Trials@uspto.gov
571-272-7822

Paper 11
Date: June 13, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS, Inc.
Petitioner,

v.

PERSONALIS, Inc.
Patent Owner.

IPR2023-00224
Patent 11,384,394 B2

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

Opinion for the Board filed by *Administrative Patent Judge* POLLOCK

Opinion Concurring filed by *Administrative Patent Judge* JENKS.

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 1–19 of U.S. Patent No. 11,384,394 B2 ("the '394 patent," Ex. 1001). Paper 1 ("Pet."). Personalis, Inc. ("Patent Owner," "Personalis") timely filed a Preliminary Response. Paper 7 ("Prelim. Resp."). With our authorization (*see* Ex. 3001), Petitioner filed a Reply to the Preliminary Response (Paper 8, "Reply"); Patent Owner filed a corresponding Sur-reply (Paper 10, "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 '394 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 6, 1.

D. Related Matters

In addition to the ’394 patent at issue here, Petitioner concurrently challenges claims of related U.S. Patent Nos. 11,408,033 (“the ’033 patent”) in IPR2023-00317. Patent Owner further identifies as “related proceedings,” Petitioner’s challenge of U.S. Patent Nos. 11,299,783 (“the ’783 patent”) and 10,450,611 (“the ’611 patent”) in IPR2023-00545 and IPR2023-00564, respectively. Paper 6, 1. The ’394, ’033, ’738, and ’611 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. 5; Paper 6, 1; Ex. 1010, 1, 3–6; IPR2023-00317, Exhibit 1010, 1 (First Amended Complaint adding ’033 patent).

E. Asserted Challenges to Patentability

Petitioner challenges the patentability of claims 1–19 on the following bases: (Pet. 18):

Ground	Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1	1–11, 13–19	§ 103(a)	Leary[1]
2	1–11, 13–19	§ 103(a)	Leary, Ley[2]

[1] 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/).

[2] Ley *et al.*, “DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome,” 456 *Nature* 66–72 (2008). Ex. 1012.

Ground	Claims Challenged	35 U.S.C. §	Reference(s)/Basis
3	1–19	§ 103(a)	Leary, Chan,[3] Liao[4]

In support of its patentability challenge, Petitioner relies on, *inter alia*, the Declaration of John Quackenbush, Ph.D. Ex. 1020. Patent Owner relies on, *inter alia*, the Declaration of Henry Morrice Furneaux, Ph.D. *See* Ex. 2007.

F. The ’394 Patent and Related Background

1) Priority

The ’394 patent, titled Methods and Systems for Genetic Analysis, issued to Bartha et al., from U.S. Application 17/548,379, filed December 10, 2021, via a series of continuation and division applications first filed on December 27, 2013, and further claims benefit of priority to U.S. provisional Application No. 61/753,828, filed on January 17, 2013. Ex. 1001, code (12), (21), (22), (54), and (60). In addressing the art of record, Petitioner presumes the earliest possible priority date (January 13, 2013). *See, e.g.*, Pet. 1, 43; Ex. 1020 ¶ 31. Patent Owner does not challenge January 13, 2013, as the priority date for ’394 patent. *See* Prelim. Resp. 10–11.

[3] Chan *et al.*, “Cancer Genome Scanning in Plasma: Detection of Tumor-Associated Copy Number Aberrations, Single-Nucleotide Variants, and Tumoral Heterogeneity by Massively Parallel Sequencing,” 59(1) *Clin. Chem.* 211–224 (2013). Ex. 1008.

[4] Liao *et al.*, “Targeted Massively Parallel Sequencing of Maternal Plasma DNA Permits Efficient and Unbiased Detection of Fetal Alleles,” 57(1) *Clin. Chem.* 92–101 (2011). Ex. 1009.

2) Abstract and Specification

The Abstract of the ’394 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 resultant “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 ’394 Specification more specifically discloses methods for “predicting, diagnosing, and/or prognosing a status or outcome of a disease or condition in a subject.” *Id.* at 55:38–50. In some embodiments, this involves the collection and analysis of sequence information derived from body fluid or tissue, including “from a subject suffering from a cancer.” *Id.* at 38:57–67, 55:51–57:8.

3) Challenged Claims

Petitioner challenges claims 1–19 of the ’394 patent, of which only claim 1 is independent.

In full, claim 1, recites:

> 1. A method for analyzing nucleic acid samples isolated from an individual, comprising:
>
> (a) generating a first subset of nucleic acid molecules from a first nucleic acid sample obtained from said individual;
>
> (b) conducting a first sequencing assay on said first subset of nucleic acid molecules to yield a first result comprising a first nucleic acid sequence wherein said first sequencing assay comprises whole genome sequencing;

> (c) generating a second subset of nucleic acid molecules from a second nucleic acid sample of said individual by contacting said second nucleic acid sample with a plurality of capture probes,
>
> wherein said plurality of capture probes hybridize to one or more polymorphisms which are based on or extracted from one or more databases of polymorphisms, observed in a population of one or more samples, or a combination thereof,
>
> wherein said first sample or said second sample is obtained from said subject at a first time point;
>
> (d) conducting a second sequencing assay on said second subset of nucleic acid molecules to yield a second result comprising a second nucleic acid sequence;
>
> (e) using said plurality of capture probes to generate an additional subset of nucleic acid molecules from an additional nucleic acid sample isolated from an additional sample obtained from said subject at an additional time point different from said first time point;
>
> (f) conducting a third sequencing assay on said additional subset of nucleic acid molecules from said additional nucleic acid sample to yield a third result comprising a third nucleic acid sequence; and
>
> (g) generating a biomedical report that includes biomedical information of said subject, which biomedical information identifies the presence or absence of said one or more polymorphisms identified by said second result or said third result.

Ex. 1001, 78:54–79:24 (paragraphing added). Claim 2 specifies that the biomedical information recited in paragraph (g) of claim 1

> is predictive, prognostic, or diagnostic of one or more biomedical features selected from the group consisting of disease state, efficacy of a drug therapy, prediction of optimal drug dosage, recommendation of one or more

> therapies, and recommendation of a course of treatment of a disease.

Id. at 79:25–31.

We further noted that, in the related litigation, Patent Owner summarized claim 1 as

> a method for analyzing nucleic acid samples isolated from an individual comprising whole genome sequencing nucleic acid molecules obtained from a first biological sample,
>
> contacting a second set of nucleic acid molecules with a set of capture probes that hybridize to polymorphisms that are based on or extracted from a database of polymorphisms or observed in a sample, or a combination thereof,
>
> sequencing the second set of nucleic acid molecules,
>
> repeating the capture probe hybridized sequencing on an additional sample from an additional time point, and
>
> generating a biomedical report that identifies the presence or absence of the polymorphisms.

Ex. 1010 ¶ 30 (paragraphing added). Petitioner does not presently contest this characterization. *See* Pet. 1.

G. Asserted Prior Art

Patent Owner does not dispute the prior art status of the asserted references in the its Preliminary Response. *See* Prelim. Resp. 5, 15.

1) Overview of Leary (Exhibit 1002)

According to Leary, "[v]irtually all tumors of clinical consequence are thought to have rearranged DNA sequences resulting from translocations and copy number alterations, and these sequences are not present in normal human plasma or nontumor tissues." Ex. 1002, 5. Leary describes methods of analyzing patient-specific translocations in solid tumors using the PARE (personalized analysis of rearranged ends) approach, which involved

comparing information derived from tumor samples with matched normal samples. *Id.* at Abstract, 1. In obtaining this information,

> [g]enomic DNA from each [of four tumor samples] was purified, sheared, and used to generate libraries with mate-paired tags ~1.4 kb apart. Libraries were digitally amplified by emulsion polymerase chain reaction (PCR) on magnetic beads (21), and 25-bp mate-paired tags were sequenced using the sequencing-by-ligation approach (15, 22). An average of 198.1 million 25-bp reads was obtained for each sample, where each read aligned perfectly and was uniquely localized in the reference human genome (hg18), resulting in 4.95 Gb of mappable sequence per sample. An average of 40 million mate-paired reads, where both tags were perfectly mapped to the reference human genome, was obtained for each sample. The total amount of genome base pairs covered by the mate pair analysis (that is, distance between mate-paired tags × number of mate-paired tags) was 53.6 Gb per sample, or an 18-fold physical coverage of the human genome.

Id. at 1.

Using the mate-paired tag/PARE approach, Leary "identified 57 regions containing putative somatic rearrangements." *Id.* at 3. "For confirmation, [Leary] designed primers to 42 of the paired-end regions and used them for PCR spanning the putative breakpoints. Thirty-five of these (83%) yielded PCR products of the expected size in the tumor samples but not in the normal samples (Fig. 2 and table S3)." *Id.* Leary reports that "Sanger sequencing of seven PCR products confirmed the rearrangements in all cases tested. Although there was variation in the number of detected alterations per sample (range, 7 to 21), all four tumor samples were found to have at least four bona fide somatic rearrangements through this approach." *Id.*

Leary also demonstrates that rearranged tumor markers identified using PARE could be detected and quantified in clinical samples, *e.g.*, in

serial patient plasma samples taken before and after tumor resection and chemotherapy. *Id.* at 4. Leary reports, for example, that

> [d]igital PCR analyses of plasma samples from patient Hx402 indicated that rearranged tumor DNA was detectable at all six time points analyzed throughout the course of treatment (Fig. 4B). The fraction of mutant DNA present in plasma samples was 37% just before surgery but decreased to 14% 1 day after resection of the primary tumor. The mutant DNA fraction decreased further after chemotherapy and subsequent removal of metastatic lesions from the right lobe of the liver.

Id. In Figure 4B (referenced above), Leary graphically displays the fraction of rearranged DNA in a patient's plasma over time, and in light of the patient's chemotherapy and surgical history. *Id.* at 4, Fig. 4. Referencing Figure 4B, Leary states that "[d]igital PCR analyses of plasma samples from patient Hx402 indicated that rearranged tumor DNA was detectable at all six time points analyzed throughout the course of treatment." *Id.* Leary concludes that, "[g]iven current enthusiasm for the personalized management of cancer patients, PARE affords a timely method for uniquely sensitive and specific tumor monitoring." *Id.* at 5.

2) Overview of Ley (Exhibit 1012)

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.

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 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).

3) Overview of Chan (Exhibit 1008)

Chan discloses "shotgun massively parallel sequencing (MPS) of plasma DNA from cancer patients to scan a cancer genome non-invasively." Ex. 1008, 211. According to Chan, "[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 219–221 (MPS analysis on patient with 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.

4) Overview of Liao (Exhibit 1009)

Liao discloses that "[m]assivley parallel sequencings has recently been used in noninvasive prenatal diagnosis," but notes that it is currently costly and sample throughput is still relatively low for a use as a molecular diagnostic. Ex. 1009, 92. According to Liao, "[r]ather than nonselectively sequencing the genome, target enrichment provides a logical approach for more efficient and cost-effective massively parallel sequencing because it increases the proportion of informative data from the targeted region(s)." *Id.* To obtain enriched DNA for sequencing, Liao used "an in-solution capture strategy" to obtain about 213-fold enrichment of fetal X chromosome DNA from maternal plasma samples. *Id.* at 92, 94 (disclosing sample set of 12 women carrying female fetuses and use of a "SureSelect Human X Chromosome Kit (Agilent)"), 98–100.

According to Liao:

> [W]e incubated 500 ng of the amplified plasma DNA library with the capture probes for 24 h at 65 °C, in accordance with the manufacturer's instructions. After hybridization, we selected captured targets by pulling down the biotinylated probe/target hybrids with streptavidin-coated magnetic beads (Dynabeads M-280 Streptavidin; Invitrogen) and purified the targets with the MinElute PCR Purification Kit (Qiagen). Finally, we enriched the targeted-DNA libraries by 12-cycle PCR amplification with the SureSelect GA PCR primers (Agilent).

Id. at 94. Samples were sequenced on a Genome Analyzer IIx (Illumina) to identify fetus-specific SNPs. *Id.*

Liao concludes:

> After target enrichment in the present study, the mean sequence coverage increased 83-fold, which allowed 95.9% of the paternally inherited alleles within the targeted region to be detected. The high probability for detecting a fetus specific allele, if present, suggests that targeted sequencing would be a powerful method for accurately measuring the proportion of fetal DNA in a particular sample.

Id. at 100.

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 each claim of the ’394 patent is unpatentable as obvious under § 103(a). 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. 8 (citing Ex. 1020 ¶¶ 5, 37–91) (numbering added).

According to Patent Owner, Petitioner's proposed definition "attempts to imbue the POSA with an array of different skills and competencies solely to artificially shore up its obviousness case." Prelim. Resp. 10. Patent Owner further argues that Petitioner's proposed definition "fails to accurately reflect the nascent state of the field of using next generation sequencing [NGS] for cancer analysis." *Id.* at 10–14 (citing e.g., Ex. 1004, 47–48; Ex. 1008, 211, 223, Ex. 1017, 2–3; Ex. 1030, 1, 10; Ex. 1031, 2; Ex. 2002, 2; Ex. 2007, 7).

Patent Owner proposes, instead, that we should define one of ordinary skill in the art as "a scientist or researcher with a Ph.D. in the biological sciences or a related field." *Id.* at 14. But Patent Owner does not address with particularity why its proposed "scientist or researcher with a Ph.D. in the biological sciences or a related field" materially differs, or should be distinguished from Petitioner's recitation of "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)." *Compare* Pet. 8, *with* Prelim. Resp. 14.

Further, and seeking to limit the knowledge and experience of the POSA, Patent Owner adds that

> [w]hile this POSA may have been aware that next generation sequencing was an emerging tool for scientific research, he or she would not have had extensive experience with such techniques, nor would he or she have had significant experience with the analysis of data from such sequencing platforms. Such work would have been the domain of specialists in

> bioinformatics. In this regard, the POSA would have had minimal, if any, experience in the use of next generation sequencing for studying cancer and would have been unsure how next generation sequencing would be employed for this purpose.

Prelim. Resp. 14

Contrary to Patent Owner's assertion that Petitioner seeks to describe "a person of ***exceptional*** skill," Petitioner's proposed definition merely indicates that one of ordinary skill in the art would have "an understanding" of relevant techniques and methods in the art. *See id.* at 12; Pet. 8. In particular, we read the "understanding" language of Petitioner's proposed definition to take into account the level of skill in the art as reflected in the prior art of record—including the asserted art and that cited on pages 12–14 of Patent Owner's Preliminary Response. *Cf. 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)). In addition to an understanding of the relevant art, the parties are, nonetheless, welcome to address at trial whether one of ordinary skill in the art would have had actual experience with next generation sequencing techniques, the analysis of NGS data, and/or some level of specialization in the field of bioinformatics.

Patent Owner further points to the definition of one of ordinary skill in the art addressed by Dr. Quackenbush in *Guardant Health*—an IPR involving different parties and an unrelated patent. *See* Prelim. Resp. 11–12. In *Guardant Health*, the Board found that one of ordinary skill in the art as of September 2012, would have had

> a Ph.D. in genetics, molecular biology, bioinformatics or a related field, and at least five years of research in an academic or industry setting, including at least two to three years of research experience in the field of cancer genomics . . . . knowledge of DNA sequencing, including next generation sequencing (NGS) and related sequencing methods, and related sample preparation techniques; bioinformatics methods for grouping and comparing sequence reads and mapping sequence reads onto genomes; and methods for identifying genetic variants in a sample.

Foundation Medicine, Inc. et al v. Guardant Health, Inc., IPR2019-00634, Paper 52, 9–10 (PTAB Dec. 4, 2019). Patent Owner does not establish that *Guardant Health* involved a comparable technological field to that at issue here. It, nevertheless, argues that definition applied in *Guardant Health* "significantly overlaps with the definition for a POSA that Petitioner now advances here," and that Dr. Quackenbush had criticized the *Guardant Health* definition as "credit[ing] a POSA with ***too much*** knowledge and ***too many*** skills." Prelim. Resp. 11–12 (citing Ex. 2026 ¶¶ 22–23, submitted in IPR2019-00634). Yet even were we to accept Patent Owner's inference that the art and other relevant evidence on the topic of the POSA's qualifications in both cases is comparable, we would find it difficult to fault Dr. Quackenbush for agreeing to a definition of ordinary skill in the art to be applied in this proceeding purportedly similar to that expressly adopted by our sister panel in the earlier IPR.[5]

---

[5] In issuing the final written decision in IPR2019-00634, our sister panel noted, but tacitly rejected, the assertion that the definition urged by petitioner there described a person of "exceptional" skill, not a POSA. *See* IPR2019-00634, Paper 52 at 10 (citing testimony of Dr. Bustamante, another of the patent owner's experts in that matter). The panel there adopted petitioner's proposed POSA level, noting that the prior art reflected the

Accordingly, and 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). We address the two claim phrases in dispute below—"whole genome sequencing" and "capture probes." And, as appropriate, we discuss aspects of the asserted prior art in this section, which helps shed light on the nature of the controversy at this preliminary stage as to the disputed claim phrases.

1) "whole genome sequencing"

Claim step 1(b) recites "conducting a first sequencing assay on said first subset of nucleic acid molecules . . . wherein said first sequencing assay comprises whole genome sequencing." Patent Owner argues that the word "whole" in this phrase modifies "genome" and, thus, "indicates that the entirety—not a part or subset—of the genome must be sequenced." Prelim.

---

appropriate level, and that patent owner's expert used petitioner's level in the expert's analysis. *Id.*

Resp. 27. In support of this position, Patent Owner contends that the '394 Specification differentiates between methods that sequence the "whole" or "entire" genome as compared to the exome[6] or other limited, sub-genomic regions defined by "high GC content, low GC content, low complexity, low mappability, known single nucleotide variations (SNVs), known inDels, known alternative sequences, . . . set of genes, set of regulatory elements, and methylation state." *Id.* at 27–28 (citing Ex. 1001, 1:23–34, 26:14–19, 33:21–22, 5:38–59, 24:41–43, 4:47–52, 17:17–35) (emphasis omitted).

Considering the above, Patent Owner contends that we should construe "whole genome sequencing" as "a sequencing technique intended to sequence all or almost all of a genome." *Id.* Relying on the testimony of Dr. Furneaux, Patent Owner further contends that this definition excludes Leary's mate-paired sequencing PARE approach because, in practice, Leary sequenced "***at most*** about half . . . of a genome." Sur-reply 2–3; Ex. 2007 ¶¶ 26–31. Patent Owner further points to Feldman (Ex. 2008)[7] and Murphy (Ex. 2009),[8] as purporting to distinguish whole genome sequencing from the mate-pair genomic sequencing used in Leary's PARE approach. Sur-reply 3

---

[6] According to the NIH National Human Genome Research Institute, "An exome is the sequence of all the exons in a genome, reflecting the protein-coding portion of a genome. In humans, the exome is about 1.5% of the genome." *See* Ex. 3002, available at https://www.genome.gov/genetics-glossary/Exome.

[7] Feldman et al., "Discovery of recurrent t(6;7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genomic sequencing," 117(3) *Blood*, January 20, 2011. Ex. 2008.

[8] Murphy et al., "Mate Pair Sequencing of Whole-Genome- Amplified DNA Following Laser Capture Microdissection of Prostate Cancer," 19 *DNA Research* 395–406, (2012). Ex. 2009.

(citing Ex. 2008, 4 ("Whole-genome sequencing currently demands resources beyond the reach of most cancer investigators. . . . Therefore, we used a mate-pair genomic DNA sequencing approach for lymphoma translocation discovery."); Ex. 2009, 11 (describing mate pair sequencing of whole-genome-amplified (WGA) DNA, and noting that "[t]he WGA DNA generated in this study is of sufficient quality and quantity for application to other next generation protocols, including whole-genome and exome capture sequencing protocols").

Petitioner argues that we "should not deviate from the plain and ordinary meaning of 'whole genome sequencing,'" but does not propose a concise definition of the term. Petitioner, nevertheless, argues that the Specification provides no support for Patent Owner's proposed definition requiring sequencing "almost all of the genome," nor guidance regarding how much of the genome must be sequenced under Patent Owner's construction, or how to assess the "inten[t]" of a given technique. Reply 2. Relevant to these criticisms, Petitioner observes that the '394 patent "acknowledges that 'whole genome sequencing' processes may have 'zero mean coverage regions,' which are portions of the genome that are not sequenced." *Id.* at 1 (citing Ex. 1001 at 1:23–24, 24:59-62, 28:33–42). And with respect to whether one of ordinary skill in the art at the time of the invention would understand Leary to encompass whole genome sequencing, Petitioner points to Forshew[9] as describing Leary (reference 18 in Forshew)

[9] Forshew, et al., "Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA," 4 *Science Translational Medicine* 136ra68 (2012). Ex. 1030.

as disclosing "identification of rearrangements using whole-genome sequencing." *Id.* (emphasis omitted); Ex. 1030, 11.

In considering the scope of "whole genome sequencing" we take particular note of the 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). In this respect, we find it pertinent that Leary's PARE studies began with sheared genomic DNA, and presumably resulted in non-targeted, randomly-distributed sequencing reads throughout the genome.[10] We also find it pertinent that Forshew, a contemporary of Leary, described the mate-paired technique as employed in Leary's PARE approach as whole genome sequencing. Ex. 1030, 10.

In light of the evidence and argument presently of record, we preliminarily interpret "whole genome sequencing," as used in claim step 1(b), to mean "a non-targeted approach to sequencing all or almost all of a genome." The panel may reconsider on the more complete record developed at trial, whether one of ordinary skill in the art would have understood that Leary's mate-paired / PARE approach to detecting genomic rearrangements to teach *or suggest* sequencing all or almost all of the genome. *See* Ex. 1020

[10] Although Patent Owner repeatedly points to Chan's description of Leary (Chan's reference 13) as having a "targeted nature," such targeting appears, at this stage, to refer to Leary's "use of MPS on tumor samples *to . . . identify specific genomic rearrangements* that can subsequently be detected in plasma," rather than to the MPS technique Leary used to generate the underlying sequence data. Ex. 1008, 211–212 (italics added); Prelim. Resp. 16, 30, 47.

¶ 65 (Dr. Quackenbush's discussion increasing coverage depth "when required by an experiment"); Ex. 1012, 67 (WGS approach for identifying single nucleotide variants (SNVs) targeting goals of 80% and 90% diploid coverage). For the purpose of institution, however, we answer this question in the affirmative.

2) "capture probes"

Claim step 1(c) involves "generating a second subset of nucleic acid molecules . . . by contacting said second nucleic acid sample with a plurality of capture probes, wherein said plurality of capture probes hybridize to one or more polymorphisms." The '394 patent provides no express definition of "capture probes," but, consistent with the plain language of step 1(c), states that they "[t]ypically . . . comprise a nucleic acid binding site . . . . that hybridizes to at least a portion of the one or more nucleic acid molecules . . . in the sample." Ex. 1001, 31:4–34; *see also id.* at 22:65–23:9, 7:57–64, 14:48–59; 14:54–56 ("The capture probe and the nucleic acid are in contact with each other."). Focusing on these functional characteristics, Petitioner and Dr. Quackenbush contend that one of ordinary skill in the art would have understood the term "capture probes" to encompass both "PCR primer capture probes and solution-based hybridization capture probes (e.g., biotinylated oligonucleotide baits)," because "none of the cited passages describe 'primers' and 'capture probes' as mutually exclusive or precludes a similarly structured nucleic acid from performing each function." Pet. 21; Reply 4; Ex. 1020 ¶¶ 100–106.

Petitioner also points to dependent claim 13's requirement that "capture probes further comprise barcodes," which Dr. Quackenbush defines as "short oligonucleotide sequence[s] that can be used to identify a particular

nucleic acid in a sequencing experiment." Reply 3–4; Ex. 1020 ¶¶ 104–105. According to Dr. Quackenbush, one of ordinary skill in the art "would have understood that barcodes were routinely employed in connection with PCR probes to allow the pooling of many samples in a single sequencing reaction. Because the barcode sequence would be incorporated into the PCR products, the barcodes can then be used to deconvolute the data." Ex. 1020 ¶ 104 (citing Ex. 1007 (Mamanova)). But, according to Dr. Quackenbush, "[w]hen hybrid capture baits are used, the capture probes themselves are not typically incorporated into the target nucleic acid" because "the capture probe (and any elements it comprises, like a barcode) remain bound to the bead while the catch is carried forward." *Id.* ¶ 105 (citing Ex. 1005 (Gnirke)).

Although Patent Owner argues that Dr. Quackenbush's reference to this "typical" use of barcodes undercuts Petitioner's claim differentiation argument, claim 13's recitation of barcodes weighs moderately in favor of Petitioner's construction. Sur-Reply 6.

Patent Owner argues that we should construe "capture probe" as "a nucleic acid sequence that hybridizes to target DNA to capture DNA for physical collection; not a primer for amplification." Prelim. Resp. 21–22. In support of its proposed construction, Patent Owner first points to the Specification's teaching to contact a nucleic acid sample with one or more capture probes to produce two subsets of nucleic acid molecules: "a first subset of nucleic acid molecules comprising one or more capture probe hybridized nucleic acid molecules and a second subset of nucleic acid molecules comprising one or more capture probe free nucleic acids." *Id.* at 22 (citing Ex. 1001, 32:26–34). Although the passage Patent Owner relies on defines subsets of nucleic acids based on whether they are hybridized to a

capture probes, nothing in the passage suggests—let alone requires—the physical collection or separation of probe-bound from probe-free molecules. *See* Reply 4 (citing Ex. 1020 ¶¶ 130–131).[11] To the contrary, these subsets are defined merely by hybridization status, and the Specification suggests that physical separation is an independent method of producing a subset. *See* Ex. 1001, 32:12–18 ("Alternatively or additionally, the one or more subsets of nucleic acids are produced by separating at least one nucleic acid molecule from another nucleic acid molecule.").

Patent Owner further argues that "the specification never describes capture probes as being used as a primer for amplification. Instead, the specification refers to capture probes and primers as separate and distinguishable from one another." Prelim. Resp. 22–23 (citing Ex. 1001, 23:23–36; 32:56–60, 41:33–36); Sur-reply 4–5. Patent Owner's relied-on passages indicate, for example, the attachment of labels "to one or more capture probes, nucleic acid molecules, beads, primers, or a combination thereof." *See* Ex. 1001, 23:23–36. Although such listings might be read to suggest that the class of capture probes is not entirely co-extensive with primers, it provides no indication as to whether the categories are overlapping, e.g., whether one of ordinary skill would understand an

[11] The '394 patent does not appear to limit the use of capture probes to solution-phase binding. Accordingly, we might imagine potential target nucleic acids affixed to a solid support, which are then exposed to a capture probe. *See, e.g.*, Southern, E.M., "Detection of specific sequences among DNA fragments separated by gel electrophoresis," 98 (3) *J. Mol. Biol.* 503-508 (1975) (Ex. 3003). Although a subset of the nucleic acids may hybridize to the capture probe, this subset cannot be physically collected or separated from unhybridized nucleic acids because both subsets are affixed to the solid support.

amplification primer to be a type of capture probe in much the same manner as both capture probes and primers are types of nucleic acid molecules. *See id.* at 41:32–36. As such, the Specification provides no indication of how, capture probes and primers are "separate and distinguishable from one another," as Patent Owner contends.

In this respect, the Specification evinces no physical characteristics differentiating capture probes from primers. Both comprise from as few as "one or more nucleotides" to "1000 or more nucleotides" (Ex. 1001, 31:35–53, 40:28–54); both include nucleotides "compris[ing] RNA, DNA, a mix of DNA and RNA . . . modified analogs . . . locked nucleic acid (LNA), or abasic sites" (41:32–36); both may—or may not—comprise a detectable label (*id.* at 14:22–47, 23:23–36, 31:54–32:5, 40:29–35, 41:38–42:3); and both may—or may not—comprise a linker (*id.* at 31:8–9, 31:54–67, 40:29–31, 41:15–26, 42:49–43:11), wherein said linker can also be a detectable label (*id.* at 14:36–42). Despite this lack of distinguishing physical characteristics in the Specification, Patent Owner cites to Gnirke (Ex. 1005) as indicating that oligonucleotides "typically used as primers for PCR" tend to be shorter than those used as capture probes for hybrid selection. *See* Prelim. Resp. 26 (citing Ex. 1005, 187). But, as the '394 Specification discloses that both primers and capture probes may comprise as little as "1 or more, 2 or more, 3 or more, 4 or more, 5 or more [or] 6 or more . . . nucleotides," this argument is unavailing. *Compare* Ex. 1001, 31:35–53, *with* 40:28–54.[12]

[12] The Specification's physical description aside, it is not clear, on the present record, how a capture probe comprising as few as a one nucleotide could provide the functionality of the capture probe recited in claim step 1(c) and described in the Specification. *See* Concurrence.

Patent Owner also contends that the ’394 patent discloses “several embodiments describ[ing] the use of capture probes as a separate step that occurs after the step of amplification of primers.” Prelim. Resp. 23 (citing Ex. 1001, 64:29–43; 65:38–50; 66:53–67). Again, at this stage, we do not discern that the different purported uses map to any physical difference between capture probes and primers sufficient to distinguish between. Indeed, reading the Specification, it would appear that the same polynucleotide could be employed as an amplification primer and a capture probe in Patent Owner’s referenced embodiment(s).

Patent Owner further relies on the prosecution history of two related applications, US 14/810,337 (“the ’337 application”) and US 15/996,215 (“the ’215 application”).[13] Prelim. Resp. 23–25 (citing Ex. 2004, 9, 17, 25. 36, 40; Ex. 2005, 19, 24, 31). In each case, applicant overcame art disclosing sequence-specific primers by amending its claims to recite “pulldown probes that selectively enrich for one or more [genetic] features.” *See id.* at 25 (citing Ex. 2004, 17 (distinguishing over Craig et al.); Ex. 2005, 9, 19, 24, 31 (distinguishing over Boers)). Petitioner responds, that “the cited applications involved the claim limitation ‘pulldown probe,’ and claims reciting ‘capture probe’ were not before the Office.” Reply 5 (emphasis omitted). At this stage, we agree with Petitioner; the above-referenced

[13] Primary Examiner Kaijiang Zhang examined the ’394 patent, the ’337 application, and the ’215 application. *See* Ex. 1001, code (74); Ex. 1078, 1; Ex. 2004, 2; Ex. 2005, 12.

prosecution history from the ’337 and ’215 applications provides insufficient further clarity on the meaning of “capture probe.”

Petitioner further argues that, prior to the amendment introducing “pulldown probe” in the ’337 application, the applicant proposed a draft claim amendment reciting the step of “producing two or more subsets of nucleic acid molecules from a nucleic acid sample . . . with the aid of probes that selectively enrich for the one or more genomic features” in at least one subset. Reply 5; Ex. 1078, 3. In a subsequent interview, the Examiner observed that the proposed amendment “would not distinguish over Craig et al. because the amplification primers used by Craig et al. could reasonably be interpreted as ‘probes’ as currently recited in the claim.” Ex. 2004, 17 (emphasis omitted). Although the cited interchange does not involve the claim term “capture probe,” it shows the Examiner understood that “probes” encompassed “amplification primers,” and that applicant addressed this understanding by amending the claims to specify a “pulldown” probe—a distinction not evident in the claims presently before us.

In view of the above, we preliminarily conclude that one of ordinary skill reading the ’394 patent would understand that there is no discernable physical distinction between capture probes and amplification primers, and that Patent Owner’s functional distinction—hybridizing to target DNA so as to form subsets of molecules that are/are not hybridized—is a commonly desired trait for polynucleotides used in hybridization-based methods including PCR. Considering the argument and evidence presently of record, we agree with Petitioner that the claimed “capture probes” encompass, at a

minimum,[14] PCR primer capture probes and solution-based hybridization capture probes (e.g., biotinylated oligonucleotide baits).

3) Other Terms

Petitioner further proposes constructions for the terms "subset" and "polymorphism," argues that the "biomedical report" of claim step 1(g) is directed to printer matter not entitled to patentable weight, and raises the issue of whether the preamble is limiting. Pet. 19–23, 31. Patent Owner does not presently address these issues. *See* Prelim. Resp. 21–28. At this stage of the proceeding, these and other claim terms do not require construction. *See Nidec*, 868 F.3d at 1017 ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

D. Ground 1: Obviousness in View of Leary

As to Ground 1, Petitioner challenges claims 1–11 and 13–19 as unpatentable for obviousness in view of Leary. Pet. 18. Supported by the testimony of Dr. Quackenbush, Petitioner provides an element-by-element comparison of the claims to the cited art. *Id.* at 28–54; Ex. 1020 ¶¶ 109–209. We focus first on the issues raised in the Patent Owner Preliminary Response. With respect to the remaining elements of claim 1, and its challenged dependent claims 2–11 and 13–19, Petitioner presents reasoned arguments for unpatentability in view of Leary supported by the testimony

[14] For the purpose of institution, we need not more precisely define the meets and bounds of this term. *But see* Concurrence.

of Dr. Quackenbush, which Patent Owner does not presently contest. *See generally* Pet. 31–54; Prelim. Resp.

4) "whole genome sequencing"

In Section II.C.1, we preliminarily define "whole genome sequencing," as used in claim step 1(b), to mean "a non-targeted approach to sequencing all or almost all of a genome." In opposing Ground 1, Patent Owner admits that "[t]he concept of 'whole genome sequencing had long been known in the art," but asserts that "Leary does not disclose anything like this." Prelim. Resp. 30 (citing Ex. 2006, R165).

Nevertheless, as also discussed in Section II.C.1, and applying our preliminary construction, it appears reasonably likely that one of ordinary skill in the art would have understood that Leary's mate-paired / PARE to teach or suggest sequencing all or almost all of the genome. *See* Section II.C.1, *supra.* As such, Petitioner has sufficiently shown that Leary discloses or renders obvious this element.

5) "capture probes"

In Section II.C.2, we construe "capture probes" as encompassing, PCR primer capture probes and solution-based hybridization capture probes (e.g., biotinylated oligonucleotide baits). According to Patent Owner, Ground 1 fails because the PCR primers Petitioner relies on in Leary "perform a different function from capture probes." Prelim. Resp. 37.

Patent Owner's argument is unavailing on the present record. Considering the intrinsic record, we discern no sufficient physical or functional distinction between capture probes as claimed and the cited primers of Leary. *See* Section II.C.2. Applying our construction of this term,

Petitioner has sufficiently shown that Leary discloses or renders obvious the use of capture probes as recited in claim step 1(c).

6) "conducting a second sequencing assay"

Claim step 1(d) recites, "conducting a second sequencing assay on said second subset of nucleic acid molecules to yield a second result comprising a second nucleic acid sequence." With respect to this element, Petitioner points to Leary's disclosure that "after generating a second subset of nucleic acid molecules by contacting the second sample with PCR primer capture probe, as described [with respect to step 1(c)], 'Sanger sequencing of seven PCR products confirmed the rearrangements in all cases tested.'" Ex. 1002, 3. Pet. 37 (citing Ex. 1020 ¶ 139). As Petitioner notes, "[t]he result of a Sanger sequencing assay is a nucleic acid sequence." Pet. 37.

Dr. Quackenbush further testifies that "[w]hen the second sample is a plasma sample from a patient, Leary discloses that the PCR products obtained by contacting such samples with its capture probes are subjected to a second sequencing assay, which results in a second nucleic acid sequence." Ex. 1020 ¶ 140 (citing Ex. 1002, 4). Dr. Quackenbush further points to Leary's disclosure that:

> To determine whether the rearranged sequences could actually be detected in clinical samples, we evaluated circulating DNA from plasma samples of patients Hx402 and Hx403. The sample from patient Hx403 was obtained before surgery, whereas the samples from patient Hx402 were obtained before and after surgery. . . . PCR amplification of plasma DNA using primers spanning the breakpoints produced products of the expected sizes only in the plasma samples from patients with disease and not in plasma from healthy controls (Fig. 4A). ***Sequencing the PCR products from plasma DNA identified the identical breakpoints observed in the tumor DNA samples***.

Id. (quoting Ex. 1002, 4) *see also, id.* (further relying on Leary's disclosure that "Digital PCR analyses of plasma samples from patient Hx402 indicated that rearranged tumor DNA was detectable at all six time points analyzed throughout the course of treatment. (Fig. 4B)").

Patent Owner takes the position that Leary does not disclose "conducting a second sequencing assay" as required by claim step 1(d), because Leary's method concluded with the detection of rearranged tumor DNA using digital PCR, and that the subsequent sequencing step relied on by Petitioner was "for the sole purpose of confirming that the designed primers truly resulted in amplification of the rearrangements." Prelim. Resp. 39–40. We do not find Patent Owner's argument persuasive on the present record.

As explained by Dr. Quackenbush, Leary discloses the step of sequencing PCR products generated from patient plasma DNA samples. *See* Ex. 1020 ¶¶ 132–134. Nothing in claim 1 or the intrinsic record prohibits conducting a step for the purpose of confirmation, and we discern no basis to disregard the relied-upon teaching merely because Leary employed Sanger sequencing to confirm the results of its digital PCR analysis. We therefore find that Petitioner has sufficiently shown that Leary discloses "conducting a second sequencing assay" as recited in claim step 1(d).

7) Secondary Considerations

Patent Owner contends that its commercial assay "is entitled to a presumption of nexus because, as detailed in the attached claim chart, Personalis's assay embodies claim 1 of the '349 Patent." Prelim. Resp. 54 (citing Ex. 2012). 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 skepticism of experts "toward solving the difficult challenges of conducing highly sensitive genome sequencing using capture probes." *Id.* at 55–56.

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, Petitioner asserts that "the alleged contribution of the ['394] patent — high sensitivity in [Patent Owner's] commercial product . . . is not claimed or even discussed in the specification." Reply 4. Moreover, to the extent Patent Owner's alleged high sensitivity derives from the use of "genome sequencing using capture probes," such techniques would appear to be encompassed by the prior art under our construction of "capture probes." *See* Section II.C.2, *supra.*

We also take into consideration Petitioner's argument that the record regarding secondary considerations, is "incomplete," such that Patent Owner's nexus evidence is supported by "only a cursory attorney-created claim chart," and Petitioner has not been afforded an opportunity to develop countervailing evidence at trial. Reply 6. As such, we agree with Petitioner that it would be premature "'to hinge the outcome of a Decision to Institute' on such an incomplete record." *Id.* (citing *Invata, LLC v. OPEX Corp.*, 2023 WL 2597830, at *4 (PTAB Mar. 17, 2023)). We will consider objective evidence of non-obviousness after development of a full trial record. The parties may, as appropriate, pursue further discovery, and present argument and evidence on this issue at trial.

8) Conclusion at to Ground 1, Claims 1–11 and 13–19

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 1–11 and 13–19 are unpatentable in view of Leary.

E. Ground 2: Obviousness in View of Leary and Ley

As to Ground 2, Petitioner further challenges claims 1–11 and 13–19 as unpatentable for obviousness in view of Leary, as discussed above, and further in view of Ley. Pet. 11, 54–58; Ex. 1020 ¶¶ 210–220. In short, Petitioner contends that the addition of "Ley[] further renders obvious alternative embodiments within the scope of the claim step 1(c), including selecting different types of polymorphisms as well as polymorphisms 'based on or extracted from one or more databases of polymorphisms' whether alone or in combination with the polymorphisms Leary identified in its samples." Pet. 54–55 (emphasis omitted). As described by Petitioner, Ley detected these polymorphisms via whole whole-genome sequencing, and then used probe-based capture techniques like Leary's to "monitor[] polymorphisms that were found in 'the coding sequences of annotated genes,'" both "at [the] time of primary tumor sampling and at relapse" *Id.* at 57 (citing Ex. 1012, 66, 70) (emphasis omitted).

In opposing Ground 2, Patent Owner argues that Ley fails to address defects previously identified in Ground 1 (based on Leary alone). Prelim. Resp. 41–42. Although Patent Owner concedes that Ley "reports on the results of whole genome sequencing of a tumor sample," it contends that

Ley's technique involves PCR amplification rather that "the claimed capture probe technique." *Id.* at 42. Patent Owner's argument regarding Ley is unavailing on the present record for essentially the reasons above with respect to Leary. Applying our construction of "capture probes," Petitioner has sufficiently shown that, like Leary, Ley's use of PCR amplification discloses or renders obvious the use of capture probes as recited in claim step 1(c). *See* Section II.D.3, *supra.*

Patent Owner also contends that Ley "does not disclose any sequencing of a sample from the patient at multiple time points, as recited in the claims of the '394 patent." Prelim. Resp. 42. In this respect, Patent Owner contends that although Ley sequenced a relapse sample from the original patient, this was "not for 'monitoring' but rather for the purpose of identifying cancer-causing mutations for the first time." *Id.* Patent Owner further argues that Ley does not enable serial monitoring—and even teaches away from the claimed invention—because Ley discloses that most of the SNVs it identified "would not have been candidates for direct resequencing on the basis of our current understanding of cancer," and that its reliance on the detection of SNVs "is 'inherently limited' and likely to 'miss key mutations.'" *Id.* at 1–2 (citing Ex. 1012, 70), 42–45 (citing, e.g., Ex. 1012, 69, 70, 71) (emphasis omitted).

Patent Owner's arguments are unavailing on the present record. First, we understand Leary alone to disclose monitoring cancer-associated mutations over time, which discloses or renders obvious at least the second sequencing assay provision of claim step 1(d). *See* Pet. 37–39, 41–44. Second, the passages in Ley relied on by Patent Owner appear to reflect Ley's focus in "establish[ing] whole-genome sequencing as an unbiased

method for discovering cancer-initiating mutations in previously unidentified genes that may respond to targeted therapies." Ex. 1012, Abstract. In the Discussion section, Ley summarizes that "we have successfully used a next-generation whole genome sequencing approach to identify new candidate genes that may be relevant for AML pathogenesis." *Id.* at 71. In light of its assertion of success, we do not read Ley's comments on the technical limitations of its technique (cited by Patent Owner) as evidence on non-enablement.

More importantly, in determining obviousness, "a reference . . . is prior art for all that it teaches." *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989). Considering the comparison of serial tumor samples illustrated in Ley's Figure 3, and the related testimony of Dr. Quackenbush (Ex. 1020 ¶¶ 81–82), we presently agree with Petitioner that one of ordinary skill in the art reading Ley, "would have been motivated to include known mutations (such as those derived from a database of known cancer mutations) in a panel of polymorphisms for serial monitoring at multiple time points; and (ii) that a POSA would have had a reasonable expectation of success in successfully monitoring such polymorphisms." *See* Pet. 56–57. And to be clear, at this stage of the proceeding, Patent Owner presents no credible evidence of teaching away.

For the reasons set forth with respect to Leary in Ground 1, and having further considered the arguments and evidence with respect to the combination of Leary and Ley in Ground 2, we determine that Petitioner has demonstrated a reasonable likelihood that claims 1–11 and 13–19 are unpatentable in view of Leary and Ley.

F. Ground 3: Obviousness in View of Leary, Chan, and Liao

As to Ground 3, Petitioner challenges claims 1–19 as unpatentable for obviousness in view of Leary, Chan, and Liao. Pet. 18, 58–77. Supported by the testimony of Dr. Quackenbush, Petitioner provides an element-by-element comparison of the claims to the cited art. *Id.* at 63–77; Ex. 1020 ¶¶ 221–252. Patent Owner opposes. Prelim. Resp. 45–57.

In short, and in addition to its arguments based on Leary alone, Petitioner points to Chan as disclosing the use of "solution-phase hybridization-based capture probes that target particular polymorphisms identified in an initial whole genome sequencing assay to serially monitor and detect cancer in a patient's plasma over time." Pet. 62; Ex. 1020 ¶ 228 (same). Petitioner asserts that "Chan's disclosures would have motivated a POSA to employ solution-phase hybridization probes, including solution-phase hybridization probes targeting additional types of polymorphisms, followed by NGS in Leary's methods." Pet. 62 (emphasis omitted); Ex. 1020 ¶ 228 (same). Petitioner further relies on Liao (an earlier publication with authorship overlapping that of Chan) as emphasizing the prior success and applicability of solution-based hybridization capture approaches in detecting single nucleic acid polymorphisms (SNPs) in plasma samples. *See, e.g.*, Pet. 66 (citing Ex. 1020 ¶ 233), 71–77; Ex. 1020 ¶ 241 (overview of combining Liao). Discussing the asserted combination with respect to dependent claim 12 (further requiring "a plurality of capture probes . . . conjugated to beads"), for example, Dr. Quackenbush testifies that

> Leary in view of Chan and Liao discloses conjugating the plurality of capture probes to beads when the hybrid capture probes are bound to magnetic beads to select the catch, as routine in the use of hybrid capture. Specifically, Liao explains that "[a]fter hybridization, we selected captured targets by

> pulling down the biotinylated probe/target hybrids with streptavidin-coated magnetic beads (Dynabeads M-280 Streptavidin; Invitrogen) and purified the targets with the MinElute PCR Purification Kit (Qiagen)." Ex. 1009 (Liao) at 94. A POSA thus would have understood that solution-phase hybridization probes will be conjugated to beads as part of the well-known enrichment process.

Ex. 1020 ¶ 251 (further citing Ex. 1005, 183 (Fig. 1)).

Patent Owner responds, "[g]iven the sheer number and scope of modifications that Petitioner proposes to make in Leary in view of Chan and Liao, it is difficult to believe that such a combination is obvious." Prelim. Resp. 49. Patent Owner's argument is not availing on the present record. Patent Owner argues first that "one would allegedly replace the targeted sequencing of Leary with the shotgun sequencing of Chan." *Id.* at 47. But as noted by Petitioner, the '394 patent expresses no preference between PCR and solution-based hybridization enrichment strategies; moreover, on the present record, we agree with Petitioner that one of ordinary skill in the art recognized the benefits of each and that they could be used "relatively interchangeably" in many applications. *See* Pet. 11–14; Ex. 1020 ¶¶ 67–78.

Patent Owner further contrasts Leary's teaching to monitor chromosomal rearrangements with Chan's focus on single nucleotide variants. Prelim. Resp. 48. Although Patent Owner suggests that Leary teaches away from monitoring single nucleotide variants because their analysis "in specific genes [is] limited by polymerase error rates at the bases of interest," Liao reports success with targeted sequencing of fetal SNPs amplified from maternal plasma. *Id.*; s*ee* Section I.G.4, *supra.* As such, we view Leary's statement regarding polymerase error rates as merely a description of the resolution of the technique rather than a caution to avoid it.

Patent Owner further argues that "a solution-phase hybrid capture technique . . . is not mentioned in Leary, and not actually used in Chan." Prelim. Resp. 48–49. At this stage of the proceeding, we agree with Dr. Quackenbush's assessment that Chan expressly contemplates "[t]he use of solution-phase hybridization followed by NGS to serially track tumor-associated polymorphisms in the blood following an initial whole-genome sequencing step," and further cites to Liao, which illustrates success using solution-phase hybridization capture probes to detect and identify single nucleotide polymorphisms in patient samples. *See* Ex. 1020 ¶¶ 225, 241; Ex. 1008, 212; Ex. 1009. As such, we do not find persuasive Patent Owner's argument that Chan does "not actually use[]" solution-phase hybrid capture.

Patent Owner also appears to argue that Chan is focused on prenatal diagnosis and fails to disclose serial monitoring of cancer. *See* Prelim. Resp. 51. We find this argument unavailing because Petitioner relies on ***Leary's*** demonstration of the serial monitoring of cancer. *See generally* Pet. 28–30; *see also id.* at 2–4 (presenting evidence that serial monitoring of genetic polymorphisms was generally known in the art). Finally, Patent Owner argues that "Chan expresses uncertainty as to whether" a targeted sequencing approach based on Chan and Leary "would work." Prelim. Resp. 52–53. In support, Patent Owner relies on the Chan's statement that:

> These data suggest that for an accurate measurement of the total tumor load in a cancer patient, the use of a genomewide shotgun approach might provide a more representative picture, compared with the more traditional approach of targeting specific tumor associated mutations. For the latter approach, ***if only a subset of the tumor cells possesses the targeted mutations, one might miss important information regarding imminent relapse or disease progression caused by tumor cells***

> not possessing the targeted mutations, or one might miss the emergence of a treatment-resistant clone.

Id. at 52 (citing Ex. 1008, 222). The cited passage compares the "genomewide shotgun approach" employed by Chan, to "the more traditional approach of targeting specific tumor-associated mutations." Ex. 1008, 222. As we read this passage, Chan's caution about potentially "miss[ing] important information," refers to the latter and, thus, is not pertinent to the whole-genome sequencing approach used by Chan (and Leary, under our present construction) and relied on by Petitioner.

For the reasons set forth with respect to Leary in Ground 1, and having further considered the arguments and evidence with respect to the combination of Leary, Chan, and Liao in Ground 3, we determine that Petitioner has demonstrated a reasonable likelihood that claims 1–19 are unpatentable in view of Leary, Chan, and Liao.

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 '394 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 1–19 of the '394 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 '394 Patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS, Inc.
Petitioner,

v.

PERSONALIS, Inc.
Patent Owner.

IPR2023-00224
Patent 11,384,394 B2

JENKS, *Administrative Patent Judge*, CONCURRING.

I concur in the determination that Petitioner has demonstrated a reasonable likelihood of success in proving that at least one challenged claim of the ’394 patent is unpatentable. I write separately to express a difference in opinion regarding the meaning of “capture probes,” as read in light of the Specification. I agree with the majority, and based on the preliminary record, that one reasonable interpretation of “capture probes” encompasses, at a minimum, PCR primer capture probes and solution-based hybridization capture probes (e.g., biotinylated oligonucleotide baits). However, I find that the ’394 patent’s disclosure is significantly broader than the interpretation put forth by the majority.

The ’394 patent describes, for example, that a “capture probe comprises a nucleic acid binding site. The capture probe may further comprise one or more linkers. The capture probes may further comprise one or more labels. The one or more linkers may attach the one or more labels to the nucleic acid binding site.” Ex. 1001, 31:7–12. The ’394 patent goes on to explain that “[t]he one or more capture probe[s] may comprise a nucleic acid binding site that hybridizes to at least a portion of the *one or more* nucleic acid molecules or variant or derivative thereof in the sample or subset of nucleic acid molecules.” *Id.* at 31:24–27 (emphasis added). According to the’394 patent, “[t]he capture probes may comprise *one or more nucleotides* . . . or 1000 or more nucleotides.” *Id.* at 31:35–43 (emphasis added). In other words, the capture probe as described by the ’394 patent Specification encompasses a nucleic acid range from 1 (one) to 1000+ nucleotides. The ’394 patent Specification further describes that the capture probe *may* but does not have to comprise a linker, nor does the capture probe require a label. *See id.* at 31:7–12. Thus, a “capture probe” as described in the ’394 patent Specification reasonably encompasses a single nucleic acid.

The ’394 patent describes that “[c]apture probes may hybridize to *one or more* nucleic acid molecules in a sample or in a subset of nucleic acid molecules. Capture probes may hybridize to *one or more* genomic regions.” Ex. 1001, 22:65–23:1 (emphasis added). The ’394 patent, however, does not define the size of a nucleic acid binding site, nor does the ’394 patent define the size of a genomic region that needs to hybridize with the capture probe. All that is required by the capture probe is that it hybridize to one or more nucleic acids. Thus, the recitation that “[t]he capture probes may comprise a

nucleic acid binding site that hybridizes to one or more genomic regions" does not further define the capture probe. *Id.* at 31: 28–29.

The '394 patent also describes that "[t]he capture probes, primers, labels, and/or beads *may comprise one or more nucleotides*. The one or more nucleotides may comprise RNA, DNA, a mix of DNA and RNA residues or their modified analogs such as 2'-OMe, or 2'-fluoro (2'-F), locked nucleic acid (LNA), or abasic sites." Ex. 1001, 41:32–36 (emphasis added). Thus, the theme throughout the '394 patent Specification is that a capture probe may encompass a single nucleotide.

It is also noteworthy that the '394 patent Specification recites neither binding conditions, nor any particular binding affinity for the capture probe; all that is required of the capture probe is that it "hybridizes to at least a portion of the one or more nucleic acid molecules or variant or derivative thereof in the sample or subset of nucleic acid molecules." Ex. 1001, 31:25–27. Under some (unspecified) conditions, and at some (unspecified) binding affinity, a single nucleic acid would be expected to hybridize with its complement and thereby meet the "capture probe" limitation as set out in the '394 patent Specification. Yet, Patent Owner does not at this stage grapple with such disclosures in its patent, and instead appears to urge a construction that is, at once, divorced from any structural aspects of a "capture probe," as described in the Specification, and is instead focused on importing a negative functional feature—that "capture probes" allegedly exclude nucleic acid sequences if they are used, or intended for use, as primers for PCR. I see no adequate support at present to justify the narrow interpretation advanced by Patent Owner.

Based on the disclosures in the ’394 patent Specification noted above, I would have preliminarily interpreted “capture probe” as encompassing nucleic acid structures as small on one nucleotide that *may but are not required to include* linkers and labels.

PETITIONER:

Andrew Krause
IRELL & MANELLA LLP
akrause@irell.com

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

PATENT OWNER:

Derek Walter
Adrian Percer
WEIL, GOTSHAL & MANGES LLP
Derek.walter@well.com
Adrian.percer@weil.com