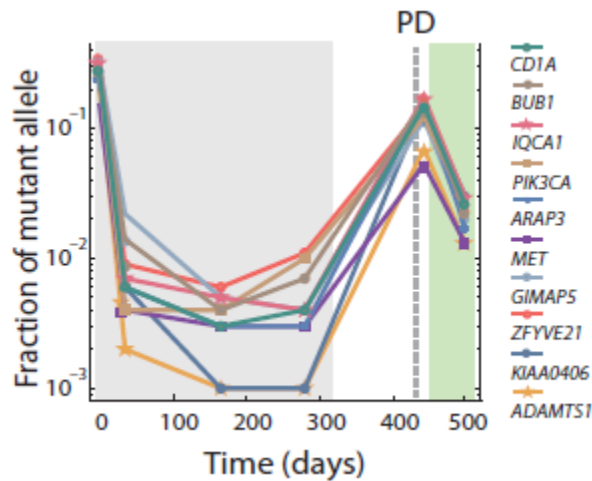


Ex. 1030, Fig. 1A. Figure 1A shows the location of eight overlapping amplicon “tiles” spanning a 650 base pair region of *TP53*, which includes exons 5 and 6. *See id.* at legend. Arrowheads within tiles indicate direction of sequencing read. *Id.*

Forsheew discloses that, for the TAm-Seq studies, the authors “designed a set of 48 primer pairs to amplify 5995 bases of genomic sequence covering coding regions (exons and exon junctions) of *TP53* and *PTEN*, and selected regions in *EGFR*, *BRAF*, *KRAS*, and *PIK3CA* (table S1) by overlapping short amplicons (Fig. 1A).” *Id.* at 3. Forsheew reports that “[t]he sequenced regions cover mutations that account for 38% of all point mutations in the COSMIC database (v55).”⁶ *Id.* According to Forsheew, the resulting data was used to “identif[y] mutations throughout the tumor suppressor gene *TP53* in circulating DNA from 46 plasma samples of advanced ovarian cancer patients,” “noninvasively identify the origin of

⁶ According to Dr. Quackenbush, COSMIC (Catalogue of Somatic Mutations in Cancer) is a publicly accessible database of human cancer sequences that “combines cancer mutation data from the scientific literature, with the output from the Cancer Genome Project (CGP).” Ex. 1020 ¶¶ 54, 242, 244 (citing <https://cancer.sanger.ac.uk/cosmic>; Ex. 1035 (Forbes et al, “COSMIC: mining complete cancer genomes in the Catalogue of Somatic Mutations in Cancer,” 39 NAR D945-950 (2011))).

metastatic relapse in a patient with multiple primary tumors;” identify “an *EGFR* mutation not found in an initial ovarian biopsy;” and “monitor tumor dynamics, and track[] 10 concomitant mutations in plasma of a metastatic breast cancer patient over 16 months.” *Id.* at Abstract; *see generally* Fig. 4 and associated legend describing “[c]linically relevant applications of plasma DNA sequencing using TAm-Seq”). The last of these is illustrated in Forshe’s Figure 4D, reproduced below.



Forshe’s Figure 4D depicts a graph of mutation load in a patient’s plasma over time illustrating the “[d]ynamics of 10 tumor-specific mutations in plasma of a breast cancer patient” during (shaded regions) and after treatment, and over a period of approximately 16 months. *See id.* at 7, 9 (noting that progressive disease (PD) was detected after 4 months off treatment, whereupon the patient resumed paclitaxel chemotherapy). According to Forshe, “The 10 mutations followed a common pattern of sharp decline in [allele frequency] upon onset of therapy and an increase in [allele frequency] upon disease progression after termination of therapy.” *Id.* at 9.

3) Overview of Dawson (Ex. 1070)

Dawson teaches that “[t]he management of metastatic breast cancer requires monitoring of the tumor burden to determine the response to treatment.” Ex. 1070, Abstract. Dawson

compared the radiographic imaging of tumors with the assay of circulating tumor DNA, [the known cancer antigen 15-3] CA 15-3, and circulating tumor cells in 30 women with metastatic breast cancer who were receiving systemic therapy.” Dawson “used targeted or whole-genome sequencing to identify somatic genomic alterations and designed personalized assays to quantify circulating tumor DNA in serially collected plasma specimens. CA 15-3 levels and numbers of circulating tumor cells were measured at identical time points.

Id.

Noting that both *PIK3CA* and *TP53* were “known to be recurrently mutated in breast cancer,” Dawson conducted targeted and whole genome sequencing of tumor samples from 52 cancer patients to screen for mutations in *PIK3CA* and *TP53*. *Id.* at 1201; Fig. 1. Serial blood samples from patients found to have such mutations were assayed for circulating tumor cells, circulating tumor DNA and CA 15-3 antigen. *See* Fig. 1.

Circulating tumor DNA was successfully detected in 29 of the 30 women (97%) in whom somatic genomic alterations were identified; CA 15-3 and circulating tumor cells were detected in 21 of 27 women (78%) and 26 of 30 women (87%), respectively. Circulating tumor DNA levels showed a greater dynamic range, and greater correlation with changes in tumor burden, than did CA 15-3 or circulating tumor cells. Among the measures tested, circulating tumor DNA provided the earliest measure of treatment response in 10 of 19 women (53%).

Id. at Abstract. Dawson concludes that

The monitoring of circulating tumor DNA levels requires the identification of somatic alterations in individual patients. Future developments will reduce the cost of whole-genome

paired-end sequencing, and targeted sequencing can be readily expanded to include other genes, in addition to *PIK3CA* and *TP53*, known to be recurrently mutated in breast cancer. Here we have demonstrated the use of two strategies to quantify circulating tumor DNA: digital PCR assay and targeted deep sequencing. Digital PCR assay provides high accuracy and sensitivity but requires the design of personalized assays, an expensive and rate-limiting step. Targeted deep sequencing of plasma DNA provides a cost-effective alternative for high-throughput analysis and may overcome limitations of initial tumor-tissue assessment by virtue of allowing for the direct identification of mutations in plasma.

Id. at 1207.

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, 2, 5–7, 9, 14, 15, 17–19, 21, 23–25, 27 are anticipated by the prior art. Pet. 14. 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 claims 1–9, 13–19, 21–29 of the ’783 patent are unpatentable as obvious under § 103(a). Pet. 14. 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. *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 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 International, 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 Industries, Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *see also Orthopedic Equip. Co. v. United States*, 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. 4–5 (citing Ex. 1020 ¶¶ 35) (numbering added). Patent Owner does not presently challenge Petitioner’s definition. Prelim. Resp. 11. Based on the record before us, Petitioner’s proposed definition is consistent with the level of skill indicated in the cited references and the problems addressed in the ’783 patent. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). For purposes of this Decision, we provisionally adopt Petitioner’s proposed definition of the person of ordinary skill in the art.

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).

1) “personalized genetic testing”

Patent Owner contends that we should construe as limiting the preamble to claim 1, “A method for personalized genetic testing.” *See* Prelim. Resp. 19–21; *see also* Sur-Reply 1–4 (arguing that Ley does not satisfy the preamble). We note, in particular, Patent Owner’s contention that this language conveys, “not merely a circumstance in which the method may be useful, but rather . . . the essence of the claimed method itself.” Prelim. Resp. 19–20 (referencing *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003)). Further focusing on the claim language, Patent Owner contends that its “essence” argument

is further supported by the use of the term “personalized probe set,” and the generation of a report, emphasizing the personalized use to which this method is directed. Divorced from the process of personalized genetic testing using a personalized probe set, the claimed method reduces to nothing more than a process for identifying the presence or absence of genetic variants in a sample—“a process whose absence of fathomable utility rather suggests the academic exercise.”

Id. at 20 (citing *E.I. Du Pont de Nemours & Co. v. Monsanto Technology LLC*, IPR2014-00333, Paper 14 at 4–5 (PTAB July 11, 2014)).⁷ Despite the opportunity of additional briefing, Patent Owner fails to identify any particular meaning for the preamble that it is proposing should be adopted and, at best, appears to distinguish genetic testing from the discovery of genetic mutations. *See* Sur-reply 2–3.⁸

In general, “the preamble does not limit the claims.” *Allen Eng’g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1346 (Fed. Cir. 2002). Moreover, “where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation.” *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997). Considering the record before us, the preamble of claim 1 merely recites a purpose or intended use for the claimed method. In general, steps (a) through (c) in the body of claim 1 require the use of “a personalized probe set” to identify the presence or absence of genetic variants in a subject, whereupon this information is used to generate a report in step (d). We presently read the body of claim 1 to define a

⁷ Pointing to isolated passages in the Specification, Patent Owner further contends that, “methods that existed at the time of invention were specific to a particular disease or cancer rather than personalized to a specific subject’s family genetics,” whereas the claimed method “is directed to personalized genetic testing and is ‘better focused on the personal characteristics of the subject.’” Prelim. Resp. 20–21 (citing Ex. 1001, 4:37–47, 31:27–28). We find this argument confusing, as we do not presently read the challenged claims as limited to a “subject’s family genetics.”

⁸ To the extent Patent Owner maintains that the preamble is both limiting and distinguishes over the applied prior art, Patent Owner should clearly and explicitly identify during trial how it proposes the preamble should be construed—identifying evidentiary support for such construction according to well-established precedents.

complete invention, with the preamble merely stating a purpose or intended use, or, in another sense, simply the result of carrying out the positively recited steps of the claim. As such, we do not presently view the preamble of claim 1 to be limiting and accord it no patentable weight.

Even if we were to find the preamble limiting, Petitioner contends that “the Petition establishes that the prior art’s methods are ‘personalized’ under any reasonable understanding of the term.” Reply 1. In addressing such an understanding, Petitioner points to the Specification’s description of

conducting personalized genetic testing “by sequencing both the tumor and germline DNA samples with a generic assay (e.g., an exome), to determine which variants are somatic. This may lead to a personalized assay with a smaller footprint.” [Ex. 1001,] 66:58-61. Similarly, the specification notes that “initial assays which sequence DNA or RNA from the subject’s tumor or a germline sample” may then be “used as the basis for designing nucleic acid sequences to be array synthesized to create a personalized assay.” *Id.* 67:17-21.

Id. at 1–2 (further citing Ex. 1001, 31:19–28).

Although we find Petitioner’s argument informative, neither party presents a particularized definition of “personalized genetic testing.” As stated above, at this stage, we are unpersuaded that the preamble is limiting.⁹ The parties are, of course, welcome to submit additional argument and evidence as to the patentable weight (if any) and meaning of the preamble language at trial.

⁹ Based on the limited argument before us, if the preamble is limiting, we would provisionally construe “personalized genetic testing” as “genetic testing of an individual using a subset of genetic loci relevant to the individual tested. Whether the preamble is non-limiting, or such a provisional construction is applied, the outcome of this institution decision remains unchanged.

2) “nucleic acid probe molecules”

Claim 1 recites the use of “nucleic acid probe molecules . . . configured to selectively enrich or amplify sequences.” Relying on the testimony of Dr. Quackenbush and disclosure of the ’783 patent, Petitioner contends that one of ordinary skill in the art “would have understood that the claimed ‘nucleic acid probe molecules’ include PCR primers, hybrid capture baits, and other such nucleic acid probe molecules for selectively amplifying or enriching sequences.” Pet. 15 (citing Ex. 1020 ¶ 95; Ex. 1001, 4:60–61, 5:23–25, 7:5–8, 7:25–26). At this stage of the proceeding, Patent Owner does not address the meaning of “nucleic acid probe molecules.” Although the term is not presently contested, Petitioner’s definition is reasonable in light of the present record, and we provisionally adopt it for clarity.

3) “report”

Claim step 1(d) entails, “generating a report identifying (i) a presence or absence of a health condition or disease of the subject in said additional biological sample based on said identified at least a subset of (c) and (ii) genetic variants which inform a therapy choice or a change in therapy for the subject.” Petitioner contends this element recites printed matter not entitled to patentable weight. Pet. 16. Patent Owner does not presently address this printed matter argument but urges that that report of claim step 1(d) must be something more than “data obtained from the experiments.” *See, e.g.*, Prelim. Resp. 4–5 (arguing that the data reported by Ley or Forshew is not a “report” as used in claim step 1(d)).

As we understand claim 1, steps 1(b)–(c) recite method steps that ultimately “identify a presence or absence of . . . genetic variants” in a biological sample. In step 1(d), this information is used in a single active

step—“generating a report.” The remainder of step 1(d) merely claims the *content* of the report, (i.e., the presence or absence of information regarding genetic variants or “a health condition or disease”) with no recitation of active steps that must be taken with the report or its content.

But the claimed report does not merely identify whether the tested genetic variants were present or absent in the sample, but employs that data in diagnosing the “presence or absence of a health condition or disease,” and further, “informing a therapy.” As such, we presently agree with Petitioner, that these elements constitute printed matter because they are not “functionally related to the substrate on which the printed matter is applied.” Pet. 16. (citing (citing e.g., *Praxair Distribution, Inc. v. Mallinckrodt Hosp. Prod. IP Ltd.*, 890 F.3d 1024, 1031 (Fed. Cir. 2018); *In re Ngai*, 367 F.3d 1336, 1339 (Fed. Cir. 2004)). Moreover, even if step 1(d) were somehow interpreted as further requiring diagnosing a medical condition and/or informing a therapy, we would agree at present with Petitioner that such “diagnosing” or “informing” encompass mere mental steps that are also not entitled to patentable weight. *See id.*; *see also Praxair*, 890 F.3d at 1033 (“a limitation that merely claims information by incorporating that information into a mental step will receive patentable weight only if the limitation is functionally related to the substrate”).

To the extent claim step 1(d) were to be accorded patentable weight, Petitioner argues that one of ordinary skill in the art would understand that “the claimed ‘report’ includes, for example, providing information for treatment of a patient as well as providing an indication of genetic variation.” Pet. 17–18 (citing Ex. 1020 ¶¶ 96–97). Petitioner further contends that, consistent with the plain meaning, Figure 1 of the ’783 patent

“shows a therapeutic intervention, which can be a report, at the end of a process that includes personalized assays.” *Id.* at 17 (citing Ex. 1001, Fig. 1). Petitioner further points to column 5, lines 20–23 of the Specification, which recites that “[s]ome embodiments comprise outputting a report that is indicative of a presence or absence of the at least the subset of the genetic variants in the subject or the at least one biological relative.” *Id.*; *see also* Ex. 1001, 9:37–39 (“Some embodiments further comprise generating a report that identifies genetic variants that are associated with a therapeutic intervention for the subject.”).

As we presently understand the Specification, any support for elements 1(d)(i) and 1(d)(ii) are disclosed at a very high level of generality. As such, and to the extent these elements were entitled to patentable weight, they would likely be anticipated or rendered obvious by a similarly general disclosure or understanding of one ordinary skill in the art, as evidenced by the prior art of record.

D. Ground 1: Anticipation by Ley

As to Ground 1, Petitioner challenges claims 1, 2, 5–7, 9, 14, 15, 17–19, 21, 23–25, and 27 as anticipated by Ley. Pet. 14, 23–42. Petitioner provides an element-by-element comparison of the claims to the cited art. *Id.* at 23–42.

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 in view of Ley supported by the testimony of Dr. Quackenbush, which Patent Owner does not presently contest. *See generally* Pet. 24–31, 35–42; Ex. 1020 ¶¶ 104–121, 132–177; Prelim. Resp.

1) Preamble

Patent Owner contends that Ley fails to disclose a method for personalized genetic testing as recited in the preamble. Prelim. Resp. 22–27; Sur-reply 1–4. But as discussed above, we provisionally construe the preamble as not limiting and accord it no patentable weight. *See* Section II.C.1, *supra*. As such, Patent Owner’s arguments are unavailing.

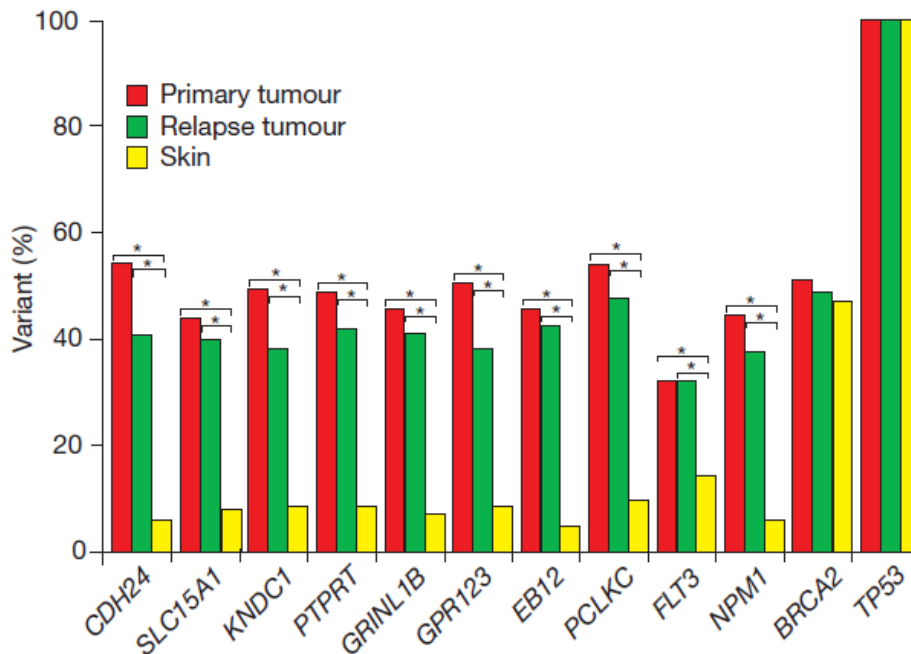
To the extent the preamble were limiting, at present it appears that the asserted prior art discloses the preamble’s subject matter. *See id.* at fn.8. At core, Patent Owner argues that Ley does not disclose personalized genetic testing because it “discloses experiments conducted *for the purpose* of discovering mutations that are responsible for initiation and pathogenesis of AML and other types of cancer across entire patient populations.” Sur-reply 1 (emphasis altered); *see* Prelim. Resp. 22–23. But to the extent Patent Owner correctly identifies one—or even a primary—purpose of Ley’s studies, “a reference . . . is prior art for all that it teaches.” *In re Antor Media Corp.*, 689 F.3d 1282, 1290 (Fed. Cir. 2012) (quoting *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989)).

For the purpose of institution (and to the extent we were to construe the preamble as limiting) we find sufficient Dr. Quackenbush’s testimony that claim 1 discloses a method for personalized genetic testing because

Ley discloses a method of genetic testing that used “massively parallel sequencing technology to sequence the genomic DNA of tumour and normal skin cells obtained from a patient” with leukemia. Ex. 1012 (Ley) at 66. The genetic testing described in Ley was “personalized” given that the assay sequenced the patient’s tumor’s genome and compared “its matched normal counterpart obtained from the same patient’s skin.” *Id.* Through this personalized genetic testing, Ley “discovered ten genes with acquired mutations; two were previously described mutations that are thought to contribute to tumour progression,

and eight were new mutations present in virtually all tumour cells at presentation and relapse. . . .” *Id.*

Ex. 1020 ¶¶ 102–103. Our own reading of Ley is also consistent with personalized genetic testing. We note, in particular, Ley’s Figure 3, reproduced below, which illustrates “the percentage of tumour cells that contained each of the discovered somatic mutations” in samples taken from a single patient:



Ex. 1012, 69, Fig. 3. As discussed in detail in Dr. Quackenbush’s Declaration, Figure 3 compares the percentage of variant alleles for ten somatic variations and two validated SNPs in a patient’s normal skin, primary tumor, and relapse tumor samples. *See* Ex. 1012 ¶¶ 81–82. As such, we presently understand Ley to disclose the use of a personalized probe set to monitor relevant alleles in a single patient.

In assessing anticipation, “it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom.” *In re Preda*,

401 F.2d 825, 826 (CCPA 1968) (citation omitted). In this respect, we note Ley's summary statement that "[w]e cannot overemphasize the importance of parallel sequencing of the patient's normal genome to determine which variants were inherited" (Ex. 1012, 71), and Dr. Quackenbush's testimony that, Ley discloses "characterizing the patient's tumor using whole-genome sequencing to identify a patient-specific polymorphic fingerprint and then using that data to target specific polymorphisms identified in the whole-genome sequencing step to track the tumor over time is a useful approach to cancer monitoring and testing." Ex. 1020 ¶ 83.

Considering the above, the present record indicates sufficiently that Ley discloses genetic testing of an individual using a subset of genetic loci relevant to the individual tested and, thus, satisfies the preamble to claim 1, to the extent it is limiting.

2) Element 1(c): "subjecting said sequencing library to sequencing to identify a presence or absence of at least a subset of said set of genetic variants in at least said additional biological sample from said subject, wherein a sequencing footprint of said sequencing of (c) is less than a sequencing footprint of said sequence data of (a)"

In asserting that Ley discloses claim step 1(c), Petitioner points to Ley's Figure 3 and Table 3 and the testimony of Dr. Quackenbush. Pet. 31–33 (citing Ex. 1012, Fig. 3, Tab. 3; Ex. 1020 ¶¶ 122–124). Dr. Quackenbush testifies, for example, that "[t]he sequencing library created by amplifying the relapsed tumour sample with the set of PCR primers identified the presence or absence of at least a subset (namely, all of the genetic variants included in Ley's panel) of genetic variants." Ex. 1020 ¶ 122 (citing Ex. 1012, 69). According to Dr. Quackenbush, "[t]he presence or absence of the genetic variants in the multiple samples is depicted in Figure 3, which

. . . shows the relative frequency of each given variant in each sample based on the results of the sequencing assay.” *Id.*

According to Patent Owner, “this does not establish that Ley discloses sequencing the relapse tumor sample for the purpose of *identifying* the absence or presence of the genetic variants. Rather, the variants in the relapse tumor sample were sequenced to validate the results obtained.”

Prelim. Resp. 25–27. In particular, Patent Owner contends that Ley identified somatic mutations associated with AML in an earlier experiment, whereas the work summarized in Figure 3 “was conducted ‘to better define the percentage tumor cells that contained each of the discovered mutations’ and define the mutation frequencies in the tumor sample.” Prelim. Resp. 26 (citing Ex. 1012, 69).

Petitioner has the better argument on the record before us. Claim step 1(c) is silent as to whether a genetic variant is identified *de novo* in an unknown sample, or identified in a previously tested sample for some validating or confirmatory purpose. In showing that 10 variant alleles were present in both primary and relapse tumor samples, Ley Figure 3 satisfies claim step 1(c) by “identify[ing] a presence . . . of at least a subset of said set of genetic variants” in a patient sample.¹⁰ In particular, we understand Figure 3 to show that for each variant allele tested, the allele was present in roughly 30 to 50 percent of cells from either tumor sample.

Considering the evidence of record, Petitioner has shown sufficiently that Ley discloses claim step 1(c).

¹⁰ We do not readily discern whether Figure 3 further “identif[ies an] . . . absence” of these variants in the patient’s normal skin biopsy, but note that element 1(c) is satisfied by the identification of either a presence or an absence.

3) Element 1(d): “generating a report identifying (i) a presence or absence of a health condition or disease of the subject in said additional biological sample based on said identified at least a subset of (c) and (ii) genetic variants which inform a therapy choice or a change in therapy for the subject”

Patent Owner contends that Ley does not disclose “generating a report” that identifies the information recited in claim elements 1(d)(i) and 1(d)(ii). Prelim. Resp. 27–29. But insofar as we presently accord these portions of claim element 1(d) no patentable weight, Patent Owner’s argument is unavailing. *See* Section II.C.3, *supra*. Rather, we find sufficient Dr. Quackenbush’s testimony that both Ley’s Table 1 and Figure 3 satisfy the requirement to “generat[e] a report.” *See* Ex. 1020 ¶¶ 125–127; Pet. 33–34.

To the extent we were to accord patentable weight to all of the language in element 1(d), we find sufficient for the purpose of institution Dr. Quackenbush’s testimony that Ley’s Figure 3 and related text “shows elevated levels of certain variants, [which] informs a therapy choice or a change (e.g., switching away from conventional therapy, or resuming therapy upon relapse) for the subject.” Ex. 1020 ¶ 127; Pet. 34. We similarly note Dr. Quackenbush’s testimony that the detailed case report in Ley’s Supplementary Information (Exhibit 1042), “provides detailed information about a number of the various mutations that had been detected in the patient’s cancer genome,” and further discloses clinical and therapeutic implications for mutations of SCL29A1, FLT3, and NMP1. Ex. 1020 ¶ 129 (testifying that one of ordinary skill in the art would understand “that the presence of the SCL29A1 would inform an oncologist that the use of this [cytarabine] was contraindicated”), ¶ 130 (“one skilled in the art would know that the characteristics of the disease and the patient’s positive

mutational in the FLT3 and NMP1 would contraindicate the use of allogenic stem cell transplant for this patient”); *see also* Pet. 34–35, 46–48 (Petitioner’s arguments and evidence as to why element 1(d) would have been obvious as per Ground 2).

4) Elements as Arranged in the Claim

Patent Owner contends that Ground 1 fails because it fails to “show all of the limitations of the claims arranged or combined in the same way as recited in the claims.” Prelim. Resp. 29 (citing *NetMoneyIN, Inc., v. Verisign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008)). In particular, Patent Owner argues that Ley’s disclosure comprises two distinct experiments: the identification of 8 genes with mutations that the authors hypothesized are responsible for initiating AML or contributing to its pathogenesis,” and the subsequent experiment “to validate these results.” *Id.* at 29–30. According to Patent Owner, Ley provides no indication “that these experiments should be or may be combined together as a going-forward method for personalized genetic testing.” *Id.* at 30. Rather, one of ordinary skill in the art reading Ley, “would be motivated to either replicate Ley to discover new driver genes or create a diagnostic test focused on the eight variants that Ley found.” *Id.*

Patent Owner’s attorney argument regarding the understanding of one of ordinary skill in the art, however, “is not evidence.” *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974). At this stage of the proceeding, we instead look to Dr. Quackenbush’s assessment that “[a] POSA would have appreciated that in Ley’s approach, which uses an initial whole-genome sequencing step to understand the nature of the patient’s tumor, the results of the whole-genome sequencing would help avoid ‘miss[ing] key mutations,’

and only after that information is collected, a specific set of probes for further sequencing of key mutations can be created.” Ex. 1020 ¶ 83 (citing Ex. 1031,¹¹ 687, 694, Fig. 2); ¶ 84 (further testifying that “Leary (Ex. 1002) and McBride (Ex. 1015) demonstrated the use of the same concept, by using whole-genome sequencing to identify structural variants (as opposed to SNVs as in Ley), and to subsequently use those identified markers as targets for serial monitoring of tumor DNA in the blood plasma of patients with solid tumors”) (citing Ex. 1002,¹² Ex. 1015,¹³ Ex. 1031, Tab. 1); *see also id.* ¶¶ 180, 195 (Dr. Quackenbush’s related testimony in the context of obviousness).

5) Conclusion on Ground 1

Considering the record presently before us, Petitioner has the better position with respect to arguments discussed above. As noted above, Petitioner presents reasoned arguments for unpatentability over Ley for the remaining elements of the claims challenged under Ground 1, which Patent Owner does not presently contest. Having considered the arguments and evidence before us, we determine that Petitioner has demonstrated a

¹¹ Meyerson, et al., “Advances in understanding cancer genomes through second-generation sequencing,” *Nature Reviews* (2010).

¹² Leary *et al.*, “Development of Personalized Tumor Biomarkers Using Massively Parallel Sequencing,” 2(20) *Science Translational Medicine* 20ra14 (2010). Ex. 1002; Ex. 1026 (supplemental materials available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2858564/>).

¹³ McBride, et al., “Use of Cancer-Specific Genomic Rearrangements to Quantify Disease Burden in Plasma from Patients with Solid Tumors,” 49(11) *Genes, Chromosomes & Cancer* 1062–1069 (2010).

reasonable likelihood that claims 1, 2, 5–7, 9, 14, 15, 17–19, 21, 23–25, and 27 are unpatentable as anticipated by Ley.

E. Ground 2: Obviousness in View of Ley

As to Ground 2, Petitioner further challenges claims 1–9, 13–19, and 21–29 as obvious in view of Ley. Pet. 14, 42–59. Petitioner relies on its arguments with respect to Ground 1, and provides further argument and evidence with respect to obviousness. *See* Pet. 42–59; Ex. 1020 ¶¶ 178–236.

Patent Owner relies on substantially the same arguments as raised with respect to Ground 1 (which we do not find availing at this stage of the proceeding), and further presents argument and evidence for secondary considerations. Prelim. Resp. 31–32, 38–43. For the additional reasons set forth below, Patent Owner’s arguments are not persuasive on the present record.

1) Secondary Considerations

Patent Owner contends that its commercial assay “is entitled to a presumption of nexus because, as detailed in . . . [a] claim chart, Personalis’ assay embodies claim 1 of the ’783 Patent.” Prelim. Resp 40 (citing Ex. 2003). Patent Owner further points to Exhibit 2001 as evidence of industry praise for the sensitivity of its commercial method “relative to other methods,” and references the alleged skepticism of experts “toward solving the difficult challenges of conducting highly sensitive genome sequencing using capture probes.” *Id.* at 41–42; *see also id.* at 2 (asserting that its commercial embodiment “can detect tumor DNA in blood plasma at levels of about one part per million (or 0.0001%)”).

Our reviewing court has made clear that “[w]here the offered secondary consideration actually results from something other than what is

both claimed and novel in the claim, there is no nexus to the merits of the claimed invention.” *In re Kao*, 639 F.3d 1057 (Fed. Cir. 2011). In this respect, Patent Owner has not pointed to anything in the challenged claims or the Specification of the ’783 patent indicative of enhanced sensitivity as compared to the prior art. At best, Patent Owner suggests (in a different section) that the invention allows for a “a dramatic reduction in the amount of sequencing required” making it “much more affordable to sequence additional pedigree members.” Prelim. Resp. 2 (citing Ex. 1001, 63:20–24, 64:40–52).

At this stage in the proceeding, Patent Owner’s nexus evidence is supported by an attorney-created claim chart, and Petitioner has not yet been afforded an opportunity to develop countervailing evidence at trial. Under the circumstances, it would be premature “to hinge the outcome of a Decision to Institute on the incomplete record before us.” *See Invata, LLC v. OPEX Corp.*, IPR2022-01604, Paper 8 at 10 (PTAB Mar. 17, 2023)). We will, to the extent necessary, consider objective evidence of non-obviousness after development of a fuller record. The parties may, as appropriate, pursue further discovery, and present argument and evidence on this issue at trial.

2) Conclusion on Ground 2

Considering the record presently before us, Petitioner has the better position with respect to arguments discussed above. Having considered the arguments and evidence before us, we determine that Petitioner has demonstrated a reasonable likelihood that claims 1–9, 13–19, and 21–29 are unpatentable as obvious in view of Ley.

F. Ground 3: Obviousness in View of Forshew and Dawson

As to Ground 2, Petitioner further challenges claims 1–9, 13–19, and 21–29 as obvious in view of Forshew and Dawson. Pet. 14, 59–79.

Petitioner provides an element-by-element comparison of the claims to the cited art. *Id.*

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 3, Petitioner presents reasoned arguments for unpatentability in view of Ley supported by the testimony of Dr. Quackenbush, which Patent Owner does not presently contest. *See generally* Pet. 59–79; Prelim. Resp.

- 1) Element 1(a): “. . . wherein said personalized probe set comprises nucleic acid probe molecules having oligonucleotide-directed genomic content comprising: (i) at least one variable portion from a result of said sequence data and (ii) at least one fixed portion independent of said result of said sequencing data”

In addressing independent claim 1, Petitioner relies on Forshew as “teaching to analyze multiple nucleic acid samples isolated from an individual by using its personalized genetic testing methods ‘to monitor tumor dynamics, and tracked 10 concomitant mutations in plasma of a metastatic breast cancer patient over 16 months.’” Pet. 59 (citing Ex. 1030, Abstract).¹⁴ According to Dr. Quackenbush, “[t]his method, ... ‘could facilitate analysis of circulating DNA as a noninvasive ‘liquid biopsy’ for personalized cancer genomics.’” *See id.*; Ex. 1020 ¶¶ 237–238.

¹⁴ We omit throughout the bold, italic font Petitioner uses solely to identify the applied references.

With respect to element 1(a), Petitioner admits that “ForsheW does not expressly disclose including PCR primers (probes) for sequences or markers that constitute a fixed portion in the breast cancer patient,” but argues that it would have been obvious to include such probes in light of, for example, ForsheW’s teaching that “mutations in the tumor suppressor gene *TP53* have been observed in 97% of cases,” and that methods to “detect and measure allele frequency (AF) of *TP53* mutations in plasma” may render it “highly applicable as a biomarker.” *See* Pet. 64–65 (citing Ex. 1030, 1, 3; Ex. 1020 ¶ 256). Petitioner similarly points to Dawson’s teaching that *TP53* is “known to be recurrently mutated in breast cancer,” and argues that Dawson “appl[ies] the Tam-Seq technique to detect variants of TP53 in breast cancer patients.” Pet. at 65 (citing Ex. 1070, 1207; Ex. 1020 ¶ 257).

Accordingly, Petitioner contends, one of ordinary skill in the art would have found it obvious to include one or more “fixed” probes in ForsheW’s breast cancer panel independent of any sequencing data in order to detect and amplify variants of TP53 in the patient. In light of ForsheW’s disclosure, the design of such probes was known, and would have involved only routine skill in the art and the application of the exact techniques disclosed in the article, and which were applied to *TP53* variants in breast cancer in Dawson.

Id. Petitioner further contends that one of ordinary skill in the art “would have had a reasonable expectation of success in monitoring *TP53* using probes designed independent of ForsheW’s whole-genome sequencing data given that it would simply involve the use of the techniques already disclosed in a related context.” *Id.* (citing Ex. 1020 ¶ 258).

Patent Owner contends “the inclusion of such additional probes is far from predictable according to the methods taught in ForsheW.” Prelim. Resp. 34. Patent Owner argues, for example, that “the 97% of cases with TP53

mutations are, according to Forshew ‘located throughout the gene are difficult to assay.’” *Id.* (citing Ex. 1030, 1) (emphasis removed). Patent Owner further points to Forshew’s Figure 1, which required 16 primer pairs to cover just exons 5 and 6 of *TP53*. *See id.*; Ex. 1030, Fig. 1. Patent Owner further argues that “neither Dawson nor Forshew provides any disclosure or motivation to include **any** fixed probe,” and the large number of ‘difficult to assay’ mutations in *TP53* would **disincentivize** a POSA from including probes to *TP53* as part of the fixed portion.” *Id.* at 34–35.

At present, however, Patent Owner’s assertions regarding the incentives of one of ordinary skill in the art amount to attorney argument that we accord little weight on this record. We also note that, as a predicate to its analysis, Forshew states:

In high-grade serous ovarian carcinomas (HGSOC), mutations in the tumor suppressor gene *TP53* have been observed in 97% of cases, but these are located throughout the gene and are difficult to assay. A cost-effective method that could detect and measure allele frequency (AF) of *TP53* mutations in plasma may be highly applicable as a biomarker for HGSOC.

Ex. 1030, 1. As we presently understand the reference, this “highly applicable” and “cost-effective method” for measuring allele frequency of *TP53* mutations refers to the disclosed Tam-Seq method. Moreover, Forshew reports at least some success in this endeavor, stating:

We identified mutations throughout the tumor suppressor gene *TP53* in circulating DNA from 46 plasma samples of advanced ovarian cancer patients. We demonstrated use of TAM-Seq to noninvasively identify the origin of metastatic relapse in a patient with multiple primary tumors.

Id. at Abstract; *see also id.* at Editor’s Summary (“In plasma obtained from 38 patients with high levels of [circulating tumor DNA], the authors were able to identify mutations in *TP53* at allelic frequencies of 2% to 65%.”).

Our reviewing court makes clear that it is “not necessary to show that a combination is “the *best* option, only that it be a *suitable* option.” *Intel Corp. v. Qualcomm Inc.*, 21 F.4th 784, 800 (Fed. Cir. 2021) (quoting *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1197–98 (Fed. Cir. 2014)). Moreover, “if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.” *Id.* (quoting *KSR*, 550 U.S. at 417). On the preliminary record before us, and in light of our present understanding of the cited art, we find sufficient Dr. Quackenbush’s testimony that one of ordinary skill in the art

would have found it obvious to include one or more “fixed” probes in Forshe’s breast cancer panel independent of any sequencing data in order to detect and amplify variants of *TP53* in the patient. In light of Forshe’s disclosure, the design of such probes was known, and would have involved only routine skill in the art and the application of the exact techniques disclosed in the article, and which were applied to *TP53* variants in breast cancer in Dawson.

Ex. 1020 ¶ 258.

- 2) Element 1(d): “generating a report identifying (i) a presence or absence of a health condition or disease of the subject in said additional biological sample based on said identified at least a subset of (c) and (ii) genetic variants which inform a therapy choice or a change in therapy for the subject”

Patent Owner contends that neither Forshe nor Dawson disclose “generating a report identifying” the information recited in claim elements 1(d)(i) and 1(d)(ii). Prelim. Resp. 35–37. But insofar as we presently accord these portions of claim element 1(d) no patentable weight, Patent Owner’s argument is unavailing. *See* Section II.C.3, *supra*. Rather, we find sufficient

Dr. Quackenbush's testimony that Forshew's Figure 4D satisfies the requirement to "generat[e] a report." *See* Ex. 1020 ¶¶ 263–265; Pet. 69–71.

To the extent we were to accord patentable weight to all of the language in element 1(d), we find sufficient for the purpose of institution Dr. Quackenbush's testimony that Forshew's Figure 4D and related text "shows the presence or absence of a health condition or disease of the subject based on multiple plasma samples over time which inform a therapy choice or change in therapy for the subject." Ex. 1020 ¶ 263; Pet. 69.

Dr. Quackenbush elaborates that

Forshew's Figure 4D "tracked dynamics of all mutations" analyzed with TAM-seq. *Id.* at 9. "The patient was treated with single-agent epirubicin (gray-shaded region). After 4 months off treatment, a CT scan showed progressive disease and the patient commenced further treatment with paclitaxel chemotherapy. The 10 mutations followed a common pattern of sharp decline in AF [allele fraction] upon onset of therapy and an increase in AF upon disease progression after termination of therapy." *Id.* Thus, Forshew's report informs therapy choice or a change in therapy based on the allele fraction of the identified alleles, including because of the observed relationship between therapy and disease status.

Ex. 1020 ¶ 265. Although Patent Owner contends that Figure 4D merely "show[s] the correlation of the results in the experiment with the already known health conditions and therapy choices for that patient," we do not presently understand the remaining language of claim element 1(d) to require anything more. *See* Prelim. Resp. 36–37.

3) Elements as Arranged in the Claim

Patent Owner contends that Ground 3 fails to "disclose or render obvious the claimed steps of the method as arranged in the claim." Prelim. Resp. 37 (capitalization normalized). With respect to obviousness, for

example, we understand Patent Owner to argue that Petitioner only addresses the obviousness of each individual step but fails to disclose or render obvious “a going-forward method for personalized genetic testing.” In this respect, Patent Owner argues that “Petitioner does not state what this “personalized genetic testing method[] is.” *Id.* at 38. As discussed in Section II.C.1, above, we do not accord patentable weight to “personalized genetic testing,” as recited in the preamble to claim 1. And to the extent it should be accorded any weight, we would provisionally apply the plain meaning of “personalized genetic testing” as “genetic testing of an individual using a subset of genetic loci relevant to the individual tested.” Applying this definition, we find that Petitioner has demonstrated a reasonable likelihood that at least claim 1 is rendered obvious in view of Forshew and Dawson for the reasons set forth in the Petition and in paragraphs 237–266 of Dr. Quackenbush’s Declaration.

1) Conclusion on Ground 3

Considering the record presently before us, Petitioner has the better position with respect to arguments discussed above. Patent Owner does not presently contest any other limitation of the claims challenged under Ground 3. As noted above, Petitioner presents reasoned arguments for unpatentability in view of Forshew and Dawson for the remaining elements of the claims challenged under Ground 3, which Patent Owner does not presently contest. *See generally* Pet. 59–79; Prelim. Resp. Having considered the arguments and evidence before us, we determine that Petitioner has demonstrated a reasonable likelihood that claims 1–9, 13–19, and 21–29 are unpatentable over Forshew and Dawson.

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 challenged claim of the '783 patent is unpatentable. We therefore institute trial on all challenged claims under all of 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; 37 C.F.R. § 42.108. 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 1–9, 13–19, and 21–29 of the '783 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 '783 Patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

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