

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS, Inc.
Petitioner,

v.

PERSONALIS, Inc.
Patent Owner.

IPR2023-00317
Patent 11,408,033 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 1–23 of U.S. Patent No. 11,408,033 B2 (“the ’033 patent,” Ex. 1001). Paper 1 (“Pet.”). Personalis, Inc. (“Patent Owner,” “Personalis”) timely filed a Preliminary Response. Paper 7 (“Prelim. Resp.”). With our authorization (*see* Exhibit 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 ’033 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. 2. 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 '033 patent at issue here, Petitioner concurrently challenges claims of related U.S. Patent Nos. 11, 384,394 B2 (“the '394 patent”) in IPR2023-00224. 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. *See* 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. 3; Paper 6, 1; Ex. 1010.

E. Asserted Challenges to Patentability

Petitioner challenges the patentability of claims 1–23 on the following bases: (Pet. 11):

Ground	Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1	1–7, 10–23	§ 102	Forshe ¹
2	1–23	§ 103	Forshe ¹ , Wag ²
3	1–9, 11–23	§ 103	Wag ² , Chan ³

¹ Tim Forshe¹, et al., “Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA,” 4 *Science Translational Medicine* 136ra68 (2012). Ex. 1030, Ex. 1032 (Supplementary Materials).

² Nikhil Wag² et al., “High-Throughput Detection of Actionable Genomic Alterations in Clinical Tumor Samples by Targeted, Massively Parallel Sequencing,” Jan. 2012 *Cancer Discovery* 83–93. Ex. 1033.

³ K.C. Allen Chan *et al.*, “Cancer Genome Scanning in Plasma: Detection of Tumor-Associated Copy Number Aberrations, Single-Nucleotide Variants,

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

F. The '033 Patent and Related Background

1) Priority

The '033 patent, titled Methods and Systems for Genetic Analysis, issued to Bartha et al., from U.S. Application 17/078,857, filed October 23, 2020, 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. 2, 4; Ex. 1020 ¶ 33. Patent Owner does not challenge January 13, 2013, as the priority date for '033 patent. *See* Prelim. Resp. 9, 13.

2) Abstract and Specification

The Abstract of the '033 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.*

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

The '033 patent 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 1–23, of which only claim 1 is independent and recites:

1. A method for analyzing a nucleic acid sample obtained from an individual, comprising:

(a) producing, with the aid of a computer processor, a plurality of capture probes, wherein said plurality of capture probes hybridize to a plurality of polymorphisms, wherein said plurality of polymorphisms are in sequences encoding genes with known biomedically interpretable variants, and wherein said plurality of polymorphisms are based on or extracted from one or more databases of polymorphisms and are observed in a population of one or more samples;

(b) contacting said nucleic acid sample with said plurality of capture probes produced in (a);

(c) conducting a sequencing assay on a subset of nucleic acid molecules generated from said nucleic acid sample in step (b) to yield a result comprising a nucleic acid sequence, thereby analyzing said nucleic acid sample; and

(d) repeating steps (b)–(c) on a subsequently obtained biological sample from said individual.

Ex. 1001, 79:46–65. Depending from claim 1, claim 2 entails “generating a biomedical report that includes biomedical information” referenced in claim step 1(a), whereas dependent claim 3 recites that this biomedical information

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 79:66–80:32.

G. Asserted Prior Art

Patent Owner does not dispute the prior art status of the asserted references in its Preliminary Response. *See* Pet. 14–15; Prelim. Resp. 2–4, 13.

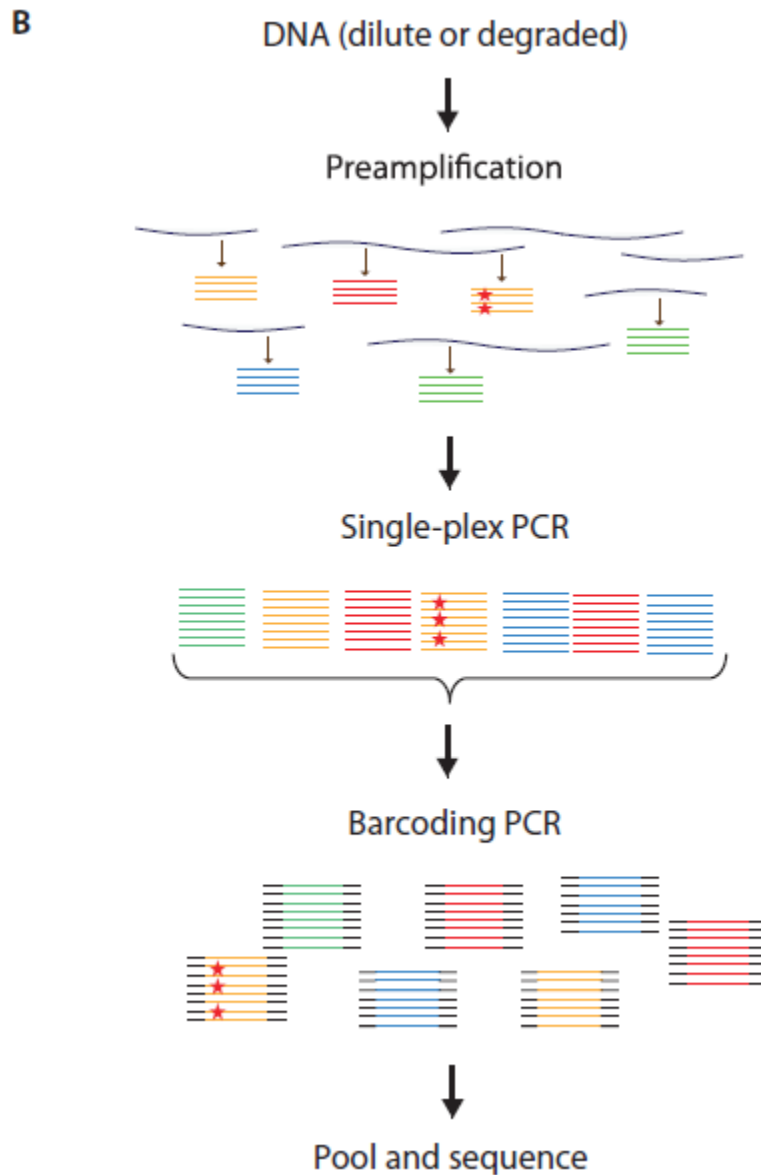
1) Overview of Forshew (Exhibits 1030, 1032)

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. 1020, 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 program⁴ to “design[] primers to

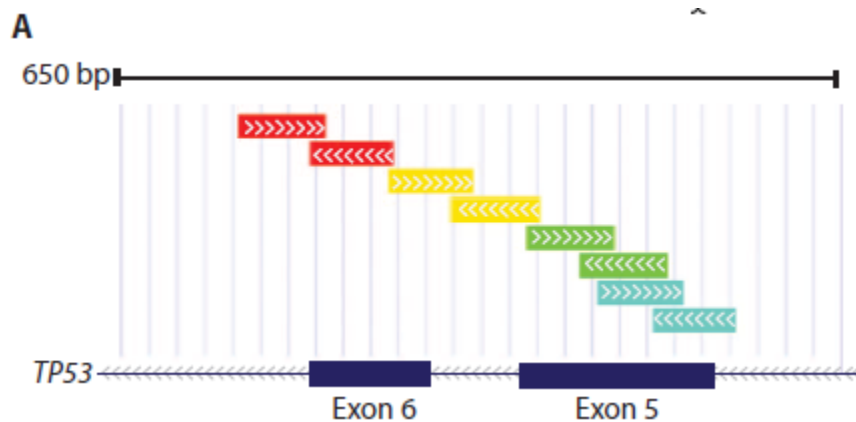
⁴ According to Dr. Quackenbush, Primer3 “was and continues to be a widely-used open source program that can pick PCR primer sequences using criteria such as oligonucleotide melting temperature, size, GC content, primer-dimer possibilities, PCR product size, and amplifying the wrong sequence.” Ex. 1020 ¶ 109 (citing <http://primer3.org>; Exhibit 1034 (Untergasser et al., “Primer3–new capabilities and interfaces,” 40(15) NAR e115 (2012))).

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.



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 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, “[w]e 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). The sequenced regions cover mutations that account for 38% of all point mutations in the COSMIC database (v55).⁵” *Id.* at 3. 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;”

⁵ According to Dr. Quackenbush, “COSMIC (Catalogue of Somatic Mutations in Cancer), was and continues to be a leading and comprehensive expert-curated database of somatic mutations in human cancers.” Ex. 1020 ¶ 111 (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)).

“noninvasively identify the origin of 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.

2) Overview of Wagle (Exhibit 1033)

Wagle discloses a “a targeted, massively parallel sequencing approach to detect tumor genomic alterations in formalin-fixed, paraffin embedded (FFPE) tumor samples.” Ex. 1033 at 83. Wagle explains that, “hybrid selection-based methods that enrich for coding sequences prior to sequencing (“exon capture”) are routinely being implemented in discovery-oriented settings. Here, we describe an adaptation of exon capture and massively parallel sequencing for robust detection of somatic genomic alterations in FFPE samples.” *Id.* at 84 (references omitted).

According to Wagle:

Massively parallel sequencing libraries (Illumina) that contain barcoded universal primers (9) were generated with the use of genomic DNA from formalin-fixed, paraffin-embedded tumor material. After preamplification and DNA quantification, equimolar pools were generated consisting of 12 barcoded tumor DNAs. These DNA pools were subjected to solution-phase hybrid capture with biotinylated RNA baits targeting all exons from 137 actionable cancer genes. Each hybrid capture reaction was sequenced in a single paired-end lane of an Illumina flow cell.

Id. at 91.

In particular, Wagle “generated a list of 137 ‘druggable’ or potentially actionable genes known to undergo somatic genomic alterations in cancer.”

Id. at 84. Wagle then used a commercially-available computer program to

design “7,021 unique biotinylated RNA baits corresponding to these genomic regions,” such that “[t]arget loci were covered with a tiling density of $\times 2$.” *Id.* at 84, 91 (“The Agilent SureSelect E-array program was used to design 7,021 unique RNA baits corresponding to the coding sequence of the 137 [cancer-related] genes described above, as well as to the 79 pharmacogenomic polymorphisms and to 24 SNPs for fingerprinting.”). Wagle further discloses that the baits were replicated 8 times on a 55,000-bait library array. *Id.* at 91.

Using this approach, Wagle detected single nucleotide variants, insertion/deletions and copy number alterations in a collection of cancer cell lines. *E.g.*, Ex. 1033 at 84 (“In total, 102 single-nucleotide variants and 6 indels (excluding known germline polymorphisms) were detected in coding sequences across the 10 cell lines, including all 21 single-nucleotide variants and 3 of 4 indels reported for these lines in the Catalogue of Somatic Mutations in Cancer database (COSMIC)”; 86 (“Comparison of overall copy number values derived by sequencing to those obtained from high density single-nucleotide polymorphism (SNP) array data (Affymetrix SNP 6.0 platform) demonstrated a robust correlation at the gene level”).

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.* 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.

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 1–7 and 10–23 are anticipated by the prior art. Pet. 11. To show anticipation under 35 U.S.C. § 102, each and every claim element, arranged as in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359 (Fed. Cir. 2008). The prior art need not, however, use the same words as the claims to find anticipation. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009). In evaluating anticipation, it is permissible to take into account not only the literal teachings of the prior art reference, but also the inferences the skilled artisan would draw from it. *Eli Lilly and Co. v. Los Angeles Biomedical Res. Inst. At Harbor-UCLA Med. Ctr.*, 849 F.3d 1073, 1074–75 (Fed. Cir. 2017) (holding that the “dispositive question regarding anticipation is whether one skilled in the art would reasonably understand or infer from a prior art reference that every claim element is disclosed in that reference”). As such, “a reference can anticipate a claim even if it does not expressly spell out all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would at once envisage the claimed arrangement or combination.” *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (internal quotation and alteration marks omitted).

Petitioner also contends that each claim of the ’033 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. 6 (citing Ex. 1020 ¶¶ 35–38) (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. 8. 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 9–13 (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 12. 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. 6, *with* Prelim. Resp. 12.

Further, and seeking to limit the knowledge and experience 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. 12–13.

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 10; Pet. 6. 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 10–12 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. 9–10. 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 the 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. 9–10 (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.⁶

⁶ 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 appropriate level, and that patent owner’s expert used petitioner’s level in the expert’s analysis. *Id.*

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 below the disputed claim term — “capture probes.”

1) “capture probes”

Claim step 1(a) involves “producing . . . a plurality of capture probes, wherein said plurality of capture probes hybridize to a plurality of polymorphisms.” Claim step 1(b) involves “contacting” a nucleic acid sample obtained from an individual with a “plurality of capture probes produced in (a)” whereupon, step 1(c) entails “conducting a sequencing assay on a subset of nucleic acid molecules generated . . . in step (b).”

The ’033 patent provides no express definition of “capture probes,” but, consistent with the plain language of step 1(b), 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 22:65–23:8, 7:57–63, 14:48–58;

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. 17; Reply 2; Ex. 1020 ¶¶ 98–104.

Petitioner also points to dependent claim 10’s requirement that the “plurality of 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.” Pet. 40–41; Reply 1–2; Ex. 1020 ¶¶ 102–103. Dr. Quackenbush testifies that 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 ¶ 102 (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.* ¶ 103 (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 10's recitation of barcodes weighs moderately in favor of Petitioner's construction. Sur-Reply 3.

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. 19. 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 20 (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 ¶¶ 110, 120–121).⁷ 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

⁷ The '033 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.

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. 20–21 (citing Ex. 1001, 23:23–36; 32:56–60, 41:33–36); Sur-reply 2–3. 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 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. 24 (citing Ex. 1005, 187). But, as the 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 unpersuasive on the record before us. *Cf.* Ex. 1001, 31:35–53 *with* 40:28–54.⁸

Patent Owner also contends that the ’033 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. 21 (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 them. 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

⁸ 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 the challenged claims and described in the Specification. *See* Concurrence.

(“the ’215 application”).⁹ Prelim. Resp. 21–23 (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* 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 3 (emphasis omitted). At this stage, we agree with Petitioner; the above-referenced 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 3; 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

⁹ Primary Examiner Kaijiang Zhang examined the ’033 patent, the ’337 application, and the ’215 application. *See* Ex. 1001, code (74); Ex. 1078, 1; Ex. 2004, 2; Ex. 2005, 12.

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 '033 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 nucleotides used as 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,¹⁰ PCR primer capture probes and solution-based hybridization capture probes (e.g., biotinylated oligonucleotide baits).

2) Other Terms

Petitioner further proposes constructions for the term “polymorphism(s)” as used in claim step 1(a), and argues that the “biomedical report” recited in claim 2, is directed to printer matter not entitled to patentable weight, and raises the issue of whether the preamble to claim 1 is limiting. Pet. 18–19, 29, 53–54. Patent Owner does not presently address these issues. *See* Prelim. Resp. 19–24. 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))).

¹⁰ For the purpose of institution, we need not more precisely define the meets and bounds of this term. *But see* Concurrence.

D. Ground 1: Anticipation by Forshew

As to Ground 1, Petitioner challenges claims 1–7, 10–23 as anticipated by Forshew. Pet. 11, 24–46. Petitioner provides an element-by-element comparison of the claims to the cited art. *Id.* at 29–46.

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 2–7 and 10–23, Petitioner presents reasoned arguments for unpatentability in view of Forshew supported by the testimony of Dr. Quackenbush, which Patent Owner does not presently contest. *See generally* Pet. 24–51; Ex. 1020 ¶¶ 107–172; Prelim. Resp.

1) “capture probes”

Claim step 1a involves “producing, with the aid of a computer processor, a plurality of capture probes.” In Section II.C.1, 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 Forshew “perform a different function from capture probes,” because “PCR do not capture a target nucleic acid for the purpose of *collecting* it.” Prelim. Resp. 26. Patent Owner’s argument is unavailing on the present record. Considering the intrinsic record, we discern no physical or functional distinction between capture probes and primers. *See* Section II.C.2 (noting for example, our view that the subsets of nucleic acids referenced in the Specification do not require physical collection or separation of probe-bound from probe-free molecules). Applying our construction of this term, Petitioner has sufficiently shown that Forshew discloses the use of capture probes.

2) “wherein said plurality of capture probes hybridize to a plurality of polymorphisms”

Claim step 1a further requires that the plurality of capture probes “hybridize to a plurality of polymorphisms.” With respect to this element, Petitioner and Dr. Quackenbush contend that “ForsheW discloses the design and use of ‘capture probes’ in the form of PCR primers that hybridize to and amplify (and thus ‘capture’) a plurality of polymorphisms in sequences encoding genes with known biomedically interpretable variants.” Pet. 30–31; Ex. 2020 ¶ 121. Consistent with this interpretation, ForsheW discloses that, “[t]he sequenced regions [i.e., those amplified by the PCR primers] cover mutations that account for 38% of all point mutations in the COSMIC database (v55).” Ex. 1030, 3. Patent Owner, however, contends that this element is not satisfied because, “even if PCR primers are capture probes ForsheW never once discloses that these primers hybridize to polymorphisms.” Prelim. Resp. 27.

As we understand the parties’ arguments, Petitioner contends that ForsheW’s capture probes hybridize to a plurality of polymorphisms because, *upon replication*, its PCR primers hybridize to DNA fragments containing a plurality of polymorphisms, for example, known point mutations in cancer-related genes. Patent owner, by contrast, more narrowly interprets claim step 1a as requiring that, *absent replication*, the nucleotide sequence of ForsheW’s PCR primers must, encompass and hybridize to, polymorphic target sites. This issue may benefit from further exploration at trial. For the purpose of institution, however, we rely on Dr. Quackenbush’s testimony that one of ordinary skill in the art would have “understood that ForsheW’s PCR primer capture probes are the claimed ‘capture probes’ because they are nucleic acid sequences that ‘hybridize to’ the

complementary sequences on the nucleic acid harboring the polymorphic gene.” Ex. 2020 ¶ 121; *see also id.* ¶¶ 119–120, 122–123.

- 3) “contacting said nucleic acid sample with said plurality of capture probes produced in (a).”

Claim step 1b requires “contacting said nucleic acid sample with said plurality of capture probes produced in (a).” Patent Owner contends that Forshew does not disclose this step because it does not disclose ‘capture probes.’” Prelim. Resp. 28. We do not find this argument availing for the reasons discussed in Section II.D.1, above.

- 4) “conducting a sequencing assay on a subset of nucleic acid molecules generated from said nucleic acid sample in step (b) to yield a result comprising a nucleic acid sequence, thereby analyzing said nucleic acid sample”

Claim step 1c requires “conducting a sequencing assay on a subset of nucleic acid molecules generated from said nucleic acid sample in step (b) to yield a result comprising a nucleic acid sequence, thereby analyzing said nucleic acid sample.” With respect to this step Petitioner and Dr. Quackenbush point to Forshew’s Figure 1B as illustrating Forshew’s teaching to “‘pool and sequence’ the amplicons generated from the nucleic acid sample in [claim step 1b]. Prelim. Resp. 33–34; Ex. 2020 ¶ 127.¹¹

According to Patent Owner, “Forshew does not disclose this step because it does not disclose performing a sequencing assay on a subset of molecules that are generated from step (b). Specifically, the sequencing assay disclosed in Forshew is conducted—not on molecules that were

¹¹ For the purpose of institution, we need not consider the parties’ arguments comparing Forshew to an allegedly infringing product, rather than to the claims before us. *See* Pet. 25; Prelim. Resp. 30–31.

captured by contacting the capture probes to the nucleic acid sample—but on molecules that result from the PCR amplification reactions.” Prelim. Resp. 29.

Patent Owner’s argument is unavailing on the present record because claim step 1c, recites that the sequencing step is conducted on “nucleic acid molecules *generated from* said nucleic acid sample in step (b).” We presently understand the plain meaning of “generated from” to be permissive of additional steps, including the PCR amplification taught by Forshew. Although Patent Owner criticizes as conclusory essentially the same interpretation from Petitioner’s expert, we understand Dr. Quackenbush’s testimony to support that one of ordinary skill in the art would similarly apply the plain and ordinary meaning to this element. *See* Prelim. Resp. 29–30; Ex. 1020 ¶ 127.

5) “repeating steps (b)–(c) on a subsequently obtained biological sample from said individual”

Claim step 1d entails “repeating steps (b)–(c) on a subsequently obtained biological sample from said individual.” Patent Owner contends that “Forshew does not disclose this step because it never conducts steps (b) and (c) to begin with, let alone repeats them.” Prelim. Resp. 31. Patent Owner’s argument is not persuasive on the present record. For the reasons set forth above, Petitioner has shown sufficiently that Forshew discloses claim steps 1b and 1c. And the present record further indicates that Forshew discloses examples wherein those steps are repeated on a subsequently obtained biological sample from an individual as required by claim step 1d. *See* Ex. 1030, 2 (stating that the disclosed method “allowed us to monitor changes in tumor burden by sampling only patient plasma over time,” Figs.

4B–D (graphics illustrating monitoring frequency of mutant DNA in cancer patients over time); Ex. 2020 ¶¶ 130–131.

6) Conclusion as to Ground 1, Claims 1–7 and 10–23

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. Patent Owner does not presently contest any other limitation of the claims challenged under Ground 1. As noted above, Petitioner presents reasoned arguments for unpatentability over Forshaw for the remaining elements of claims 1–7 and 10–23, which Patent Owner does not presently contest. *See generally* Pet. 24–51; Prelim. Resp. Having considered the arguments and evidence before us, we determine that Petitioner has demonstrated a reasonable likelihood that claims 1–7 and 10–23 are unpatentable over Forshaw.

E. Ground 2: Obviousness in View of Forshaw and Wagle

As to Ground 2, Petitioner further challenges claims 1–23 as obvious in view of Forshaw and Wagle. Petitioner provides an element-by-element comparison of the claims to the cited art. *Id.* at 46–51

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 2–23, Petitioner presents reasoned arguments for unpatentability in view of Forshaw supported by the testimony of Dr. Quackenbush, which Patent Owner does not presently contest. *See generally* Pet. 46–51; Ex. 1020 ¶¶ 173–190; Prelim. Resp.

Petitioner relies on Wagle as disclosing the “hybridization array” and “plurality of capture probes . . . conjugated to beads” recited in claims 8 and 9, respectively. Pet. 49–51.

With respect to claims 1–7 and 10–23—and to the extent we would decline to interpret “capture probes” as encompassing Forshew’s PCR primers—Petitioner relies on Wagle as “disclosing the use of RNA bait hybridization probes in a similar context to Forshew’s method.” *See id.* at 47; Section II.C.1, above. As articulated by Dr. Quackenbush, Petitioner contends that one of ordinary skill in the art “would have been motivated to combine Forshew and Wagle by using Wagle’s solution-phase hybridization RNA baits as capture probes, either in place of, or in addition to, Forshew’s PCR primer capture probes,” because (1) “a POSA would have considered these amplification techniques to be relatively interchangeable;” (2) in light of Wagle’s “suggest[ion] that in certain circumstances, PCR-capture based techniques may be less optimal (although not ineffective);” and (3) in view of Wagle’s proposal to use “its exon capture approach as a related technique suitable for the capture portion of the general workflow.” *See Ex. 1020 ¶ 182* (explanatory footnote citing Ex. 1033, 83 omitted).

In addressing reasonable expectation of success, Dr. Quackenbush further testifies that Forshew’s PCR and Wagle’s RNA bait-based hybridization “techniques are not mutually exclusive, as a POSA could have been motivated to use hybridization followed by PCR, or vice-versa, in certain applications, for example, in some scenarios in order to further enrich a target sequence to[]further improve and refine results as compared to performing either step alone.” *Id.* ¶ 184. Dr. Quackenbush further testifies that one of ordinary skill in the art

would have reasonably expected to succeed in using Wagle’s RNA bait-based probes in place of Forshew’s PCR primer capture probes in the capture step. Both techniques essentially involve enrichment of targeted sequences using hybridization of probes to targets. Wagle’s approach enriches by isolating the

targets and removing them from non-targeted nucleic acids in the sample. Forshew's approach captures the targets through base-pairing hybridization and copies the targets and thereby enriches them over non-targeted nucleic acids.

Id. ¶ 183.

1) Teaching Away

Patent Owner contends that Forshew teaches away from the use of capture probes, "calling them 'expensive' and 'difficult to implement on a routine basis,'" and further asserts that "Wagle does not cure this deficiency." Prelim. Resp. 32–33 (referencing Ex. 1030, 10, Ex. 1033, 84, 90). Patent Owner's arguments are not persuasive on the present record.

A reference may teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the invention. "A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination." *Syntex (USA) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005). "The fact that the motivating benefit comes at the expense of another benefit . . . should not nullify its use as a basis to modify the disclosure of one reference with the teachings of another. Instead, the benefits, both lost and gained, should be weighed against one another." *Medichem, S.A. v. Rolabo S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006).

Here, the passage in Forshew that Patent Owner relies on recites:

Previously proposed methods for personalized monitoring of tumor dynamics relied on expensive custom-designed probes (3) or identification of rearrangements using whole-genome sequencing (18, 19). These have better analytical sensitivity than currently achieved by TAm-Seq, but are difficult to implement on a routine basis.

Ex. 1030, 10. On this record, we do not read the above passage as indicating that the asserted expense or difficulty in implementing earlier methods “on a routine basis” teaches away from their use in at least some applications, particularly in view of Forshew’s disclosure that the earlier methods “have better analytical sensitivity than currently achieved by TAm-Seq.” *See id.*

Patent Owner also contends that “Wagle acknowledges that cost is a ‘significant consideration in *clinical sequencing*’ and, at most, stands for the proposition that ‘hybrid selection-based methods that enrich for coding sequences prior to sequencing ... are routinely being implemented in *discovery-oriented* settings.” Prelim. Resp. 33 (citing Ex. 1033, 90). This fails to support Patent Owner’s teaching away argument at least because the challenged claims are not limited to clinical applications¹² and Wagle expressly teaches that “hybrid selection-based methods . . . are routinely being implemented in discovery-oriented settings.” *See* Ex. 1033, 90.

2) Reasons to Combine

In paragraph 184 of his declaration, Dr. Quackenbush reproduces Figure 2 of Mamanova¹³ to illustrate that solution-based hybrid capture and PCR were two well-known types of target enrichment techniques that could

¹² To the extent the claims were so limited, Wagle merely notes that cost is a “significant consideration,” yet, as discussed above, the evidence also suggests that more costly methods could also provide greater sensitivity. We further note Patent Owner’s citation to Chan as referencing articles by Liao and Lo that allegedly “acknowledge that the cost of NGS was, at that time, a challenge for routine clinical applications.” *See* Prelim. Resp. 41, n.1. As with Wagle, we do not find Patent Owner’s cost-based argument persuasive on the present record.

¹³ Mamanova *et al.*, “Target-enrichment strategies for next-generation sequencing,” 7(2) *Nature* 111–118 (2010). Ex. 1007.

be applied at the choice of the POSA, and in some scenarios the techniques were known to have overlapping applicability. Ex. 1020 ¶ 184 (citing Ex. 1007). Mamanova's Figure 2 is reproduced below.

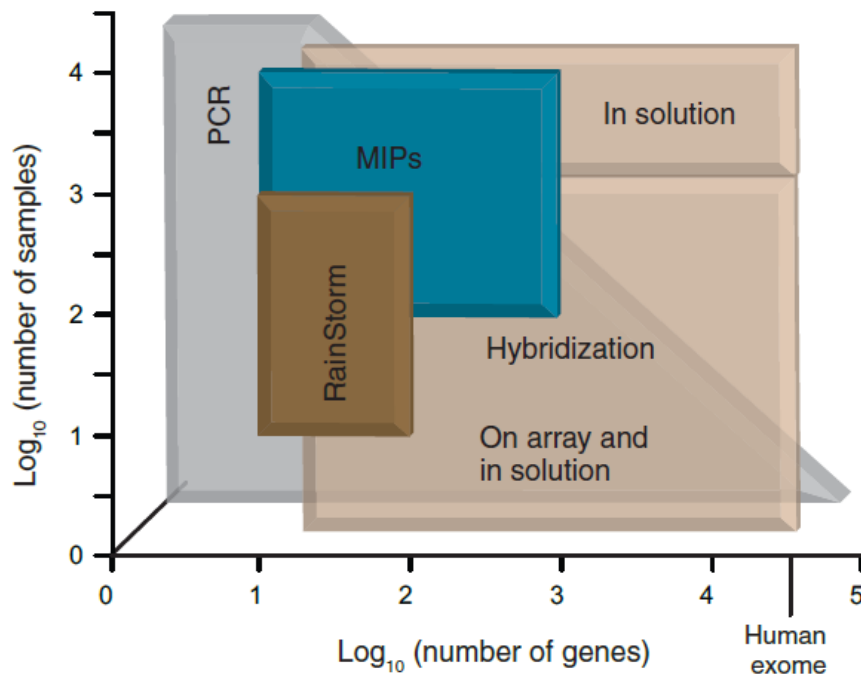


Figure 2 | Suitability of different target-enrichment strategies to different combinations of target size and sample number. Suitability was estimated from the perspective of the feasibility with which each method could be applied to the various combinations of target size and sample number, rather than the cost.

Ex. 1007, Fig. 2. Figure 2 is a graph, plotting the number of genes (x-axis) against the number of samples (y-axis), with both variables in Log₁₀ scale, and provides an estimate of “suitability” for different target-enrichment strategies “from the perspective of the feasibility with which each method could be applied to the various combinations of target size and sample number, rather than cost.” *Id.* at legend. Mamanova's Figure 2 shows, for example, the suitability of PCR (gray, triangular shading) and on-array and in-solution hybridization (beige, square shading) as a function of number of samples and number of genes to be analyzed.

Focusing on Mamanova's Figure 2, Patent Owner contends that one of ordinary skill in the art would not have been motivated to combine Forshew's PCR-based method with Wagle's solution-based hybrid capture method because Forshew only assayed six genes, which is below the minimum of roughly 12–13 genes Mamanova's Figure 2 shows as "suitabl[e]" for hybrid capture. *See* Prelim. Resp. 34–35; Ex. 1007, Fig. 2. Conversely, Patent Owner contends that Wagle's method *would* be suitable for both PCR and hybrid capture because Wagle assayed 137 genes, which Mamanova shows within the region of overlap for PCR and hybrid capture. *Id.* At this stage of the proceedings, however, Patent Owner's position is supported only by attorney argument interpreting Mamanova's illustration, with no rebuttal evidence to account for how the skilled artisan would interpret Mamanova, or the prior art as a whole. For the purpose of institution we rely, instead, on Dr. Quackenbush's testimony that one of ordinary skill in the art "would have been motivated to combine Forshew and Wagle by using Wagle's solution-phase hybridization RNA baits as capture probes, either in place of, or in addition to, Forshew's PCR primer capture probes," with a reasonable expectation of success. *See* Ex. 1020 ¶¶ 182–188.

3) 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 '033 Patent." Prelim. Resp 46 (citing Ex. 2008). 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 48.

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 [’033] 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.1, *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 yet been afforded an opportunity to develop countervailing evidence at trial. Reply 4. 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, to the extent necessary, 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.

4) Conclusion as to Ground 2, Claims 1–23

Considering the record presently before us, and in light of our constructions based on the current record, we determine that 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 2. As noted above, Petitioner presents reasoned arguments for unpatentability over Forshew and Wagle for the remaining elements of claims 1–23, which Patent Owner does not presently contest. *See generally* Pet. 46–51; Prelim. Resp. Having considered the arguments and evidence before us, we determine that Petitioner has demonstrated a reasonable likelihood that claims 1–23 are unpatentable over Forshew and Wagle.

F. Ground 3: Obviousness in View of Wagle and Chan

As to Ground 3, Petitioner challenges claims 1–9 and 11–23 as unpatentable for obviousness in view of Wagle and Chan. Pet. 11, 51–80. Petitioner provides an element-by-element comparison of the claims to the cited art. *Id.* at 63–77. Patent Owner opposes. Prelim. Resp. 35–44.

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 2–9 and 11–23, Petitioner presents reasoned arguments for unpatentability in view of Wagle and Chan supported by the testimony of Dr. Quackenbush, which Patent Owner does not presently contest. *See generally* Pet. 53–80; Ex. 1020 ¶¶ 191–265; Prelim. Resp.

1) Reasons to Combine

Patent Owner argues that one of ordinary skill in the art would not have been motivated to combine Chan and Wagle because “Wagle reflects a targeted approach to the sequencing of DNA from a tumor,” whereas Chan

discloses “a nontargeted random—or shotgun—sequencing approach” to tumor analysis and “criticizes targeted approaches because they ‘might miss important information regarding imminent relapse or disease progression.’” Prelim. Resp. 36–39; Ex. 1008, 212, 222. According to Patent Owner, Chan and Wagle, thus, “operate according to fundamentally different principles,” such that to combine the two, “one would have to abandon the underlying principle of operation of at least one of them.” Prelim. Resp. 38–39 (*citing e.g., Plas-Pak Indus., Inc. v. Sulzer Mixpac AG*, 600 F. App’x 755, 759 (Fed. Cir. 2015)). As an initial matter, Patent Owner’s argument would appear somewhat at odds with Chan’s teaching that “the targeted and shotgun approaches can be used in combination for cancer detection and monitoring.” *See* Ex. 1008, 223.

As with Patent Owner’s assertions regarding Mamanova with respect to Ground 2, Patent Owner’s argument regarding motivation to combine (and its subsumed teaching away argument) would benefit from further development at trial, including with respect to the understanding of one of ordinary skill in the art. *See* Section II.E.1–2, above. For the purpose of institution, however, we rely on the reasons to combine the two references articulated by Dr. Quackenbush who testifies that one of ordinary skill in the art

would have been motivated to add to the fundamental methodology set forth in Wagle the analysis of the additional types of polymorphisms (e.g., SNVs/SNPs and CNVs) that Chan found to be present in greater numerical quantities in patients’ cancer samples. *Id.* (Table 3) (monitoring group of 2,216 SNVs. Adding the monitoring of such polymorphisms to Wagle’s methods would also have further motivated the use of solution phase hybridization probes as disclosed in both references.

Ex. 1020 ¶ 209; *see also* Pet. 62 (similar).

- 2) “repeating steps (b)–(c) on a subsequently obtained biological sample from said individual”

Claim step 1d recites, “repeating steps (b)–(c) on a subsequently obtained biological sample from said individual,” which we understand to encompass serial monitoring of a patient under treatment for cancer. Patent Owner appears to argue that the combination of Wagle and Chan fails to enable, disclose, or suggest claim step 1d. *See* Prelim. Resp. 39–44.

As an initial matter, Patent Owner’s argument alleging lack of enablement lacks sufficient explanation and is confusing. Patent Owner references Chan’s statement that, in contrast to its shotgun approach, and under some circumstances, a targeting approach “might miss important information regarding imminent relapse or disease progression caused by tumor cells.” *Id.* at 43–44 (citing Ex. 1008, 222). On the preliminary record before us, we fail to understand how Chan’s caution regarding the potential limits of a targeting approach equates to non-enablement. Further with respect to enablement, Patent Owner argues that “[t]here is no direction whatsoever in Chan as to how [serial monitoring] might work.” *Id.* at 42–43. We note that—but for its reason to combine argument—Patent Owner does not presently challenge Petitioner’s arguments with respect to claim steps 1b and 1c under this Ground. One might surmise that if one of ordinary skill could have performed steps 1b and 1c then the mere repetition of those steps in claim step 1d would likely have been enabled.

Although Petitioner admits that at least Wagle does not expressly disclose repeating claim steps 1b and 1c as required by claim step 1d (Pet. 67), this element is arguably implicit in Chan’s statements that “targeted

shotgun approaches can be used in combination for cancer detection ***and monitoring***” (Ex. 1008, 221) (emphasis added); “[the disclosed] 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.*) (emphasis added); and that “[t]he presence of tumor-derived DNA in the plasma of cancer patients offers exciting opportunities for the detection ***and monitoring*** of cancer.” *Id.* at 222 (emphasis added). *See also* Ex. 1020 ¶ 194 (Dr. Quackenbush’s testimony that “the use of solution-phase hybridization followed by NGS to serially track tumor-associated polymorphisms is expressly contemplated by Chan. Ex. 1008.”), ¶ 213 (similar).

To the extent Chan does not disclose the elements of claim step 1d, our understanding of the present record suggests that this element would have been obvious to one of ordinary skill in the art, particularly in light of Chan’s above-quoted references to cancer monitoring. As noted by Dr. Quackenbush, the use of DNA marker analysis to serially monitor tumor DNA in a patient’s blood plasma was well known in the art. *See e.g.*, Ex. 1020 ¶ 85 (citing Ex. 1002¹⁴ (Leary); Ex. 1015¹⁵ (McBride), Ex. 1031¹⁶ (Meyerson)); ¶¶ 131, 133 (citing Ex. 1030 (Forsheew)). With this

¹⁴ 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/>).

¹⁵ 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).

¹⁶ Meyerson, *et. al.*, “Advances in understanding cancer genomes through second-generation sequencing,” 11 *Nature Reviews* 685–696 (2010)

background, one might plausibly read Chan’s assertion that “[o]ne can also envision the possibility of using shotgun sequencing of a plasma sample upon presentation of a cancer patient, mining the shotgun sequencing data of plasma DNA for copy number aberrations and SNVs, ***and then specifically targeting such sequences for serial monitoring purposes,***” as more than the “speculation and conjecture,” referenced by Patent Owner. Prelim. Resp. 41; Ex. 1008, 223 (emphasis added); Ex. 1020 ¶ 213.

3) Conclusion as to 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 Wagle and Chan for the remaining elements of claims 1–9 and 11–23, which Patent Owner does not presently contest. *See generally* Pet. 53–80; Prelim. Resp. Having considered the arguments and evidence before us, we determine that Petitioner has demonstrated a reasonable likelihood that claims 1–9 and 11–23 are unpatentable over Wagle and Chan.

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 ’033 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; 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 1–23 of the ’033 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 ’033 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.

IPR2023-00317
Patent 11,408,033 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 '033 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 '033 patent's disclosure is significantly broader than the interpretation put forth by the majority.

The '033 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 '033 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 '033 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 '033 patent Specification encompasses a nucleic acid range from 1 (one) to 1000+ nucleotides. The '033 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 '033 patent Specification reasonably encompasses a single nucleic acid.

The '033 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 '033 patent, however, does not define the size of a nucleic acid binding site, nor does the '033 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 '033 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 '033 patent Specification is that a capture probe may encompass a single nucleotide.

It is also noteworthy that the '033 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 '033 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 '033 patent Specification noted above, I would have preliminarily interpreted “capture probe” as encompassing nucleic acid structures as small as one nucleotide that *may but are not required to include* linkers and labels.

IPR2023-00317
Patent 11,408,033 B2

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