UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS INC.,

Petitioner,

v.

PERSONALIS, INC.,

Patent Owner.

IPR2023-00224
U.S. Patent No. 11,384,394

PRELIMINARY RESPONSE TO PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,384,394

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PATENT OWNER'S EXHIBIT LIST

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2002	Raphael, B., et al., "Identifying driver mutations in sequenced cancer genomes: computational approaches to enable precision medicine," Genome Medicine 2014, 6:5
2003	Swanton, C., "Plasma-Derived Tumor DNA Analysis at Whole-Genome Resolution," Clinical Chemistry 59:1 6-8 (2013)
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	Mardis, E., et al., "Cancer genome sequencing: a review," Human Molecular Genetics, 2009, Vol. 18, Review Issue 2
2007	Declaration of Dr. Henry Morrice Furneaux
2008	Feldman, A., et al., "Discovery of recurrent t(6;7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genomic sequencing," Blood, January, 20 2011 Volume 117, Number 3
2009	Murphy, S., et al., "Mate Pair Sequencing of Whole-Genome-Amplified DNA Following Laser Capture Microdissection of Prostate Cancer," DNA Research 19, 395–406, (2012)
2010	*Curriculum Vitae* of Dr. Henry Morrice Furneaux
2011	"Whole Genome Sequencing," NIH National Cancer Institution, Genetics Dictionary, available at https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/whole-genome-sequencing (last accessed Mar. 23, 2023)
2012	Embodying Product Claim Chart for U.S. Patent No. 11,384,394
2013	"Whole Genome Sequencing," Centers for Disease Control and Prevention, available at https://www.cdc.gov/pulsenet/pathogens/wgs.html (last accessed Mar. 23, 2023)
2014	Schwarze, K; Buchanan, J; Taylor, Jc; Wordsworth, S (May 2018). "Are whole Exome and whole Genome Sequencing

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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. 11,384,394 ("Petition"). For the reasons stated below, the Board should not institute review.

U.S. Patent No. 11,384,394 ("the '394 Patent") represents a novel approach to cancer detection and monitoring based on the use of whole genome 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 '394 Patent recite a specific process that starts with the use of "whole genome sequencing" to query the entire genome of, for instance, a tumor sample taken from a cancer patient. As the '394 Patent explains, prior art methods based on whole genome sequencing alone were costly and could "fail to capture many biomedically important variants," not to mention perform poorly in certain regions of the genome. Ex. 1001 at 1:23-34.

The inventors of the '394 Patent recognized that such problems could be overcome by coupling whole genome sequencing with a subsequent targeted sequencing assay based on first using "capture probes" to collect nucleic acids associated with particular "polymorphisms" that may be associated with, for instance, cancer. *See, e.g.*, *id.* Claim 1. The targeted assay is then repeated using

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capture probes on an additional sample from the patient at an additional time point. *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 ’394 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:

NeXT Personal™ Personalis

THE SCIENTIST STAFF

Small quantities of cancer cells can linger in the body after tumor removal, a phenomenon known as minimal or molecular residual disease (MRD) that, if left undetected, can lead to recurrence. Personalis's NeXT Personal™ assay, unveiled in December 2021, uses a patient's own tumors to detect, quantify, and monitor circulating tumor DNA in order to spot MRD and track responses to therapy.

Using 1 mm^3 of tumor tissue sampled from a patient, Personalis's lab performs whole genome sequencing to identify up to 1,800 single-nucleotide variants. These patient-specific mutations are used to design a panel of primers targeting those regions for sequencing in future blood biopsies. The assay also includes primers for other known cancer-related genes, says Dan Norton, associate director for product management at Personalis. "We can see if there are other variants emerging that have a precision therapy associated that may be more effective for that patient."

See Ex. 2001.

Now, years after the Personalis inventors conceived of their approach, Petitioner contends that the ’394 Patent is invalid in view of prior art. Tellingly, Petitioner does not identify any anticipatory prior art, but at most contends that the ’394 Patent is obvious in view of certain references, including Leary, which is

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Petitioner's primary reference. Yet, as proven herein, Leary is nowhere close to the '394 Patent:

- Rather than teaching whole genome sequencing, Leary teaches at most an approach based on attempting to sequence a subset of the genome that includes certain types of mutations, specifically, chromosomal rearrangements. Nowhere does Leary mention whole genome sequencing. Petitioner's reliance on its expert to contend that Leary teaches whole genome sequencing is, at best, based on a misunderstanding of Leary and, at worst, a distortion.
- Likewise, while the '394 Patent claims recite the use of probes to physically capture nucleic acid molecules, the Leary reference instead adopts a very different approach based on a complicated PCR amplification. While Petitioner attempts to argue that PCR amplification and capture probes are one and the same, this argument is contrary to not just the intrinsic evidence, but also its own extrinsic evidence.
- Finally, while the claims of the '394 Patent require the use of multiple sequencing assays, Leary instead detects nucleic acid targets through the use of PCR amplification. Petitioner attempts to pass off some ancillary uses of sequencing in Leary as corresponding to the claimed

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methods, but the sequencing disclosure relied upon by Petitioner is ***not*** part of Leary's method, and Petitioner presents no argument as to why the POSA would be motivated to substitute Leary's PCR amplification approach with sequencing.

Although Petitioner attempts to plug some of these gaps with a few secondary references, its secondary references simply confirm that Petitioner's obviousness theory is without merit. For instance, while Petitioner contends that Chan can be combined with Leary to render obvious certain claims of the Personalis targeted approach based on the use of capture probes, Chan characterizes such an approach as offering only a "partial glimpse" of a tumor genome in cancer patients. Ex. 1008 at 212. To the extent Chan even considers such targeted approaches, it is only to vaguely speculate about them as future possibilities, thus confirming how ahead of its time the Personalis approach was. Indeed, an article published in the same issue as Chan teaches away from the use of personalized panels to detect recurrence and instead advocates for the continued use of shotgun sequencing so as to overcome the problem of tumor heterogeneity. *See* Ex. 2003 at 7 ("these data support the use of unbiased shotgun MPS approaches to ctDNA analysis").

Consistent with this, the Ley reference relied upon by Petitioner as allegedly rendering obvious claims 1 and 4-5 expressly teaches against targeted approaches of

the type claimed in the ’394 Patent as being “inherently limited” and likely to “miss key mutations:”

> Our results strongly support the notion that hypothesis driven (for example, candidate gene-based) examination of tumour genomes by PCR-directed or capture-based methods is ***inherently limited, and will miss key mutations***.

Ex. 1012 at 70. Petitioner’s contention that prior art which teaches that capture-based methods are “inherently limited” renders obvious methods that rely on capture underscores the weakness of its positions.

The Board should not institute review.

II. BACKGROUND

A. Overview Of The ’394 Patent

The ’394 Patent relates to methods for processing and data analysis of nucleic acid samples for producing biomedical reports and the diagnosis, monitoring, treatment, and prevention of diseases. Ex. 1001 at Abstract. Representative claim 1 recites:

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

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sequence wherein said first sequencing assay comprises whole genome sequencing;

(c) generating a second subset of nucleic acid molecules from a second nucleic acid sample of said individual by contacting said second nucleic acid sample with a plurality of capture probes, wherein said plurality of capture probes hybridize to one or more polymorphisms which are based on or extracted from one or more databases of polymorphisms, observed in a population of one or more samples, or a combination thereof, wherein said first sample or said second sample is obtained from said subject at a first time point;

(d) conducting a second sequencing assay on said second subset of nucleic acid molecules to yield a second result comprising a second nucleic acid sequence;

(e) using said plurality of capture probes to generate an additional subset of nucleic acid molecules from an additional nucleic acid sample isolated from an additional sample obtained from said subject at an additional time point different from said first time point;

(f) conducting a third sequencing assay on said additional subset of nucleic acid molecules from said additional nucleic acid sample to yield a third result comprising a third nucleic acid sequence; and

(g) generating a biomedical report that includes biomedical information of said subject, which biomedical information identifies the presence or absence of said one or more polymorphisms identified by said second result or said third result.

Ex. 1001, Claim 1.

The claimed method first requires obtaining a nucleic acid sample from, for example, tissue or organ of an individual, and generating a first subset of nucleic acid molecules. Ex. 1001 at 38:56-39:13. "The samples disclosed herein may be from a subject suffering from a cancer." *Id.* at 55:51-52. This first subset undergoes

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a first sequencing assay whereby the entirety of the genome is sequenced—*i.e.*, whole genome sequencing. *See, e.g.*, *id.* at 5:57-59.

One or more capture probes are then produced with the aid of a computer processor. The capture probes are designed to hybridize to one or more polymorphisms, which are associated with, for example, cancer, and which "are based on or extracted from one or more databases" and/or are "observed in a population of one or more samples." *Id.* at 2:47-54. The selective capture probes are used to generate a second subset of nucleic acid molecules—*i.e.*, selectively collect the polymorphisms for physical collection. *Id.* at 2:46-59, 31:4-32:5. The second subset is generated from a sample obtained from the same individual at a first time point. *Id.* at 38:40-56. A second sequencing assay is then conducted on this subset to identify the sequences of the polymorphisms. *Id.*

At another time, a third sample is obtained from the same individual. The capture probes are then used to collect a third subset of nucleic acid molecules generated from that sample, and a "third sequencing assay" is conducted on this third subset. Finally, a biomedical report is generated, which contains various information, including the "presence or absence of said one or more polymorphisms identified by" the second or third sequencing results. *Id*. at Claim 1(g). Based on the resulting biomedical reports, the claimed method allows for "predicting, diagnosing, and/or prognosing a status or outcome of a disease or condition in a

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subject." *Id.* at 55:38-50. For example, by analyzing the second sequencing result and the third sequencing result 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.* ("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 '394 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.* For example, Illumina TruSeq exome enrichment followed by Illumina sequencing is a "typical example" of targeted DNA sequencing. *Id.* at 69:49-51. This process, however, can "fail to target many biomedically interesting non-exomic[—polymorphism—]as well as exomic regions for enrichment," "fail to adequately sequence many of the regions it does target," and result in unacceptably high error rates for many of the sequenced regions. *Id.* at 69:51-70:20.

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The inventors of the ’394 Patent overcame these problems by coupling whole genome sequencing with a subsequent targeted sequencing assay. Indeed, many of the aforementioned gaps and 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 ’394 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 other techniques for cancer detection and monitoring that addresses problems and limitations with prior art methods.

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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 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 8 (citing Quackenbush ¶¶ 35, 38-91).

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

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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 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.

Forshew, a reference from 2012, eschewed the use of capture probes in the context of cancer monitoring, complaining that they were “expensive.” Ex. 1030 at 10. More generally, Forshew 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 (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

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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. 2003 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.

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C. The Prior Art

The petition asserts the following prior art:

- Ex. 1002, "Development of Personalized Tumor Biomarkers Using Massively Parallel Sequencing" ("Leary")
- Ex. 1012, "DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome" ("Ley")
- 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")
- Ex. 1009, "Targeted Massively Parallel Sequencing of Maternal Plasma DNA Permits Efficient and Unbiased Detection of Fetal Alleles" ("Liao")

Each of these references is summarized in turn below.

1. Leary

Leary is the primary reference for each of Petitioner's grounds, and is titled "Development of Personalized Tumor Biomarkers Using Massively Parallel Sequencing." Leary describes a method involving ***targeted*** sequencing of chromosomal rearrangements followed by PCR amplification to detect the presence of the "chromosomal rearrangements" in patients. Leary's method was specifically

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directed solely to such chromosomal rearrangements because Leary deemed them to be "exquisitely specific" as a tool for identifying cancer. Ex. 1002 at 1.

Specifically, Leary uses an approach called personalized analysis of rearranged ends ("PARE") to identify chromosomal translocations in solid tumors. First, Leary describes generating so-called "mate-pair" libraries from samples of cancer DNA and normal DNA. *Id.* at 5. The DNA is first sheared into approximately 1.4kb fragments, coupled to beads via an adapter sequence, and hybridized to sequencing primers via the adaptor sequences. *Id.* The resulting library consists of short fragments comprised of DNA segments that were originally separated by approximately 1.4kb—*i.e.*, paired ends or mate pairs. *Id.*

Second, Leary describes that only these 25 bp mate-paired tags—rather than the entire genome—are sequenced. *See id.* Indeed, Petitioner admits that "approaches like those of Leary…have a 'targeted nature,' which may 'provide only a partial glimpse of the tumor genome in the plasma of cancer patients.'" *Id.* (citing Ex. 1008 at 212). The sequences derived from the tumor DNA and normal DNA are then compared to ostensibly identify somatic rearrangements. *Id.*

Third, Leary describes certain steps to confirm whether the identified somatic rearrangements could be detected in circulating DNA from plasma samples. *Id.* at 3, 4. Specifically, Leary describes designing PCR primers to 42 of the paired-end regions and using them "for PCR spanning the putative breakpoints." *Id.* at 3. "The

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candidate rearrangement was confirmed if a PCR product of the expected size was seen in the tumor but not in the matched normal sample." *Id.* at 6.

Entirely separate from the PARE method and PCR detection of rearrangements, Leary explains that the PCR product was also Sanger sequenced in this particular instance for the sole purpose of confirming that the designed primers truly resulted in amplification of the rearrangements and nothing else. *See id.* at 3.

Leary concludes by speculating that the PARE approach could "be used to develop personalized biomarkers based on somatic rearrangements," but that the approach "is not without limitations," including "the cost of identifying a patient-specific alteration," that "some rearranged sequences could be lost during tumor progression," and that "there are clinical settings in where the fraction of any DNA tumors, including rearranged sequences, in the patient plasma is exceedingly small and undetectable." *Id.* at 5.

2. Ley

Ley is titled "DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome," and describes a sequencing approach to identify new candidate genes that may be responsible for cause acute myeloid leukaemia ("AML"). Ley's approach involves parallel sequencing of the patient's normal genome to determine which variants were inherited and which variants are the true somatic mutations in the tumor genome.

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Specifically, Ley describes a study in which both the tumor genome of a single AML patient and the matched non-cancerous genome of the same patient are sequenced. Ex. 1012 at 67. Sequence variants in the tumor genome are identified by aligning the sequence to the human reference genome. *Id.* The identified variants are then compared to the patient's normal sequence, a national database of single nucleotide polymorphisms, and variants reported for two other human genomes. *Id.* Ley reports that somatic mutations were detected in genes not previously implicated in AML pathogenesis. *Id.* This, according to Ley, confirms "the need for unbiased whole-genome approaches to discover all mutations associated with cancer pathogenesis." *Id.*

Petitioner does not argue that Ley discloses "capture probes" as recited in the claims. Instead, Petitioner relies on Ley for the limitation of claim 1(c) of selecting different types of polymorphisms, as well as polymorphisms "based on or extracted from one or more databases of polymorphisms." Petition at 54. Petitioner also relies on Ley to purportedly confirm that a POSA would have been motivated to include known mutations in a panel of polymorphisms for serial monitoring at multiple time points. Quackenbush Decl. at ¶ 217. Like Leary, however, Ley does not mention the use of capture probes.

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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 Leary, 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. Finally, Chan never uses any technique to capture or enrich for nucleic acid targets.

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4. Liao

Liao describes the use of targeted sequencing to selectively amplify or capture targeted regions from a DNA sample pre-sequencing. Ex. 1009 at 93. The reference purports to adopt an in-solution capture strategy for targeted sequencing of plasma DNA, in view of the relatively small amounts of DNA required for this approach. *Id.* (citing Gnirke, Ex. 1005).

III. TECHNOLOGY BACKGROUND

An overview of the patented invention is provided above. *See supra* Part II.A. 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

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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 constructions of “capture probe” and “whole genome sequencing.”

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 21 (citing Quackenbush ¶¶100-106). 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

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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 probe" 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 31:24-27; *see, e.g.*, *id.* at 22:65-23:9 ("Capture probes may hybridize to one or more nucleic acid molecules in a sample…."); *id.* at 7:57-64, 14:48-59.

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

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("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…. Hybrization 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 '394 Patent. *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

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scope of a common term in a second patent stemming from the same parent application."). During prosecution of two patents from the same family as the '394 Patent, for instance, the patent examiner acknowledged that capture probes were different from PCR primers. During the prosecution of 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 p. 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' in Craig are not pulldown probes . . . Craig nowhere teaches or discloses using probes for pulling down sequences from a

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solution for enrichment." *Id.* at 25. In view of the amendment, the examiner allowed the claims. *Id*. at pp. 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. According to the examiner, 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* p. 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

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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 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.

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B. "whole genome sequencing"

The term "whole genome sequencing" should be construed as "a sequencing technique intended to sequence all or almost all of a genome." This construction is supported by the plain language of the term, the specification, and extrinsic evidence.

As to the claim language, the use of the word "whole" to modify "genome" indicates that the ***entirety***—not a part or subset—of the genome must be sequenced. This alone confirms that Patent Owner's construction is correct.

The specification, for its part, consistently distinguishes methods that sequence the "whole genome" from methods that sequence only a portion of the genome, such as the "exome." Ex. 1001, 1:23-34 ("Often, ***whole genome and/or exome sequencing*** using standard sequencing methods performs poorly in content regions having very high CG content (>70%)"). For example, the specification defines "exome" as only part of the genome (*id.*, 26:14-19), and consistently refers to "whole genome sequencing" as a separate category of sequencing than "exome sequencing." *Id.* at 33:21-22 ("The sequencing reactions may comprise whole genome sequencing or exome sequencing."); *id.* at 5:38-59 ("Conducting one or more sequencing reactions comprises ***whole genome sequencing or exome sequencing***.").

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The specification also explains that "genomic regions" can be selected based on various traits, and "may comprise an entire genome or a portion thereof." *Id*. at 24:42-43; *see e.g., id*. at 4:47-52 ("The one or more genomic regions may be selected from the group comprising high GC content, low GC content, low complexity, low mappability, known single nucleotide variations (SNVs), known inDels, known alternative sequences, ***entire genome, entire exome, set of genes***, set of regulatory elements, and methylation state."); *id.* at 17:17-35 (same).

Finally, the P.T.A.B. has previously distinguished between sequencing only parts of a genome and the entire sequence. *See Progenity, Inc. v. Natera, Inc.,* IPR2021-00266, Paper 12 at 13 (P.T.A.B. June 7, 2021) ("Shimkets discloses determining changes in copy number for portions of the genome on a genomic scale, analyzing whole chromosomes, and analyzing whole genomes of cells/individuals."). Indeed, numerous government-led research institutions agree that "whole genome sequencing" involves precisely what its name implies: "A laboratory process that is used to determine nearly all of the approximately 3 billion nucleotides of an individual's complete DNA sequence, including non-coding sequence." Ex. 2011; Ex. 2013; Ex. 2014.

In view of both the intrinsic and extrinsic evidence presented above, whole genome sequencing should be understood as "a sequencing technique intended to sequence all or almost all of a genome."

V. REASONS WHY THE PETITION SHOULD BE DENIED

A. Ground 1: Leary Does Not Render The '394 Patent Obvious

Leary in view of the knowledge of a POSA does not render the challenged claims obvious. Leary describes an older, unused, and less sensitive method than the '394 Patent, and fails to disclose at least: step b) whole genome sequencing; step c) use of "capture probes"; and step d) "conducting a second sequencing assay." Because Leary fails to disclose so many elements of claim 1 of the '394 Patent, it cannot possibly render claim 1 obvious. *See, e.g., Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1062 (Fed. Cir. 2016) (denying JMOL of invalidity, explaining that "Apple also presented substantial evidence on which a reasonable jury could find that the combination of Robinson and Xrgomics failed to disclose every claimed element."); *St. Jude Med., Inc. v. Access Closure, Inc.*, 729 F.3d 1369, 1381 (Fed. Cir. 2013) ("We see no error in the district court's legal conclusion of nonobviousness. Neither Takayasu nor Smiley discloses a balloon configured to operate as a positioning device to prevent a plug from entering a blood vessel as claimed in the Fowler patents. Takayasu discloses no balloon at all, and Smiley discloses a balloon that is used to control the bleeding of a gunshot wound or an abdominal aneurism."); *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993) (reversing obviousness rejection where prior art did not teach or suggest all claim limitations).

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a. Leary Does Not Use Whole Genome Sequencing

Claim 1 of the '394 Patent recites "whole genome sequencing." Ex. 1001 at Claim Element 1(b). As documented above, whole genome sequencing is a method that is intended to sequence an entire genome, which in humans, is comprised of approximately 3.2 billion nucleotides. *See supra* Part IV.B.

Leary does not disclose anything like this. The concept of "whole genome sequencing" had been in the art long before the publication of Leary in 2010. For instance, a 2009 publication by Mardis in the journal *Human Molecule Genetics* includes an entire section related to "Whole Genome Sequencing," citing the Ley publication relied upon by Petitioner as supposedly teaching whole genome sequencing of a leukemia tumor. *See* Ex. 2006 at R165.

Yet, despite the fact that whole genome sequencing was known in the art as an emerging technique, Leary never once refers to "whole genome sequencing." If Leary was truly contemplating a method that would use whole genome sequencing, its authors surely would have referred to "whole genome sequencing." But they never do. Indeed, Petitioner ultimately admits that Leary is not whole genome sequencing, asserting that "approaches like those of Leary…have a 'targeted nature,' which may 'provide only a partial glimpse of the tumor genome in the plasma of cancer patients.'" *Id.* (citing Ex. 1008 at 212).

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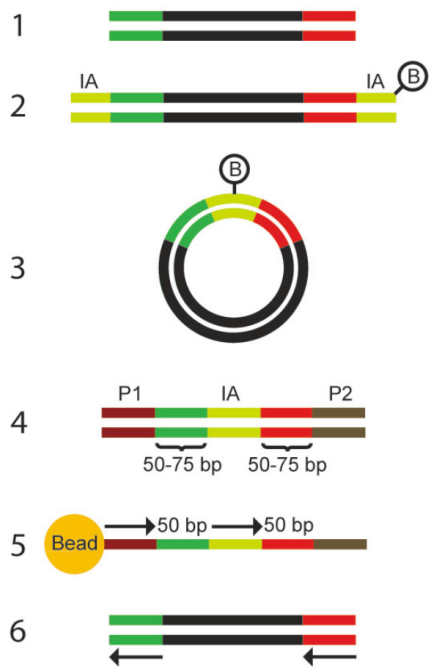
Unable to point to any express disclosure of whole genome sequencing in Leary, Petitioner points to the amount of sequence data allegedly generated in Leary by its mate paired sequencing method. Based on this, Petitioner contends that Leary is, in fact, performing whole genome sequencing, even though Leary never actually says this. *See* Petition at 31-32. Petitioner misunderstands Leary.

The mate pair sequencing process may be illustrated by the figure below:



Ex. 2007 ¶ 27. As the figure shows, mate pair sequencing starts with double-stranded DNA molecules, which are then chemically altered to include a biotin molecule, shown by the circle labeled "B." *Id.* This biotin molecule allows the double-stranded DNA fragments to be linked at their ends, so as to be circularized. *Id.* The circularized DNA fragments are then fragmented into small chunks.

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Id. ¶ 28. The individual chunks that include only the endpoints of the original DNA molecule are then captured (using the biotin molecule). *Id.* These specific molecules are then sequenced. *Id.*

The advantage of the mate pair sequencing approach is that when one sequences the captured molecules, one can rapidly obtain information about the DNA sequences that were at the ***ends*** of an original, larger DNA molecule. As Leary explains, this approach allows one to identify individual molecules having two DNA sequences that should ***not*** appear together on the same molecule, which correspond to mutated "rearrangements" of chromosomes, which can cause cancer. *See, e.g.*, Ex. 1002 at 1 ("The first approach involved searching for tags whose mate pairs were derived from different chromosomes (interchromosomal rearrangements)."). According to Leary, identifying such rearrangements may constitute an "exquisitely specific" indicator of cancer. *See id.* ("Such alterations are not present in normal cells and should be exquisitely specific."). Regardless, the key point is that mate pair sequencing is far from whole genome sequencing, but rather yields sequence information from only a small portion of the genome.

Consistent with this, contemporaneous literature from the relevant time frame expressly distinguishes mate pair sequencing and whole genome sequencing. *See, e.g.*, Ex. 2008 ("Whole-genome sequencing currently demands resources beyond the reach of most cancer investigators….Therefore, we used a mate-pair genomic DNA

sequencing approach for lymphoma translocation discovery."); Ex. 2009 at 405 ("The reduced size of DNA yielded from formalin fixed paraffin embedded (FFPE) tissues (generally <500 bp) also precludes its application to the [mate pair ("MP")] protocol and most [whole-genome amplification ("WGA")] techniques. Interrogation of large genomic rearrangements in DNA from FFPE tissues currently requires whole genome sequencing…. While more robust methods are now available for WGA from FFPE tissues, these methodologies target the smaller species of DNA present in these tissues, generally <500 bp which still precludes their application to current MP protocols.").

Looking closer at Leary confirms that the mate pair sequencing it performed is also not remotely whole genome sequencing. Patent Owner's declarant, Dr. Henry Furneaux, explains in detail why this is the case. *See generally* Ex. 2007.

As Leary explains, it sequences "25-bp mate paired tags." *See, e.g.*, Ex. 1002 at 1 ("Libraries were digitally amplified by emulsion polymerase chain reaction (PCR) on magnetic beads, and *25-bp mate-paired tags were sequenced* using the sequencing by ligation approach") (citations omitted). This means that such "mate pair" in Leary's approach contains about 50 bases of DNA sequence (*i.e.*, 2 times 25-bp mate paired tags). As such, to cover the whole human genome using the mate pair approach in Leary, one would need to sequence about 64 million non-overlapping mate-pairs (*i.e.*, 3.2 billion divided by 50). Ex. 2007 ¶ 29.

But ***none*** of the samples described in Leary have enough non-overlapping mate-paired tags to cover the whole human genome. *Id.* at Table 1; Ex. 2007 ¶ 30 This is confirmed by Table 1 of Leary, which reports a maximum value of 59,019,031 mate-paired tags matching the human genome. This accounts for a maximum of only 2.9 billion bases (59 million times 50-base pairs), which is far less than the 3.2 billion bases actually present in a human genome. Ex. 2007 ¶ 30. In fact, the samples in Table 1 of Leary uniformly involved far less than the 64 million (averaging approximately 40 million across 10 samples), and one of which includes ***only*** 11 million tags. What's more, as Dr. Furneaux explains, the mate-paired tags in Leary are actually ***overlapping.*** Ex. 2007 ¶ 31. The overlap factor is roughly 1.7, meaning that every nucleotide that is sequenced is actually sequenced 1.7 times on average. *See id.* ¶¶ 32-33. Thus, as Dr. Furneaux explains, in the example in Table 1 of Leary involving 59,019,031 mate-paired tags and 2.9 billion bases sequenced, only about 1.71 Gb of the genome is potentially covered. *See id.* ¶ 33. Thus, it is clear that the mate-paired sequencing in Leary—which is the only thing Petitioner relies upon—is not whole genome sequencing.

Significantly, Petitioner offers no explanation for how "mate pair" sequencing corresponds to "whole genome sequencing." Petitioner instead selectively quotes Leary's statement that "[t]he total amount of genome base pairs covered by the mate paired analysis…was 53.6 Gb per sample, or an 18-fold physical coverage of the

human genome" in an attempt to support its position that the method of Leary involves sequencing the entire genome. Petition at 32-33 (Ex. 1002 at 1). But the portions of the quote that Petitioner excluded (indicated in italics and bold) establish that the opposite is true:

> The total amount of genome base pairs covered by the mate paired analysis ***(that is, distance between mate-paired tags × number of mate-paired tags)*** was 53.6 Gb per sample, or an 18-fold physical coverage of the human genome.

Ex. 1002 at 1 (emphasis added).

As the excluded text establishes, and as Dr. Furneaux confirms, Leary's statement that the "total amount of genome base pairs covered by the mate paired analysis" "was 53.6 Gb" or "an 18-fold physical coverage" ***does not*** refer to the sequence information that is generated, but only to the circularized molecules that are generated ***before*** sequencing. Ex. 2007 ¶¶ 34-35. In other words, the circularized molecules "physically" cover the genome 18 times. But Leary does not disclose sequencing the entirety of these molecules so as to sequence the genome 18 times. Rather, in Leary, only the 25 bases at the ***ends*** of the circularized molecules—*i.e.*, the mate pairs—are sequenced. *Id.* The "~1.4 kb" in between the mate-paired tags were not sequenced at all. *Id.* As such, DNA sequence data was only generated for about 3-4% of each molecule. The other 96-97% of each molecule was not sequenced. Given that the molecules that were used in the sequencing covered the

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genome 18 times, and given that only about 3% of each individual molecule was sequenced, one easily sees that ***at most*** about half (*i.e.* 0.03 × 18) of a genome was sequenced in Leary.

It is unsurprising that Leary does not actually sequence the entire genome because, unlike the '394 Patent, Leary is not focused on identifying a broad cross-section of mutation types that may be indicative of disease. Rather, as noted above, Leary focuses solely on a type of mutation referred to as "chromosomal rearrangements," where pieces of chromosomes are missing, duplicated, or moved around. Ex. 1002 at 1. The authors of Leary believed that using such mutations would lead to an "exquisitely specific" technique because they are not present in normal cells. *Id.* Leary therefore describes a sequencing approach that would ostensibly allow it to efficiently identify such mutations, rather than a whole sequencing approach for the purpose of identifying a wide range of mutations.

Leary does not disclose whole genome sequencing, but at most a targeted mate-pair approach that yields information regarding only a fraction of the genome and that gives sensitivity that is only a fraction of that which can be obtained using the claimed method.

b. Leary Does Not Use Capture Probes

Leary does not teach the use of "capture probes" as recited in step (c) of claim 1 of the '394 Patent. Ex. 1001, element 1(c). As detailed above, the patent

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specification describes "capture probe" as performing the function of hybridizing to target DNA to capture the DNA for physical collection. *See* Section III A. And claim element 1(c) requires that the capture probes hybridize to one or more polymorphisms. *Id.*

Leary does not reference a capture probe at all, and Petitioner does not contend otherwise. Instead, Petitioner's expert conflates capture probes with PCR primers, asserting that "Leary designed PCR primers that would hybridize to, and hence 'capture' nucleic acid sequences." Ex. 1020 ¶¶ 113, 131. But as explained above PCR primers are different from capture probes, and a teaching of one does not amount to a teaching of another. *See supra* Parts III, IV.A. Petitioner does not even contend that it would have been obvious to swap out the PCR primers disclosed in Leary with capture probes. This is fatal to Petitioner's burden.

As explained, PCR primers perform a different function from capture probes. Capture probes match the target sequence to capture templates from DNA molecules. *See* Ex. 1005 at 182. Whereas, PCR primers 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***.

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Indeed, the ’394 Patent describes “primers” and “capture probes” as distinct concepts stating, for instance, the “***capture probes***, ***primers***, labels and/or beads may comprise one or more nucleotides.” Ex.1001 at 41:33-34. Moreover, other references cited 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 at 187. The Gnirke reference further acknowledges the distinction between capture probes and PCR primers, stating 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.*

Therefore, Leary only discloses the use of PCR primers, but does not disclose capture probes, as required by the ’394 Patent.

c. Leary Does Not Disclose the Second Sequencing Assay

Leary does not disclose step (d) of claim 1, which recites “conducting a second sequencing assay.” Instead, Leary proposes to detect “chromosomal rearrangements” using PCR. *See, e.g.*, Ex. 1002 at 4 (“PCR amplification of plasma DNA using primers spanning the breakpoints produced products of the expected sizes only in the plasma samples from patients with disease and not in plasma from healthy controls….”); *id.* (“Digital PCR analyses of plasma samples from patient Hx402 indicated that rearranged tumor DNA was detectable at all six time points

analyzed throughout the course of treatment (Fig. 4B)."). Petitioner even acknowledges as much. *See* Petition at 40 ("Leary shows the detection of tumor specific rearrangements in plasma of cancer patient Hx402 'at different time points using digital PCR….'").

Petitioner and Dr. Quackenbush argue that two statements from Leary disclose this limitation:

- "Sanger sequencing of seven PCR products confirmed the rearrangements in all cases tested." Ex. 1002 at 3.
- "Sequencing the PCR products from plasma DNA identified the identical breakpoints observed in the tumor DNA samples." *Id.* at 4.

The sequencing referenced in these statements is not a step in Leary's proposed method. Rather, when put into context, it is clear that the PCR product was sequenced in this particular instance for the sole purpose of confirming that the designed primers truly resulted in amplification of the rearrangements and nothing else, such as a region that is not of interest. *See id.* at 3.

Leary explains that the authors had identified certain putative somatic rearrangements by using the PARE method. *Id.* For "confirmation" (*id.* at 3) and "[t]o determine whether the rearranged sequences could actually be detected in…plasma samples" (*id.* at 4), they used primers of the paired-end regions "for PCR spanning the putative breakpoints." *Id.* at 3, 4. The candidate rearrangement was

confirmed because this resulted in a PCR product of the expected size seen in the tumor but not in the matched normal sample. *Id.* at 3 ("Thirty-five of these (83%) yielded PCR products of the expected size in the tumor samples but not in the normal samples (Fig. 2 and table S3)."); *id.* at 4 ("PCR amplification of plasma DNA using primers spanning the breakpoints produced products of the expected sizes only in the plasma samples from patients with disease and not in plasma from healthy controls (Fig. 4A)."). Leary's proposed method ended there. Indeed, by confirming the PCR product size, Leary had ostensibly achieved its goal of "determin[ing] whether the rearranged sequences could actually be detected in clinical samples." *Id.* at 4.

After achieving this express goal, Leary notes that the PCR products were sequenced. *Id.* at 3, 4. This sequencing was not done as part of Leary's method, but rather as post-hoc confirmation that the PCR primers had resulted in amplification of the regions of interest—*i.e.*, the rearrangements—and nothing else. For that reason, Leary describes "Sanger sequencing of seven PCR products" only to "***confirm[]*** the rearrangements in all cases tested." *Id.* at 3. Leary in no way purports to add the step of "conducting a second sequencing assay" to its method.

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B. Ground 2: Leary Does Not Render The Claimed Invention Obvious In View of Ley

In Ground 2, Petitioner relies upon the combination of Leary with Ley as allegedly rendering obvious claims 1 and 4-5. Ley, however, is irrelevant to the claims of the '394 Patent and does not cure any of the defects in Leary. If anything, Ley unambiguously counsels ***against*** approaches of the type utilized in the '394 Patent. As such, it cannot possibly render any of the claims of the '394 Patent obvious.

Ley is a rudimentary study reflective of the early stages of using massively parallel sequencing for studying cancer. Rather than presenting any new diagnostic techniques or methods for monitoring cancer, Ley simply reports on the results of whole genome sequencing of a tumor sample taken from a single patient suffering from acute myeloid leukemia. Ex. 1002 at 66. The idea was to hopefully identify the specific cancer-causing mutations. *Id*.

To sequence the tumor sample, the authors of Ley simply used a commercially available Illumina instrument. *See id.* at 71 ("Sequence end reads (average length for tumour genome, 32 bp, and for skin, 35 bp) were generated from Illumina/Solexa fragment libraries derived from the tumour or skin cells of patient 933124, using the Illumina Genome Analyser."). Prior to the sequencing analysis, the authors in Ley did not perform any special sample preparation steps, such as capture of specific

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sequences using probes or amplification of specific sequences using PCR. *See id.* Likewise, Ley does not disclose any sequencing of a sample from the patient at multiple time points, as recited in the claims of the '394 Patent. Thus, the Ley reference, at best, parallels the deficient disclosure of Leary.

Petitioner nonetheless asserts that based on Ley "a POSA would have had a reasonable expectation of success in successfully monitoring" polymorphisms at "serial time points," and that "Ley successfully did just that" using "probe-based capture techniques…" Petition at 56-57. Petitioner further contends that Ley teaches the "desirability" of directed re-sequencing. *Id.* This is all false.

First, there was no "probe-based capture" in Ley. At most, Ley teaches sequencing of PCR amplicons. *See* Ex. 1012 at 69 ("By sequencing polymerase chain reaction (PCR)-generated amplicons from the tumour and skin samples (and also from the relapse tumour sample obtained 11 months after the original presentation)…."). As documented above, PCR amplification is not the same thing as the claimed capture probe technique. *See supra* Part IV.A.

Second, there was no "monitoring" of polymorphisms at "serial time points" in Ley. Rather, there was at most sequencing of a relapse sample not for "monitoring," but rather for the purpose of identifying cancer-causing mutations for the first time. As Ley explains, this approach confirmed that the initial whole genome sequencing was insufficient to identify several mutations:

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> Of the coding sequence variants, 60 were synonymous, and not further evaluated. The remaining 181 variants were either non-synonymous, or were predicted to alter splice site function. By sequencing polymerase chain reaction (PCR)-generated amplicons from the tumour and skin samples (and also from the relapse tumour sample obtained 11 months after the original presentation), ***we determined that 152 of these variants were false positive (that is, wild type) calls***, 14 were inherited SNPs, and eight were somatic mutations in both the original tumour and the relapse sample (Table 2). ***Seven variants could not be validated, either because the regions involved were repetitive, or because all attempts to obtain PCR amplicons failed.***

Ex. 1012 at 69. Far from suggesting that sequencing at multiple time points can be used to ***monitor*** cancer, Ley teaches that such an approach may not work because the initial whole genome sequencing may not even be sufficient to identify all the necessary mutations at the outset.

Finally, Petitioner's suggestion that Ley teaches the "desirability" of directed resequencing is unambiguously contradicted by Ley itself. Indeed, Ley first states that most of the genes it had identified "would not have been candidates for directed re-sequencing:"

> These mutations affect genes participating in several well described pathways that are known to contribute to cancer pathogenesis, but most of these genes ***would not have been candidates for directed re-sequencing*** on the basis of our current understanding of cancer. Hence,

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> ***these results justify the use of next-generation whole genome sequencing*** approaches to reveal somatic mutations in cancer genomes.

Id. at 70. Far from teaching the desirability of "directed re-sequencing," Ley teaches only the use of "next-generation whole genome sequencing," in direct contrast to the claims of the '394 Patent.

Ultimately, Ley concludes that directed resequencing based on capture—as is claimed in the '394 Patent—is "inherently limited" and likely to "miss key mutations:"

> Our results strongly support the notion that hypothesis driven (for example, candidate gene-based) examination of tumour genomes by PCR-directed or capture-based methods is ***inherently limited, and will miss key mutations***.

Id.; *see also id.* at 71 ("even if the transcriptome had been sequenced, extensive characterization of the normal genome would have been required to distinguish inherited variants from somatic mutations…."); *id.* ("relevant non-synonymous mutations could be missed by cDNA sequencing…."). "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.

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While Petitioner contends that Ley sets the stage for subsequent work using massively parallel sequencing of cancer genomes and would motivate the selection of mutations from a database for cancer monitoring, Ley simply expresses doubt about this too. Specifically, Ley acknowledges in its concluding Discussion section that "until hundreds (or perhaps thousands) of normal genomes and other AML tumours are sequenced, the contextual relevance of the mutations found in this genome ***will be unknown***." Ex. 1012 at 71.

Like Petitioner's other references, Ley is a poor reference that comes nowhere close to rendering obvious the claims of the '394 Patent.

C. Ground 3: Leary Does Not Render The Claimed Invention Obvious In View Of The Knowledge Of A POSA, Chan, And Liao

Petitioner alleges that claims 1–19 of the '394 Patent would have been obvious over Leary in view of the knowledge of a POSA, Chan, and Liao. Petition at 58. As documented below, however, Petitioner's proposed obviousness combination would require a wholesale redesign of Leary to transmogrify it into a new method, allegedly based on the teachings of Chan. But the POSA would never have been motivated to make the drastic changes to Leary that are called for in the Petition, and certainly would not have been motivated to do so based on Chan, which teaches a method nothing like that of either Leary or the claims of the '394 Patent.

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To understand why Petitioner's proposed combination of Leary and Chan is without merit, one must first understand just how radically different these references are. As summarized above, the Leary method involves ***targeted*** sequencing of chromosomal rearrangements followed by PCR amplification to detect the presence of the "chromosomal rearrangements." Leary's method was specifically directed solely to such chromosomal rearrangements because Leary deemed them to be "exquisitely specific" as a tool for identifying cancer. Ex. 1002 at 1. Unlike the claimed invention, Leary never uses capture probes. *See supra* Part V.A.b.

Chan, if anything, is the exact opposite of Leary. Unlike Leary, which uses targeted sequencing of specific genomic regions to identify rearrangements, Chan uses "shotgun" sequencing, which ***indiscriminately*** sequences a genome. *See* Ex. 1008 at 212. Chan cites Leary's targeted approach, but only to criticize it as providing "only a partial glimpse of the tumor genome in the plasma of cancer patients." *Id.* at 212. Further, unlike Leary, which focuses only on chromosomal rearrangements, Chan attempts only to identify single nucleotide variants, an entirely different mutation type. *Id.* at 214 ("We sequenced the paired tumor and constitutional DNA samples to identify the tumor-associated single nucleotide variants (SNVs)."). While the claimed methods of the '394 Patent further require the use of capture probes in advance of subsequent sequencing assays, and while Leary uses PCR to enrich for target sequences, Chan never uses any such technique

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to collect or enrich for nucleic acid targets, whether it be capture or PCR. At most, Chan mentions capture techniques ***once*** in passing at the end of its discussion section, speculating that because such methods had been used for prenatal diagnosis they might be used in connection with cancer (and citing as the basis for such speculation 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, and (3) significantly, teach away from whole genome sequencing). *See id.* at 223.

Thus, in order to supposedly reach the claimed methods of the '394 Patent based on smashing Chan and Leary together, Petitioner is forced to propose a host of modifications to Leary:

- First, one would allegedly replace the targeted sequencing of Leary with the shotgun sequencing of Chan in order to achieve the claimed whole genome sequencing. *See* Petition at 61 ("Chan further observes that approaches like those of Leary and McBride have a 'targeted nature,'…Chan then proposes an approach in which a 'genomewide view of the tumor genome in the circulation' is obtained by using 'a nontargeted random—or shotgun—sequencing approach' is used.").

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- Second, instead of focusing solely on chromosomal rearrangements as in Leary, one would tack on to Leary additional sequencing steps directed specifically to SNVs. *Id.* at 65 ("Thus, a POSA would have been motivated to add to the fundamental methodology set forth in Leary 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."). In fact, Leary specifically teaches away from the use of SNVs due to high false positive rates. *Id*. at 5 ("[A]pproaches that rely on monitoring of residual disease by analysis of somatic single-base alterations in specific genes are limited by polymerase error rates at the bases of interest (25)").
- Third, rather than monitoring chromosomal rearrangements over time, as was allegedly done in Leary, one would supposedly modify Leary to monitor SNVs over time (even though Leary never does this). *Id.* ("Chan highlighted the desirability of monitoring SNVs, which would have motivated a POSA to analyze them in a serial monitoring protocol….").
- Fourth, one would add on top of Leary a solution-phase hybrid capture technique that is not mentioned in Leary, and not actually used in Chan

either. *Id.* at 65-66 ("In view of Chan, a POSA would have performed step 1(c) by using solution-phase hybridization probes targeting polymorphisms such as SNPs and CNVs, in addition to the PCR primer capture probes targeting rearrangements taught by Leary.").

Given the sheer number and scope of modifications that Petitioner proposes to make to Leary in view of Chan and Liao, it is difficult to believe that such a combination would be obvious. And, in fact, the law has been clear for over half a century that precisely this fact pattern involving an overly complex reconfiguration of a prior art reference to achieve a claimed invention weighs against obviousness. *See, e.g.*, *In re Ratti*, 270 F.2d 810, 813 (C.C.P.A. Sept. 30, 1959) (reversing obviousness rejection where the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown" in the prior art "as well as a change in the basic principles under which the [prior art] construction was designed to operate"); *see also* M.P.E.P. § 2143.

Consistent with this, Petitioner provides no persuasive explanation for why the POSA would have been driven to make such extensive modification to Leary based on Chan. Petitioner, for instance, asserts that the POSA would have been motivated to utilize targeted sequencing to achieve step 1(c) of claim 1 of the '394 Patent based on Chan because Chan teaches that shotgun sequencing is "relatively

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expensive compared with many targeted approaches." *See* Petition at 66. Yet, even though targeted approaches had previously been published, Chan ***uses*** shotgun sequencing. And, far from expressing concern about the cost of shotgun sequencing, the authors of Chan are, in fact, clear that they do not actually believe cost is a barrier, explaining 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.

Petitioner further asserts that the POSA would be motivated to modify Leary 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 68. 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 Leary about possibilities that one might "envision." *See id.* at 223. 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 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.").

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 ’394 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 Leary 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.

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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 ’394 Patent.

Petitioner’s hindsight-based argument based on reconstructing Leary into an entirely new method based on speculation and conjecture in Chan falls far short of establishing that the claims of the ’394 Patent are unpatentable.

D. The Petition Fails To Address Secondary Considerations Supporting The Nonobviousness 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

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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 objective indicia 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 '394 Patent. Ex. 2012.

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.

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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 '394 Patent earned the #1 ranking. *See* Ex. 2001.

Indeed, the differences between the method used in Leary and the method claimed in the '394 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:

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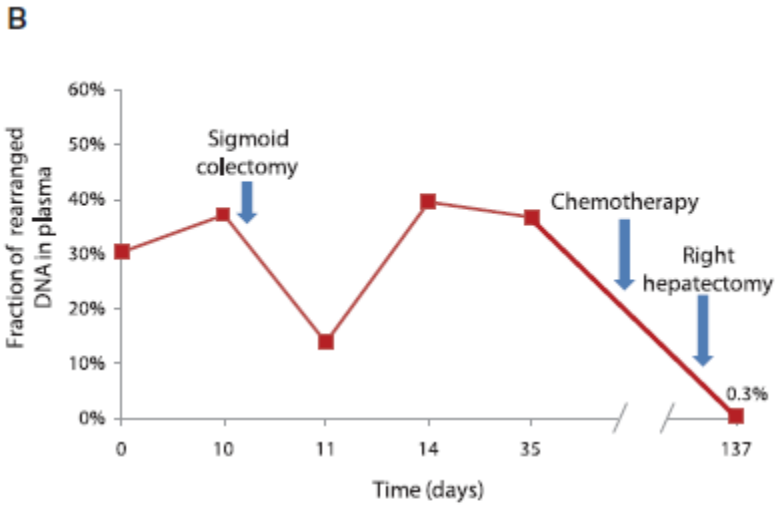

Fig. 4. Detection of tumor-specific rearrangements in plasma of cancer patients. (**A**) The identified chromosome 4:8 and 16 rearrangements were used to design PCR primers spanning breakpoints and to amplify rearranged DNA from tumor tissue and plasma from patients Hx402 and Hx403, respectively. A plasma 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 '394 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 genome sequencing using capture probes. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335 ("Evidence of industry skepticism is a question of fact that weighs in favor of

non-obviousness.") (Fed. Cir. 2016). 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 '394 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 '394 Patent are nonobvious and, consequently, Petitioner's attempt to demonstrate that a claim of the '394 Patent is unpatentable fails.

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VI. CONCLUSION

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

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Respectfully submitted,

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Dated: March 23, 2023

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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 12,487 words as calculated by the "Word Count" feature of Microsoft Word 2016, the word processing program used to create it.

Respectfully submitted,

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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. 11,384,394** is being served on March 23, 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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