

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS INC.,

Petitioner,

v.

PERSONALIS, INC.,

Patent Owner.

IPR2023-00317

U.S. Patent No. 11,408,033

**PRELIMINARY RESPONSE TO PETITION FOR *INTER PARTES*
REVIEW OF U.S. PATENT NO. 11,408,033**

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PATENT OWNER'S EXHIBIT LIST

Exhibit No.	Description
2001	The Scientist Staff, "2022 Top 10 Innovations," Dec. 12, 2022, available at https://www.the-scientist.com/features/2022-top-10-innovations-70792
2002	Raphael, B., et al., "Identifying driver mutations in sequenced cancer genomes: computational approaches to enable precision medicine," Genome Medicine 2014, 6:5
2003	Supplementary Figures 1-3 for Wagle, N., et al., "High-Throughput Detection of Actionable Genomic Alterations in Clinical Tumor Samples by Targeted, Massively Parallel Sequencing," Cancer Discovery (2012) available at https://aacrjournals.org/cancerdiscovery/article/2/1/82/2910/High-Throughput-Detection-of-Actionable-Genomic
2004	Excerpt from U.S. Patent Appl. No. 14/810,337 prosecution history
2005	Excerpt from U.S. Patent Appl. No. 15/996,215 prosecution history
2006	Foresight Diagnostics Patent Issued for Minimal Residual Disease Detection Technology, dated Sept. 27, 2022 available at https://foresight-dx.com/news/foresight-diagnostics-patent-issued-for-minimal-residual-disease-detection-technology-1
2007	Swanton, C., "Plasma-Derived Tumor DNA Analysis at Whole-Genome Resolution," Clinical Chemistry 59:1 6-8 (2013)
2008	Embodying Product Claim Chart for U.S. Patent No. 11,403,033

I. INTRODUCTION

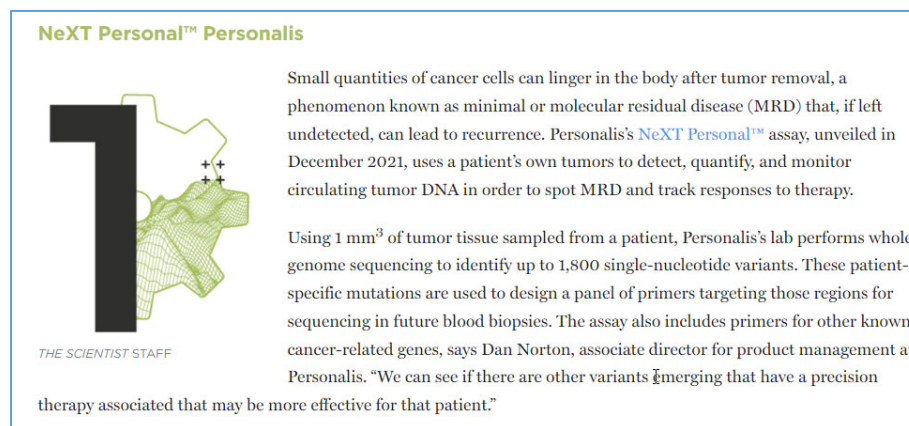
Patent Owner Personalis Inc. (“Personalis” or “Patent Owner”) submits this Preliminary Response to Petitioner Foresight Diagnostic Inc.’s (“Foresight” or Petitioner”) Petition for *Inter Partes* Review of U.S. Patent No. 11,408,033 (“Petition”). For the reasons stated below, the Board should not institute review.

The instant case is related to IPR2023-00224, where Petitioner attacks the claims of U.S. Patent No. 11,384,394 (“the ’394 Patent”). The claims of the ’033 Patent recite an approach that shares several similarities with the approach claimed in the ’394 Patent. Like the ’394 Patent, the claims of the ’033 Patent represent a novel approach to cancer detection and monitoring based on the use of capture probes and serial DNA sequencing that was far ahead of its time when the invention was made in 2013, and that continues to receive acclaim to this day.

Briefly, the claims of the ’033 Patent recite a specific process that starts with producing capture probes directed to polymorphisms that are associated with a disease or indication. *See* Ex. 1001, claim 1. By applying these probes to a nucleic acid sample, one can collect nucleic acid that is likely to include disease-causing mutations in, for instance, the tumor genome of a cancer patient. DNA sequencing can then be used to identify the specific mutations at issue in the patient. Once these mutations have been identified, the process of capturing DNA with capture probes

and sequencing can be repeated over time, allowing one to monitor disease over time. *See id.*

By using this approach, Patent Owner was able to pioneer new frontiers in techniques for detecting and monitoring disease in cancer patients with utmost sensitivity. The Personalis assay that practices the '033 Patent, for instance, can detect tumor DNA in blood plasma at levels of about one part per million (or 0.0001%). Recently, *The Scientist* magazine hailed the Personalis assay as the #1 scientific innovation of 2022:



See Ex. 2001.

Now, years after the Personalis inventors conceived of their approach, Petitioner contends that the '033 Patent is invalid in view of prior art. Petitioner relies primarily on Forshew as an alleged anticipatory reference. Forshew, however, does not even teach the most basic element of the claim, specifically, the use of capture probes. Rather than using capture probes, Forshew relies upon PCR, a

method that Patent Owner's own prior art distinguishes over and over. Indeed, Forshew itself distinguishes its PCR-based approach from the claimed capture probe methods of the '033 Patent, criticizing the use of "expensive custom-designed probes" and asserting that they "are difficult to implement on a routine basis." Ex. 1030 at 10.

While Petitioner's expert attempts to conflate PCR and capture probes, this theory is overwhelmingly contradicted by the remaining evidence. And, even if there were some merit to the contention that capture probes and PCR are the same, this is irrelevant because Forshew does not even use PCR to target polymorphisms, as recited in the '033 Patent claims. Rather, Forshew targets a large contiguous section of the genome. At bottom, Forshew is nothing like the claimed invention.

The backup obviousness theories that Petitioner presents are just as defective as its anticipation theory. Effectively acknowledging that its anticipation theory based on Forshew fails, Petitioner relies, for instance, on Wagle as allegedly disclosing capture probes. Yet, Wagle is simply an early rudimentary report on the use of massively parallel sequencing to analyze a tumor. Petitioner acknowledges that "a POSA would note that Wagle does not expressly disclose repeating steps (b)-(c) on a subsequently obtained sample from said individual...." Petition at 67. In other words, Wagle bears little, if any, relevance to the claimed inventions of the '033 Patent.

Likewise, the Chan reference relied upon by Petitioner is the exact opposite of the claimed personalized approach. Chan, in fact, criticizes personalized approaches of the claimed invention because they “might miss important information regarding imminent relapse or disease progression:”

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.

Ex. 1008 at 222. Such guidance in Chan precludes any contention that it can form the basis of an obviousness challenge against the '033 Patent.

The Board should not institute review of the '033 Patent.

II. BACKGROUND

A. The '033 Patent

The '033 Patent relates to systems and methods for sample processing and analysis to aid in the diagnosis, monitoring, treatment, and prevention of diseases.

Ex. 1001 at Abstract. Representative claim 1 recites:

1. A method for analyzing nucleic acid samples 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, Claim 1.

The claimed method first requires producing capture probes, with the aid of a computer processor, that hybridize to polymorphisms, which “are based on or extracted from one or more databases” and are “observed in a population of one or more samples.” *Id.* at 2:47-54. The polymorphisms are in sequences encoding genes with known biomedically interpretable variants—*i.e.*, are known to be “associated with a disease or indication,” such as “cystic fibrosis (CF) mutations, muscular dystrophy mutations, p53 mutations, Rb mutations, [or] cell cycle regulators.” *Id.* at 27:19-31.

Those capture probes are then contacted with a nucleic acid sample, which may comprise, for example, blood from an individual suffering from cancer. Ex. 1001 at 38:56-39:13, 55:51-52. The selective capture probes are used to generate a subset of nucleic acid molecules—*i.e.*, selectively collect the polymorphisms for physical collection. *Id.* at 2:46-59, 31:4-32:5. The resulting nucleic acid molecules are then sequenced to analyze the nucleic acid sample. *Id.* at 15:52-16:5. Finally, the steps of using capture probes to selectively collect the polymorphisms and sequencing the polymorphisms are repeated on subsequently obtained biological samples from the same individual. *Id.* at 5:9-21.

By analyzing the results of the first and subsequent sequencing assays to determine if the polymorphisms are present in the patient's sample, a medical provider may determine whether a patient's cancer has returned or whether a patient is in remission. *Id.* at 55:38-50 (“Predicting, diagnosing, and/or prognosing a status or outcome of a disease in a subject may comprise diagnosing a disease or condition, identifying a disease or condition, determining the stage of a disease or condition, assessing the risk of a disease or condition, assessing the risk of disease recurrence...”).

The '033 Patent explains that prior art methods based on whole genome sequencing alone were not only costly, but could “fail to capture many biomedically important variants.” *Id.* at 1:23-34. Specifically, standard methods often “fail[ed]

to target biomedically interesting non-exomic and exomic regions,” and would perform poorly in certain regions of the genome. *Id.* The inventors of the ’033 Patent overcame this problems by using a personalized sequencing assay. Indeed, many of the failures of the prior art methods were due to specific problems that are difficult to address in bulk sequencing, but can “be more adequately addressed by specialized sequencing protocols and technologies.” *Id.* at 70:20-24. The specification is replete with examples.

For example, regions with high GC content have elevated melting temperatures, which results in poor amplification. *Id.* at 71:30-72:40. In standard sequencing, these regions are either skipped or perform poorly. *Id.* But the inventors of the ’033 Patent developed an enrichment process and customized sample preparation and sequencing protocols to specifically improve performance by optimizing temperatures, incubation times, buffers, and enzymes. *Id.*; *see also id.* at Table 11. Another problem that cannot be addressed in standard bulk sequencing is that “[r]epetitive elements in a genome and other genomic regions outside of the exome can be difficult to sequence, align and/or assemble.” *Id.* at 73:18-74:40. In standard sequencing, these regions are skipped or perform poorly. *Id.* But the inventors addressed these problems by developing a specific enrichment pulldown and protocol to extract these regions. *Id.*

Personalis pioneered the use of these and others technique for cancer detection and monitoring that addresses problems and limitations with prior art methods.

B. The Level of Ordinary Skill in the Art

Petitioner proposes an expansive definition for a POSA. Specifically, Petitioner contends that as of January 2013 a POSA would “have had an advanced degree (such as an M.D. or the equivalent of a Ph.D. in a life or physical sciences, engineering, or mathematics discipline), and through further education or postdoctoral experience, an understanding of various sequencing and next generation sequencing methods, sample preparation methods, targeted enrichment methods, bioinformatics methods for interpreting sequencing data, and methods for identifying genetic variants in a sample. A POSA also would have had an understanding of the clinical applications of sequencing technology to conditions associated with nucleic acid variation, such as cancer, non-invasive prenatal testing, and transplant rejection. Additionally, a POSA would have had an understanding of cancer biology as it relates to mutations associated with tumor diagnosis, progression, and treatment, as well as awareness of the various types of mutations that can occur in and influence the course of a patient’s cancer.” Petition at 6 (citing Quackenbush ¶¶ 35-38).

By its definition, Petitioner attempts to imbue the POSA with an array of different skills and competencies solely to artificially shore up its obviousness case.

As documented below, however, Petitioner's definition for a POSA fails to accurately reflect the nascent state of the field of using next generation sequencing for cancer analysis at the time of the January 2013 priority date. Petitioner's proposed definition is overwhelmingly contrary to record evidence and should not be adopted.

Indeed, Petitioner's own expert, Dr. John Quackenbush, apparently does not even agree with Petitioner's definition. This is clear from a recent *inter partes* review related to the use of DNA sequencing for cancer testing, where Dr. Quackenbush presented opinions on behalf of a cancer diagnostics company known as Guardant Health.

There, Guardant Health's opponent argued that a POSA in 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," and that a POSA also "would have had 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 sequencing reads onto genomes, and methods for identifying genetic variants in a sample." *Foundation Medicine, Inc. et al v. Guardant Health, Inc.*, IPR2019-00634, Ex. 2026 ¶ 22 (P.T.A.B. Dec. 4, 2019).

While this definition from the *Guardant Health* case overlaps significantly with the definition for a POSA that Petitioner now advances here, it actually imputes to a POSA *fewer* specific skills and competencies relative to Petitioner's proposed POSA.

Yet, when testifying on behalf of Guardant Health, Dr. Quackenbush criticized this definition, opining that it credited a POSA with *too much* knowledge and *too many* skills. As Dr. Quackenbush opined, this definition erroneously “describes a person of *exceptional* skill, not a person of ordinary skill....” *Id.* ¶ 23. The Board should reject Petitioner's inflated definition of a POSA based on Dr. Quackenbush's own statements, which confirm that a POSA in January 2013 would not have such advanced knowledge in the field. Indeed, Petitioner's own cited art demonstrates that Dr. Quackenbush's original opinions from the *Guardant Health* case regarding the level of ordinary skill were correct.

Chan, for example, is a 2013 reference that describes only a “shotgun” approach to DNA sequencing as a “valuable approach for studying tumoral heterogeneity,” and otherwise states that the “advent” of NGS has prompted some investigation into incorporating that approach. Ex. 1008 at 211. The authors of Chan characterize the use of NGS for cancer as in its earliest stages. *Id.* at 223; *see also* Ex. 1004 at 47-48 (A “few groups have proposed alternative sequencing methods that determine the sequence of the DNA template by the distinct chemical

and/or physical properties of each nucleotide without the use of polymerase or fluorescent labels....However, difficult engineering challenges must be overcome before these technologies could become commercially viable.”).

Likewise, Lo describes the use of NGS to “profile the cancer genome” as a new approach that experts in the field were merely investigating as of January 3, 2013. Ex. 1017 at 2. It further describes the main difficulties that experts were still encountering at that time, including figuring out “how to handle the massive amount of sequencing data.” *Id.* at 3.

Forsheew, a reference from 2012 that Petitioner relies upon here, eschewed the use of capture probes in the context of cancer monitoring, complaining that they were “expensive.” Ex. 1030 at 10. More generally, Forsheew discusses how “identifying mutations across sizeable genomic regions spanning entire genes at an AF as low as 2%, or in few nanograms of fragments template from circulating DNA, has been more **challenging**.” *Id.* at 1; *see also* Ex. 1031 at 2 (discussing “the key challenges in cancer genome sequencing” as of October 2010).

Even after January 2013, research in the field of DNA sequencing, especially in the field of cancer research, had not yet solved the problems and challenges associated with sequencing large, complicated datasets using predictive, computational approaches and other methods. Ex. 2002. Indeed, by 2014, “a standard pipeline for the analysis of high-throughput cancer genome sequencing data

ha[d] yet to emerge,” and survey studies could “include only a fraction of possible approaches.” *Id.* at 2. A POSA as of January 2013 could not have been expected to have had knowledge of such nascent approaches, especially in the context of cancer research, when the experts in the field had not yet overcome the associated challenges and were concerned that targeted approaches would struggle with tumor heterogeneity. *See* Ex. 2007 at 7 (“these data support the use of unbiased shotgun MPS approaches to ctDNA analysis”).

The Board should therefore reject Petitioner’s proposed definition of the level of ordinary skill in the art, and instead adopt a definition that recognizes that techniques for cancer detection and monitoring based on DNA sequencing were only beginning to be developed and came with challenges as of January 2013. Specifically, the Board should define the POSA to be a scientist or researcher with a Ph.D. in the biological sciences or a related field. While 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.

C. The Prior Art

The Petition asserts the following prior art:

- Ex. 1030, Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA” (“Forshaw”)
- Ex. 1033, “High-Throughput Detection of Actionable Genomic Alterations in Clinical Tumor Samples by Targeted, Massively Parallel Sequencing” (“Wagle”)
- Ex. 1008, “Cancer Genome Scanning in Plasma: Detection of Tumor-Associated Copy Number Aberrations, Single-Nucleotide Variants, and Tumoral Heterogeneity by Massively Parallel Sequencing” (“Chan”)

Each of these references is summarized in turn below.

1. Forshaw

Petitioner relies primarily on Forshaw, which is a study describing a method for tagged-amplicon deep sequencing (“TAm-Seq”) of entire genes to detect cancer mutations in circulating DNA. Ex. 1030 at 1. Forshaw explains that individual mutations that are present in circulating DNA at higher allele frequencies (“AF”) and/or comprise a greater percentage of the circulating DNA had previously been

sequenced through targeted methods. *Id.* It explains, “[h]owever, that identifying mutations across sizable genomic regions spanning entire genes at an AF as low as 2%, or in few nanograms of fragmented template from circulating DNA, has been more challenging.” *Id.* The solution, according to Forshew, was the use of TAm-Seq, “which allows amplification and deep sequencing of **genomic regions spanning thousands of bases** from as little as individual copies of fragmented DNA.” *Id.*

TAm-Seq involves the following steps: (1) hybridizing universal primers that span the entire gene in a pre-amplification process; (2) amplifying the template using (single-plex) PCR amplification; (3) attaching sequencing adapters and sample-specific barcodes to the amplicons in a further PCR. *See Id.* at 2, Fig. 1B. Forshew explains that this process involves “DNA molecules that carry mutations...being amplified alongside **wild-type molecules**”—*i.e.*, molecules that do not carry mutations or polymorphisms. *Id.*

In the study described in Forshew, the authors designed 48 PCR primers that were directed to a broad region of the genome encompassing 5995 bases of genomic sequence covering the following 6 genes: TP53, PTEN, EGFR, BRAF, KRAS, and PIK3CA. *Id.* at 3. The authors used TAm-Seq to obtain sequence data for 44 samples, which spanned 43 mutations. *Id.* Thus, rather than “apply[] TAm-Seq to

measure a predefined mutation” in a targeted manner, Forshew describes “screening [for] thousands of possible substitutions.” *Id.*

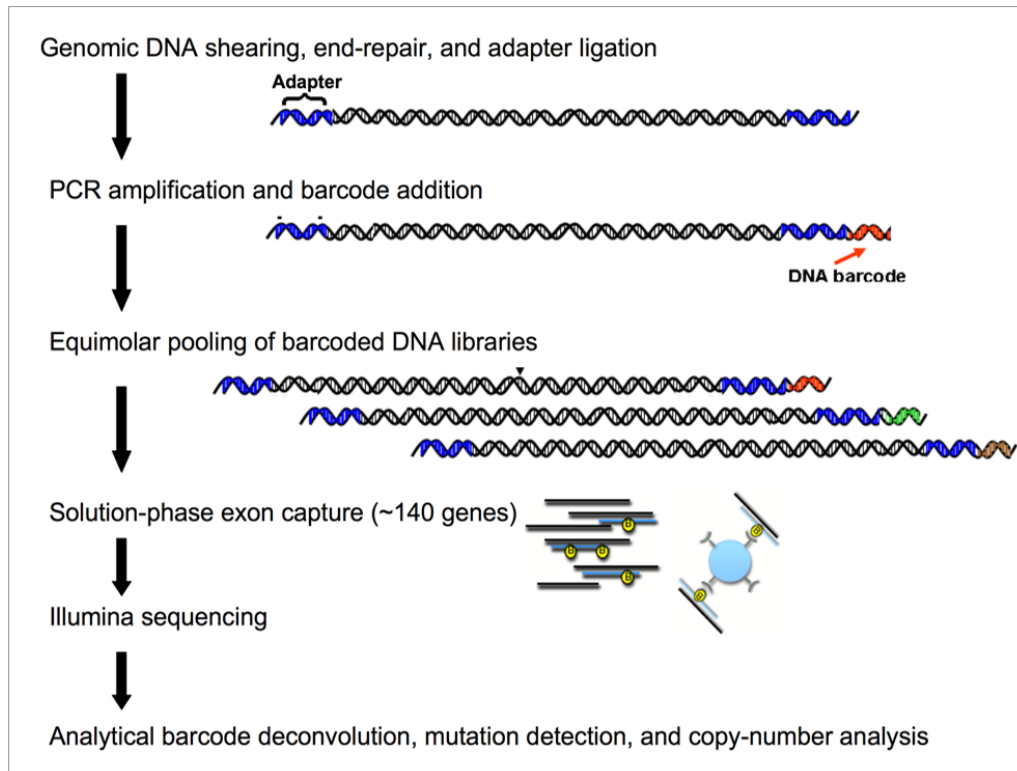
This is consistent with the fact that, instead of targeted capture probes, Forshew uses PCR primers that span broad genomic regions encompassing 5995 bases. *Id.* at 3. Indeed, Forshew distinguishes its PCR-based approach, and specifically disparages the use of capture probes, stating that “expensive custom-designed probes” “are difficult to implement on a routine basis” despite the fact that they “have better analytical sensitivity than currently achieved by TAm-Seq.” *Id.* at 10.

It further distinguishes targeted approaches from its approach, noting that “[a] current limitation of TAm-Seq is the detection limit compared to assays that target individual loci[], which have been shown to detect two to three orders of magnitude lower frequencies.” *Id.* Accordingly, the editor’s summary of the article notes that “TAm-Seq will need to achieve a more sensitive detection limit (<2% allele frequency) to identify mutations in the plasma of patients with less advanced cancers.”). *See* Ex. 1030 at Editor’s Summary.

2. Wagle

Wagle is entitled “High-Throughput Detection of Actionable Genomic Alterations in Clinical Tumor Samples by Targeted, Massively Parallel Sequencing.” Ex. 1033 at Title. Wagle describes an adaptation of exon capture and

massively parallel sequencing to detect genomic alterations in formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples. *Id.* at 84. The method is illustrated below:



Ex. 2003 (Supplementary Fig. S1).

As shown above, the method involves generating libraries containing bar coded DNA from FFPE tumor DNA samples. Following pre-amplification, pools were generated consisting of 12 bar coded tumor DNAs. These DNA pools were subjected to solution-phase hybrid capture with baits targeting all exons from 137 known cancer genes and 400,000 coding bases. Ex. 1033 at 89, 91. Notably, since Wagle was merely a proof of concept (with limited sample size), the method does

not include repeating the targeted assay on additional samples from the patient at an additional time point. Ultimately, Wagle is nothing more than an early attempt at the use of DNA sequencing to characterize tumor DNA at a single time point.

3. Chan

Chan is titled “Cancer Genome Scanning in Plasma: Detection of Tumor-Associated Copy Number Aberrations, Single-Nucleotide Variants, and Tumoral Heterogeneity by Massively Parallel Sequencing.” Chan describes using “shotgun” sequencing to identify single nucleotide variants (“SNVs”) and other aberrations by non-invasively sequencing tumor-derived DNA from plasma rather than DNA derived from tumor tissue that is resected during surgery. Ex. 1008 at 211. Specifically, Chan describes obtaining tumor DNA from plasma and tissue at a single point in time, and, after shotgun sequencing both samples, identifying and comparing the SNVs and aberrations of each. *Id.* at 219-222.

Unlike other, more targeted approaches like Forshew, which Chan criticizes as providing “only a partial glimpse of the tumor genome in the plasma of cancer patients,” Chan’s shotgun sequencing *indiscriminately* sequences a genome. *See* Ex. 1008 at 212. Additionally, although Chan acknowledges that shotgun sequencing can be expensive, it explains that, “[w]ith the continuing and, thus far, rapid reduction in sequencing costs, cost is not expected to be as much of an obstacle

in the near future.” Ex. 1008 at 223. Unlike the claimed invention of the ’033 Patent, Chan never uses any technique to capture or enrich for nucleic acid targets.

III. TECHNOLOGY BACKGROUND

An overview of the patented invention is provided above. *See supra* Part II.A **Error! Reference source not found..** For the purposes of the instant preliminary response, additional information regarding the distinction between capture probes and PCR primers is helpful.

The patented invention claims the use of capture probes. Capture probes are short sequences of nucleic acids that physically “capture” nucleic acid molecules of interest. Specifically, capture probes hybridize to complementary sequences of other nucleic acid molecules. Ex. 1001 at 31:24-27 (describing that capture probes comprise “a nucleic acid binding site that hybridizes to at least a portion of the one or more nucleic acid molecules....”). This hybridization allows for the physical “capture” of molecules so that they may be analyzed. *Id.* at 32:26-34 (“[B]y contacting the nucleic acid sample with one or more capture probes to produce 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 acid molecules.”).

Polymerase Chain Reaction (“PCR”) is a “presequencing sample preparation technique” that results in amplification of a sample through the use of PCR primers.

Ex. 1007 at 112. PCR primers are short nucleic acid sequences that hybridize to complementary sequences of other nucleic acid molecules. *Id.* Unlike capture probes, however, PCR primers do not capture the molecules for physical collection. Rather, PCR primers provide the starting point for replication of the sample. *See id.*

IV. CLAIM CONSTRUCTION

For the reasons stated below, the Board should adopt Patent Owner's below proposed construction of "capture probe."

A. "capture probe"

Petitioner contends that a POSA would have understood the term "capture probe" to encompass at least "PCR primer capture probes and solution-based hybridization capture probes (e.g., biotinylated oligonucleotide baits)." Petition at 17 (citing Quackenbush ¶¶98-104). Petitioner's proposed construction, however, is an unsupported attempt to read the claims on to the prior art Petitioner has identified. Petitioner seeks to lump together capture probes and PCR primers, two distinct and functionally different components for two different techniques. As proven below, the term "capture probe" should be construed to mean "a nucleic acid sequence that hybridizes to target DNA to capture the DNA for physical collection; not a primer for amplification." This construction is supported by extensive evidence in the specification as well as extrinsic evidence.

Beginning with the intrinsic evidence, the specification describes “capture probes” as performing the function of hybridizing to target DNA to capture the DNA for physical collection. Specifically, the specification describes capture probes as comprising “a nucleic acid binding site that hybridizes to at least a portion of the one or more nucleic acid molecules....” Ex. 1001 at 31:24-29; *see, e.g., id.* at 22:65-23:8 (“Capture probes may hybridize to one or more nucleic acid molecules in a sample....”); *id.* at 7:57-63; *id.* at 14:48-58.

Importantly, the specification goes on to describe precisely *how* capture probes are used to capture DNA for physical collection. *Id.* at 32:26-34 (“methods disclosed herein may comprise producing two or more subsets of nucleic acids...by contacting the nucleic acid sample with one or more capture probes to produce 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 acid molecules.”).

In contrast, the specification never describes captures 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. *See e.g., id.* at 23:23-36 (“The methods disclosed herein may comprise one or more labels. The one or more labels may be attached to one or more *capture probes*, nucleic acid molecules, beads, *primers*, or a combination thereof.”); *id.* at 32:56-60 (“The assays may comprise one

or more techniques, reagents, *capture probes*, *primers*, labels, and/or components for the detection, quantification, and/or analysis of one or more nucleic acid molecules.”); *id.* at 41:33-36 (“The *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.”).

Moreover, several embodiments describe the use of capture probes as a separate step that occurs after the step of amplification using primers. *See e.g., id.* at 64:29-43 (“The ligated DNA was amplified by adding 25 µL of 2x kappa hifi polymerase and 5 µL of *primer* to each ligated DNA sample and by running a PCR with 8 cycles.... Hybridization reactions were performed on the ESP, HGCP, and LRP samples using ESP, HGCP and LRP *specific capture probes*.”); *id.* at 65:38-50, 66:53-67.

Petitioner’s proposed construction is also contradicted by the prosecution histories of two patents from the same family as the ’033 Patent, wherein the patent examiner acknowledged that capture probes were different from PCR primers. *See Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1349 (Fed. Cir. 2004) (“[W]e have held that the prosecution history of one patent is relevant to an understanding of the scope of a common term in a second patent stemming from the same parent application.”). During the prosecution of Pat. Appl. No. 14/810,337,

which issued as U.S. Patent No. 10,266,890, the examiner rejected then pending claims (31-33, 37-43, and 46) as being anticipated by Craig et al. (Nature Methods 2008 5:887-893). The examiner stated that Craig taught the amplification of particular genomic regions using “primers *specific* to said different genomic region.” Ex. 2004 at 36. At that time, the claims did not specify how the different subsets were created. The examiner also cited Boers et al., PLoS One 2012 7(7):e39630 as pertinent because “it anticipates at least claim 31 in a similar way as the Craig reference.” *Id.* at 40.

During a phone interview, the examiner appeared to erroneously equate primers with probes. *See id.* at 17 (Applicant-Initiated Interview Summary) (“The examiner pointed out that amended claim 31, as currently proposed, would not distinguish over Craig et al. because the amplification primers used by Craig et al. could be reasonably interpreted as ‘probes’ as currently recited in the claim”). In response to the Examiner’s rejection, the applicant amended the claims to recite “pulldown probes” noting that the “‘primers’ of Craig are not pulldown probes . . . Craig nowhere teaches or discloses using probes for pulling down sequences from a solution for enrichment.” *Id.* at 25. In view of the amendment, the examiner allowed the claims. *Id.* at 9 (Notice of Allowance).

Similarly, during prosecution of Pat. App. No. 15/996,215 (which issued as U.S. Patent No. 10,415,091), the examiner relied on the Boers reference to reject

then pending claims 1, 4-14, 18, and 24-25. Boers disclosed using “*primers* that are specific for each gene of the bacterial species under study. These target-specific primers are provided at the 5’ end with universal tails.” *See* Ex. 2005 at 19.

In response, the applicant amended the claims to recite “pulldown probes that selectively enrich for one or more features....” The applicant noted that “[t]he ‘primers’ of Boers are not pulldown probes.” *See id.* at 19, 24; *see also id.* at 31 (summary of interview) (“it was agreed that the feature of using pulldown probes to selectively enrich, when the selectively enriched first and second subsets of nucleic acids differ by the recited ‘one or more features’, would distinguish over the Boers reference.”). In view of this amendment, the examiner allowed the claims. In other words, the examiner explicitly recognized the distinction between capture probes and primers.

Extrinsic evidence in the form of Petitioner’s own record evidence confirms the understanding that capture probes and PCR primers are different—not overlapping—technologies. For example, the Petition includes an article by Mamanova et al. *See* Ex. 1007. The Mamanova article notes that the “specificity of **PCR** will almost certainly always exceed that of **hybrid capture**, and its uniformity may never be matched by either **hybrid capture** . . . the chief advantage of **these alternative methods** is their ability to capture large target regions in a single experiment, **more rapidly and conveniently than PCR.**” *Id.* at 117.

Further illustrating that hybrid capture probes and PCR primers are different methods, Mamanova establishes that the suitability of a particular target enrichment technique depends on a combination of target size, the number of samples, and whether or not sample multiplexing is required. *See id.* at 112, 113, Fig 2. For instance, conventional PCR is not suitable to target genomic regions that are several megabases in size because of the high cost of primers and reagents and the DNA input requirements, particularly in large sample sets. *Id.* at 114 (citing Fig. 2). Whereas, solution capture yields superior sequence coverage of the target regions for projects involving target sizes of 3.5Mb. *See id.* at 114. Finally, the Gnirke reference also acknowledges the distinction between capture probes and PCR primers. Ex. 1005 at 187 (“One advantage of hybrid selection is that long *capture probes* are more tolerant to polymorphisms than the *shorter sequences typically used as primers for PCR* or multiplex amplification.” *Id.*

In view of the intrinsic and extrinsic evidence, the Board should adopt Patent Owner’s proposed construction of capture probe.

V. PETITIONER HAS FAILED TO CARRY ITS BURDEN OF PROVING THAT THERE IS A LIKELIHOOD THAT ANY CHALLENGED CLAIMS IS UNPATENTABLE

A. Forshaw Does Not Anticipate The '033 Patent Because It Does Not Teach Key Elements Of The Claimed Invention (Ground 1)

Petitioner alleges that claims 1–7 and 10-23 of the '033 Patent should be cancelled as anticipated by Forshaw. Petition at 24. This argument fails at least because Forshaw does not disclose use of capture probes, a key element of the invention. In fact, Forshaw teaches away from using capture probes. Given these deficiencies, Forshaw fails to teach the subsequent steps of the claimed invention.

1. Forshaw Does Not Disclose Using “Capture Probes”

Forshaw does not disclose “producing...capture probes” as recited in step (a) of claim 1 of the '033 Patent. Ex. 1001, element 1(a). Instead, Forshaw teaches away from the use of capture probes. As detailed above, the patent specification describes “capture probes” as performing the function of hybridizing to target DNA to capture the DNA for physical collection. *See* Sections III, VIA. And claim element 1(a) requires that the capture probes *hybridize to a plurality of polymorphisms*. *Id.* As explained below, Forshaw does not teach either of these aspects of the claim element.

First, the method disclosed in Forshaw does not use capture probes, and Petitioner cannot contend otherwise. Indeed, Forshaw only references capture probes to criticize targeted sequencing approaches that employ capture probes.

Specifically, Forshew states that “expensive custom-designed probes” are “difficult to implement on a routine basis.” Ex. 1030 at 10.

Rather than address this express teaching away, Petitioner conflates capture probes with PCR primers, asserting that “Forshew discloses the design and use of ‘capture probes’ in the form of PCR primers.” Petition at 30; *see also* Ex. 1020 (Quackenbush Decl.) ¶ 121; *id.* ¶ 110 (claiming that “Forshew’s primers are ‘capture probes’). But, as discussed above, PCR primers are different from capture probes, and a teaching of one does not amount to a teaching of the other.

PCR primers perform a different function than capture probes. Capture probes match the target sequence to capture templates from DNA molecules for physical collection. *See* Ex. 1005 at 182. PCR primers, on the other hand, are small fragments of single-stranded DNA designed to bind specifically to a single region in the genome to allow for ***amplification*** of the diagnostic target area. Primers do not capture a target nucleic acid for the purpose of ***collecting*** it, but are rather short nucleic acids that hybridize to a target and allow for DNA synthesis to be initiated so that the target can be ***copied***.

As documented above, the ’033 Patent describes “primers” and “capture probes” as distinct concepts. *See supra* Part IV.A. For example, the specification states that the “***capture probes, primers***, labels and/or beads may comprise one or more nucleotides.” Ex.1001 at 41:33-34. Moreover, other references in the petition

identify PCR primers as being used to prepare the capture probes, noting that “to prepare the *bait* (‘capture probe’), we *amplify* the complex pool of synthetic oligonucleotides twice by *PCR*.” Ex. 1005 (Gnirke) at 187. The Gnirke reference further acknowledges the distinction between capture probes and PCR primers, noting that “[o]ne advantage of hybrid selection is that long *capture probes* are more tolerant to polymorphisms than the *shorter sequences typically used as primers for PCR* or multiplex amplification.” *Id.*

Second, even if PCR primers were capture probes—which they are not—Forsheiw does not disclose designing primers that *hybridize to polymorphisms* of known biomedically interpretable variants, as required by element 1(a). The primers in Forsheiw span a broad region of the genome encompassing 5995 bases of sequence covering the following 6 genes: TP53 and PTEN, and selected regions in EGFR, BRAF, KRAS, and PIK3CA. Ex. 1030 at 3. The primers generate amplicons that tile regions of interest in short segments of about 150-200 bases incorporating universal adapters. *Id.* at 3. Forsheiw never once discloses that these primers hybridize to polymorphisms, nor does it ever identify any particular polymorphism(s) of interest. Forsheiw acknowledges that its approach is not targeted to “measure a predefined mutation” and instead “screen[s] thousands of possible substitutions.” *Id.*

The Petitioner implies that the Forshew primers hybridize to polymorphisms because the “sequenced regions cover mutations that account for 38% of all point mutations in the COSMIC database[.]” Petition at 31. But the fact that the primers might result in amplification (and subsequent sequencing) of regions that cover polymorphisms does not establish that the primers hybridize to the polymorphisms. Indeed, primers by design indiscriminately result in amplification of any and all sequences that are downstream from where the primer hybridizes. Accordingly, the sequenced regions in Forshew cover not only polymorphisms, but also vast amounts of non-polymorphic sequence that do not appear in the COSMIC database.

Therefore, Forshew does not disclose claim element 1(a).

2. Forshew Does Not Teach Steps (b)-(d) Of Claim 1 Of The '033 Patent

Forshew does not disclose steps (b)-(d) of claim 1 of the '033 Patent, each of which require the use capture probes. *See* Ex. 1001.

Step (b) requires “contacting said nucleic acid sample with said plurality of capture probes produced in (a).” Ex. 1001. Forshew does not disclose this step because it does not disclose “capture probes” for the reasons explained *supra* Section.IV.A.1.

Step (c) 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

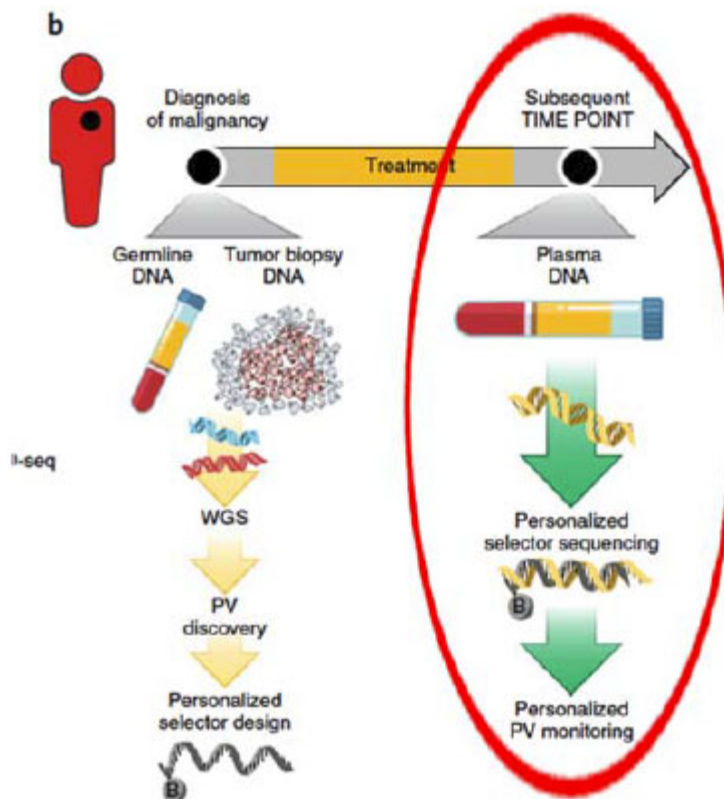
comprising a nucleic acid sequence[.]” Ex. 1001. Forshew does not disclose this step because it does not disclose performing a sequencing assay on a subset of molecules that are generated from step (b). Specifically, the sequencing assay disclosed in Forshew is conducted—not on molecules that were captured by contacting the capture probes to the nucleic acid sample—but on molecules that result from the PCR amplification reactions. Ex. 1030 at 2 (discussing sequencing of “amplicons” resulting from PCR).

Petitioner contends that “Forshew’s disclosure of PCR reactions using the primer probes, discussed above for step (b), creates a subset of nucleic acid molecules (*i.e.*, amplicons targeted by the primer probes) which are then subjected to the ‘sequencing assay’ of step (c).” Petition at 34-35. But Petitioner provides no evidentiary support for this leap.

Petitioner’s only support is Dr. Quackenbush’s Declaration, which parrots Petitioner’s assertion. Ex. 1020 ¶ 127 (“Forshew’s disclosure of PCR reactions using the primer probes...creates a subset of nucleic acid molecules (*i.e.*, amplicons targeted by, and generated through the use of, the primer capture probes) which are then subjected to the “sequencing assay” of step (c).”). *Id.* But declarations that “merely offer[] conclusory assertions without underlying factual support and repeat[], *verbatim* Petitioner’s conclusory arguments” are “giv[en] little weight. *In re Xerox Corp., et al.*, IPR2022-00624, Paper 12 at 5 (P.T.A.B. Feb. 10, 2023); *see*

also In re Xerox Corp., et al., IPR2022-00624, Paper 9 at 16 (P.T.A.B. Aug. 24, 2022) (Petitioner’s expert “offers only a *verbatim* restatement of the assertion being supported, without any supporting evidence or technical reasoning....This is particularly problematic in cases where, like here, expert testimony is offered not simply to provide a motivation to combine prior-art teachings, ***but rather to supply a limitation missing from the prior art.***”); (37 C.F.R. § 42.65(a) (“Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.”)).

Petitioner also attempts to support its position by relying on a faulty reading of Patent Owner’s complaint alleging that Petitioner’s sequencing assay infringes step (c). Petitioner presumes that this allegation is based on a contention that “Forshew will involve some nucleic acid molecules that are ultimately not sequenced because of stochastic losses in sequencing and the fact that only an aliquot (*i.e.*, portion) of the sequencing library is loaded into the sequencer, thereby satisfying the ‘sequencing assay on a subset of nucleic acid molecules generated from said nucleic acid sample in step (b)’ language of claim 1.” Petition at 35. But Patent Owner makes no such presumption in its complaint. Rather the complaint merely states that Petitioner’s accused product “conducts a sequencing assay on a subset of nucleic acids generated from the plasma DNA sample” based on the below diagram:



Ex. 1037 at 4-5.

Indeed, the method of Forshew, which the authors admit “screen[s] thousands of possible substitutions” rather than a “predefined mutation” (Ex. 1030 at 3), is distinguishable from Petitioner’s accused product, which Petitioner markets as a targeted test “custom designed for each patient to track phased variants identified from tumor tissue samples using whole genome sequencing.” Ex. 2006.

Finally, step (d) recites “repeating steps (b)-(c) on a subsequently obtained biological sample from said individual.” Forshew does not disclose this step because it never conducts steps (b) and (c) to begin with, let alone repeats them.

B. Petitioner Fails To Demonstrate That The Claims Are Unpatentable Over The Combination Of Forshew And Wagle (Ground 2)

Petitioner alleges that claims 1–23 of the '033 Patent are unpatentable because it would have been obvious to combine the teachings of Forshew with the use of hybridization probes (or baits) to capture nucleic acids of interest for subsequent sequencing, as disclosed in Wagle. This argument fails, however, because Forshew specifically teaches away from the use of capture probes, and because a POSA would not have been motivated to combine the two references. Petitioner's hindsight-based arguments fail to demonstrate that the claims are unpatentable. *See, e.g., In re Fritch*, 972 F.2d 1260, 1266 (Fed. 1992) ("It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious.").

1. Forshew Teaches Away From Capture Probes And Wagle Does Not Cure This Deficiency

There would have been no reason to use capture probes instead of the primers of Forshew because Forshew teaches away from capture probes. Specifically, Forshew disparages methods that use capture probes, calling them "expensive" and "difficult to implement on a routine basis." Ex. 1030 at 10. The Petition fails to address or account for these criticisms of capture probes in Forshew.

Wagle does not cure this deficiency. Indeed, while Wagle discusses the use of probes, like Forshew, Wagle does not disclose a targeted approach to capture specific mutations. Rather, Wagle is directed to sequencing approximately 400,000 bases in large, contiguous regions. Ex. 1033 at 84 (“The approach leverages a targeted exon capture technique to enrich for a cancer-relevant genomic territory consisting of 137 genes (~400,000 coding bases).”). Furthermore, 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.” Ex. 1033 at 90.

2. Petitioner Fails To Show Why A POSA Would Have Been Motivated To Combine Forshew And Wagle To Make The Claimed Invention

Even if the combination of Wagle and Forshew had encompassed a disclosure of the claimed capture probes, which it did not, Petitioner’s ground still fails because a POSA would not have been motivated to combine the different methods described in Forshew and Wagle. Specifically, Forshew describes PCR, whereas Wagle describes solution-based hybrid capture. Under the conditions used in the two references, the two approaches are not interchangeable.

Petitioner cites Mamanova for the proposition that hybrid capture and PCR are “two well-known target enrichment strategies” that were known to have

“overlapping applicability.” Specifically, Petitioner cite the figure below from Mamanova:

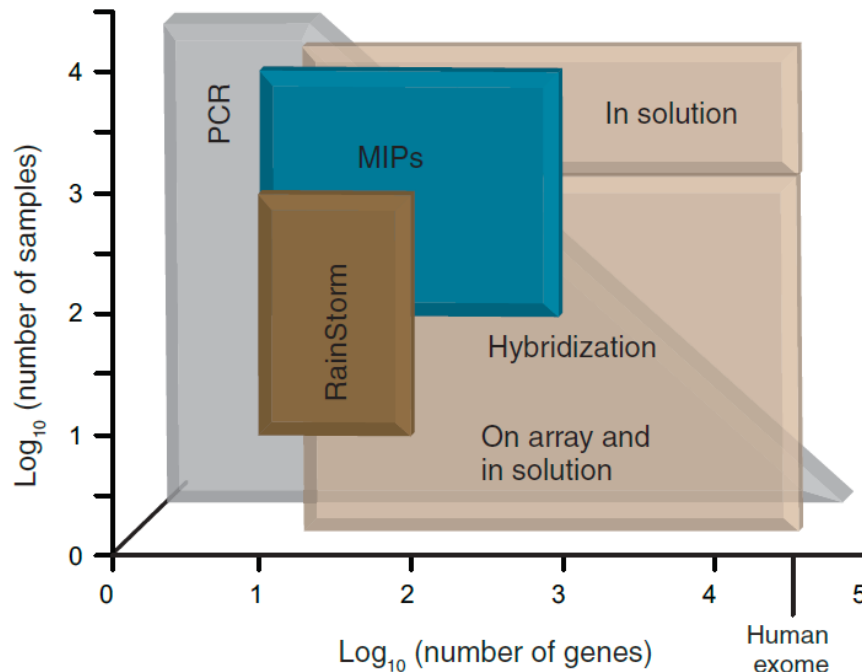


Figure 2 | Suitability of different target-enrichment strategies to different combinations of target size and sample number. Suitability was estimated from the perspective of the feasibility with which each method could be applied to the various combinations of target size and sample number, rather than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

Ex. 1007 at 113. According to Mamanova, the chart represents the suitability of different target-enrichment strategies depending on the combinations of target size and sample number. *Id.* The x-axis represents the logarithm of the number of genes, and the y-axis represents the logarithm of the number of samples.

The method in Forsheo describes using six genes ($\log(6) = 0.77$). Ex. 1030 at 3 (“We 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).”). According to the chart in Mamanova, Forshew’s method would therefore be suitable only for PCR amplification no matter the sample size. The method in Wagle uses 137 genes ($\log(137) = 2.14$). Ex. 1033 at 84 (“The approach leverages a targeted exon capture technique to enrich for a cancer-relevant genomic territory consisting of 137 genes (~400,000 coding bases).”). Wagle’s method, therefore, would be suitable for both PCR and hybrid capture. A POSA would therefore not consider Forshew’s PCR method interchangeable with Wagle’s method.

C. Petitioner Has Failed To Demonstrate That The Claims Are Unpatentable Over The Combination Of Wagle And Chan (Ground 3)

Petitioner alleges that claims 1–9 and 11–23 of the ’033 Patent would have been obvious based on the combination of Wagle and Chan. Wagle and Chan, however, operate according to fundamentally different principles, and the POSA would not be motivated to combine them at all. Moreover, Wagle and Chan, are simply rudimentary studies regarding the use of sequencing to identify cancer-causing mutations in a tumor. While Chan may offer some vague conjecture about using sequencing to monitor cancer over time, neither Wagle nor Chan actually teach a bona fide method based on serial sequencing assays, as claimed in the ’033 Patent. Wagle and Chan thus cannot possibly render the claims of the ’033 Patent obvious.

1. Wagle And Chan Operate According To Fundamentally Different Principles And The Skilled Artisan Would Not Be Motivated To Combine Them

As documented above, both Wagle and Chan are early studies that describe nothing more than the use of next generation sequencing to analyze a tumor sample at a single time point. *See* Section II.C, V.B. Yet, despite this facial similarity, the approaches adopted in these two studies are diametric opposites.

Wagle, which was published in 2012 before Chan, adopted an approach based on the use of hybrid capture to pre-select roughly 433 kilobases of the genome. *See, e.g.*, Ex. 1033 (“Altogether, these genes comprise 2,372 exons encoding 433,159 bases.”). Wagle’s strategy is to “enrich for a cancer-relevant genomic territory” so as to “reduce the complexity of tumor genomic DNA for clinically oriented sequencing.” *Id.* at 84. In this regard, Wagle reflects a targeted approach to the sequencing of DNA from a tumor.

Chan, on the other hand, discloses an indiscriminate, shotgun sequencing approach with no targeting whatsoever. *See, e.g.*, Ex, 1008 at 223 (The “shotgun sequencing approach we have described . . . In summary we have demonstrated the performance of cancer genome scanning via shotgun sequencing of plasma DNA.”). The authors of Chan were well aware of targeted approaches, like Wagle’s, but specifically rejected them in view of the perceived disadvantages of the targeted approach. For instance, Chan explains that such targeted approaches provide only a

“partial glimpse” of a tumor: “Owing to their targeted nature, the approaches outlined above can provide only a *partial glimpse* of the tumor genome in the plasma of cancer patients.” Ex. 1008 at 212.

Chan likewise criticizes targeted approaches because they “might miss important information regarding imminent relapse or disease progression:”

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 222; *see also id.* at 212 (“For a genomewide view of the tumor genome in the circulation, a nontargeted random—or shotgun—sequencing approach would be desirable.”). Ultimately, Chan characterizes its shotgun sequencing approach as a breakaway from the inferior targeted approaches like those employed in Wagle:

Our data indicate that shotgun sequencing of plasma samples from cancer patients would allow cancer associated copy number aberrations and mutations to be analyzed noninvasively and in a genomewide fashion (Figs. 1 and 4). *This finding is an important step forward from*

previous work, which has generally been focused on detecting a small number of tumor associated genetic changes in plasma (1).

Ex. 1008 at 221.

Given that Chan and Wagle operate according to fundamentally different principles, it makes little sense to believe one would seek to combine these two references. Indeed, to combine the references, one would have to abandon the underlying principle of operation of at least one of them. The law is clear, however, that “[s]uch a change in a reference’s ‘principle of operation’ is unlikely to motivate a person of ordinary skill to pursue a combination with that reference.” *Plas-Pak Indus., Inc. v. Sulzer Mixpac AG*, 600 F. App’x 755, 759 (Fed. Cir. 2015); *see also Apple Inc. v. INVT SPE LLC*, 851 F. App’x 200, 203 (Fed. Cir. 2021) (“Given these disparities, a reasonable fact finder could conclude there was no motivation to combine Keskitalo and Lindell.”).

While Petitioner attempts to portray Wagle and Chan as being similar because they both focus on the use of sequencing for cancer analysis, this “apparent similarity between the prior art references....is an illusion built upon hindsight bias.” *Knauf Insulation, Inc. v. Rockwool Int’l A/S*, 788 F. App’x 728, 733 (Fed. Cir. 2019) (“The key reactants, nature of the reactions, and products of the reactions taught in Helbing and Wallace/Worthington are distinct. The alleged similarity of the references does not support the conclusion that an ordinary artisan would find it obvious to replace

the polyhydroxy component in Helbing with a reducing sugar (thus changing the fundamental teaching of Helbing).”).

If anything, Chan’s repeated identification of the shortcomings of targeted approaches like those of Wagle expressly teaches against any purported combination of Chan with Wagle. “A reference that properly teaches away can preclude a determination that the reference renders a claim obvious.” *In re Mouttet*, 686 F.3d 1322, 1333 (Fed. Cir. 2012). That is the case here.

2. The Combination Of Wagle And Chan Fails To Enable And Teach Serial Sequencing Assays

While the POSA would not have been motivated to combine Wagle and Chan under any circumstances, even if he or she did attempt to combine the references, the result could not possibly be the claimed inventions of the ’033 Patent. This is because neither Wagle nor Chan include sufficient disclosure of step 1(d) of claim 1 of the ’033 Patent, which recites “repeating” the capture probe and sequencing processes in steps (b)-(c) on a “subsequently obtained biological sample from said individual.”

As to Wagle, Petitioner acknowledges that there is no disclosure whatsoever of claim element 1(d), stating that “a POSA would note that Wagle does not expressly disclose repeating steps (b)-(c) on a subsequently obtained sample from said individual....” Petition at 67. Even though there is no hint of such an approach

in Wagle, Petitioner nonetheless suggests that it would have been obvious to add this to Wagle based on Chan.

Chan's method, however, does not use anything like step 1(d) either. As documented above, Chan's method involves nothing more than the application of indiscriminate shotgun sequencing to a tumor sample at a single time point. *See supra* Part II.C.3. As Petitioner states, Chan "discloses 'the use of shotgun massively parallel sequencing (MPS) of plasma DNA from cancer patients to scan a cancer genome noninvasively.'" Petition at 54 (quoting Ex. 1008 art Background). The method disclosed in Chan is solely focused on the initial identification of cancer-causing mutations in a tumor, not monitoring cancer over time.

To nonetheless try and find some disclosure of the repeated use of capture probes and DNA sequencing, Petitioner further asserts that the POSA would be motivated to modify Wagle because Chan "expressly" teaches "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." Petition at 64. Chan, however, does not remotely "expressly" teach such a method, but rather teaches only shotgun sequencing of a tumor sample at a single time point to identify potential mutations. *See, e.g.*, Ex. 1008 at 212 ("In this article, we report the use of shotgun MPS to obtain a

noninvasive, genomewide view of cancer associated copy number variations and mutations in DNA in plasma.”).

Petitioner’s alleged “express” teaching of a method in Chan that involves shotgun sequencing followed by serial monitoring using hybrid capture is derived from nothing more than a speculative passage at the end of Chan about possibilities that one might “envision.” *See* Ex. 1008 at 223.¹

The law is clear, however, that such speculation and conjecture does not establish obviousness. *See, e.g., Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1375-76 (Fed. Cir. 2011) (prior art’s “speculative and tentative disclosure of what ‘might’ or ‘may’ [explain the cause of a desired effect] does not sufficiently direct or instruct one of skill in this art”); *Los Angeles Biomedical Rsch. Inst. at Harbor-UCLA Med. Ctr. v. Eli Lilly & Co.*, 849 F.3d 1049, 1065–66 (Fed. Cir. 2017) (“Indeed, Whitaker makes clear that the observation about “vascular conditioning” and its cause is speculative.... As such, Whitaker’s observation cannot

¹ As the basis for such speculation, Chan cites the Liao reference and a 2012 article from Lo and colleagues, both of which (1) acknowledge that the cost of NGS was, at that time, a challenge for routine clinical applications, (2) utilize capture techniques solely to focus on a limited subset of one or, at most, a few chromosomes specifically relevant to non-invasive prenatal diagnosis.

serve as an express or implicit teaching.”); *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1290 (Fed. Cir. 2006) (“[L]egal determinations of obviousness, as with such determinations generally, should be based on evidence rather than on mere speculation or conjecture.”). Nor do such statements establish that a POSA would have had a reasonable expectation of success in combining these references. *See cf. Los Angeles Biomedical Rsch. Inst. at Harbor-UCLA Med. Ctr. v. Eli Lilly & Co.*, 849 F.3d 1049, 1065 (Fed. Cir. 2017) (remanding Board’s finding of obviousness because Board’s finding of reasonable expectation of success relied on “speculative” and “theorized” statements in asserted reference, which “cannot serve as an express or implicit teaching[.]”); *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1375-76 (Fed. Cir. 2011) (finding that prior art’s “speculative and tentative disclosure of what ‘might’ or ‘may’ [explain the cause of a desired effect] does not sufficiently direct or instruct one of skill in this art”).

Consistent with this, the law is also clear that to “render a claim obvious, the prior art, taken as a whole, must enable a skilled artisan to make and use the claimed invention.” *Raytheon Techs. Corp. v. Gen. Elec. Co.*, 993 F.3d 1374, 1380 (Fed. Cir. 2021). To the extent Chan speculates about serial monitoring of cancer using DNA sequencing, it otherwise includes no experimental protocols, no data, no working examples, and no discussion of the key requirements for such an approach to be successful. There is no direction whatsoever in Chan as to how such an

approach might work. The limited speculation that Chan offers on this approach is drawn from work that had been done in the area of “prenatal diagnosis,” which does not require serial monitoring. *See* Ex. 1008 at 223. Chan cites two publications in this area, neither of which disclose serial monitoring and neither of which Petitioner discusses further. *See id*

This lack of disclosure in Chan is critical because, as documented above, the use of sequencing in the area of cancer analysis was in its earliest stages at the time of the invention of the '033 Patent. *See supra* Part II.B. The POSA at the time of invention would have had little, if any, experience with the relevant technology and tools and would have been uncertain as to the proper approach. *Id.* This is exemplified by Chan itself. While Petitioner contends that Chan could be combined with the Wagle approach based on targeted sequencing, Chan expresses uncertainty as to whether such an approach would even work:

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.

Ex. 1008 at 222. In this regard, the *Wands* factors that are used in assessing enablement uniformly confirm that Chan does not enable the claimed inventions of the '033 Patent.

In sum, Chan neither enables nor teaches an approach based on the serial use of capture probes and sequencing, as recited in step 1(d). Because neither Chan nor Wagle teach or enable this step, their combination cannot render the '033 Patent obvious. *See, e.g., Hyosung TNS Inc. v. Int'l Trade Comm'n*, 926 F.3d 1353, 1360 (Fed. Cir. 2019) (“Hyosung has failed to show that the prior art combination rendered the asserted claims obvious. In particular, Hyosung has failed to show that the alleged prior art combination satisfied the limitation of reading a check's MICR line information ‘regardless of the facing position of the check.’”); *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014) (“We first must determine whether TWi carried its burden to prove that all claimed limitations are disclosed in the prior art.”).

**D. The Petition Fails To Address Secondary Considerations
Supporting The Non-obviousness Of The Claimed Invention**

As explained above, Petitioner has failed to make a *prima facie* showing obviousness under the asserted prior art combinations. Even if Petitioner had made such a showing, however, evidence of secondary considerations must be carefully evaluated to avoid introducing hindsight bias into the obviousness analysis. *See*

Crocs, Inc. v. Int’l Trade Comm’n, 598 F.3d 1294, 1310 (Fed. Cir. 2010). Indeed, evidence of secondary considerations “can be the most probative evidence of nonobviousness in the record,” and “may often establish that an invention appearing to have been obvious in light of the prior art was not.” *Id.* Petitioner failed to address secondary considerations of nonobviousness in its Petition. Petitioner’s failure to consider known evidence of industry praise among other secondary considerations of nonobviousness, dooms its Petition. *Stryker Corp. v. KFX Medical, LLC*, IPR2019-00817, Paper 10 at 28–29 (P.T.A.B. Sept. 16, 2019) (“[P]etitions may be denied if they do not address known evidence of secondary considerations.”) (collecting cases).

1. Nexus

To receive “substantial weight in the obviousness analysis, the evidence of secondary considerations must have a ‘nexus’ to the claims.” *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019). Nexus can be shown in two ways. First, a nexus is presumed when the patentee shows that the objective evidence is tied to a specific product and that product “embodies the claimed features, and is coextensive with them.” *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018) (citation omitted). Once the patentee has established a presumed nexus, it falls to the challenger to rebut that presumption with evidence that the secondary considerations of nonobviousness were caused by

“extraneous factors other than the patented invention.” *Id.* Here, Patent Owner is entitled to a presumption of nexus because, as detailed in the attached claim chart, Personalis’s assay embodies claim 1 of the ’033 Patent. Ex. 2008.

Second, even if a presumption of nexus does not apply, “the patent owner is still afforded an opportunity to prove nexus.” *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019). The evidence discussed below independently shows the existence of a nexus. Therefore, Patent Owner has carried its burden.

2. Industry Praise

Personalis’s assay has received widespread industry attention and praise due in part to its sensitivity relative to other methods. *Arctic Cat Inc. v. Bombardier Recreational Prod. Inc.*, 876 F.3d 1350, 1364 (Fed. Cir. 2017) (“Evidence that the industry praised a claimed invention or a product that embodies the patent claims weighs against an assertion that the same claimed invention would have been obvious.”). For example, last December, *The Scientist* magazine published its list of the Top 10 Innovations of 2022. The patented approach disclosed in the ’033 Patent earned the #1 ranking. *See* Ex. 2001.

Indeed, the differences between the method used in Leary (a prior art reference Petitioner asserts in the related IPR2023-00224) and the method claimed in the ’033 Patent yield radically different results. Personalis’s assay can detect tumor in DNA in blood plasma at levels of about one part per million (or 0.0001%).

By comparison, the best sensitivity from plasma DNA in the Leary reference was about 0.3%, which is several hundred times less sensitive than the claimed method. Ex. 1002 at 4 (“However, the fraction of mutant tumor DNA did not reach zero (remaining at 0.3% at day 137), consistent with the fact that this patient had residual metastatic lesions in the remaining left lobe of the liver”). This is shown below by the right most end of the graph in Fig. 4B of Leary:

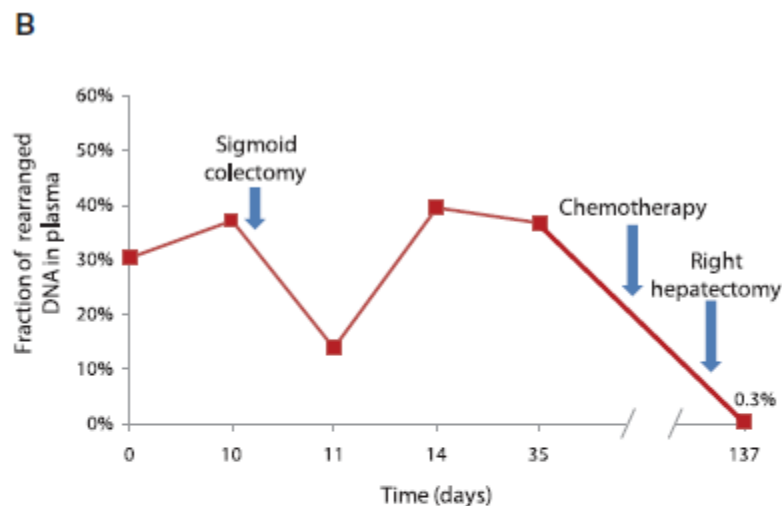


Fig. 4. Detection of tumor-specific rearrangements in plasma of cancer patients. (A) The identified chromosome 4:8 and 16 rearrangements were used to design PCR primers spanning breakpoints and to amplify rearranged DNA from tumor tissue and plasma from patients Hx402 and Hx403, respectively. A plasma sample from an unrelated healthy individual was used as a control for both rearrangements. (B) Plasma samples from patient Hx402 were analyzed at different time points using digital PCR to determine the fraction of genomic equivalents of plasma DNA containing the chromosome 4:8 rearrangement. The fraction of rearranged DNA at day 137 was 0.3%, consistent with residual metastatic lesions present in the remaining lobe of the liver.

Ex. 1002 at Fig. 4. If it were really true that others had conceived of and disclosed the patented techniques “long before” the inventors of the ’033 Patent, as Petitioner

alleges, then this patented technique would not be lauded by independent judges as the top scientific innovation of 2022.

3. Skepticism of Experts

Art cited by Petitioner demonstrates that the industry's experts held skepticism toward solving the difficult challenges of conducting highly sensitive and genome sequencing through use of capture probes. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335 (Fed. Cir. 2016) (“Evidence of industry skepticism weighs in favor of non-obviousness.”). Forshew acknowledges that using capture probes for cancer monitoring was “expensive” and that achieving sensitive monitoring for mutations across entire genes has been “more challenging.” Ex. 1030 at 10; *id.* at 1; *see also* Ex. 1031 (discussing “the key challenges in cancer genome sequencing” as of October 2010). Experts in the field were clearly skeptical of the capture probes Forshew described as “difficult to implement on a routine basis.” Ex. 1030 at 10.

Other references outline clear industry-wide problems with NGS at the time, which were unexpectedly solved by the methods in the '033 patent. For example, a review paper by Anderson et al. emphasizes that “difficult engineering challenges must be overcome before these technologies could become commercially viable.” Ex. 1004 at 48. Further, Lo identifies difficulties facing experts regarding “how to handle the massive amount of sequencing data” when utilizing NGS for profiling cancer genomes.” Ex. 1017 at 3.

These objective real-world evidence supports a finding that the claims of the '033 Patent are nonobvious and, consequently, Petitioner's attempt to demonstrate that a claim of the '033 Patent is unpatentable fails.

VI. CONCLUSION

For the reasons set forth above, Foresight's Petition for *Inter Partes* Review should be denied in its entirety.

Respectfully submitted,

WEIL, GOTSHAL AND MANGES LLP

Dated: March 24, 2023

By: /Derek C. Walter/

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 et seq., the undersigned certifies that this document complies with the type-volume limitations. This document contains 10,295 words as calculated by the “Word Count” feature of Microsoft Word 2016, the word processing program used to create it.

Respectfully submitted,

WEIL, GOTSHAL AND MANGES LLP

Dated: March 24, 2023

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PATENT OWNER'S PRELIMINARY RESPONSE TO PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 11,408,033** is being served on March 24, 2023, via email pursuant to 37 C.F.R. § 42.107 to counsel for Foresight Diagnostics, Inc., at the addresses below:

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