

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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FORESIGHT DIAGNOSTICS INC.,  
Petitioner,

v.

PERSONALIS, INC.  
Patent Owner.

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Case IPR2023-00545  
U.S. Patent No. 11,299,783

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**PATENT OWNER RESPONSE**

## TABLE OF CONTENTS

|                                                                                                | Page No. |
|------------------------------------------------------------------------------------------------|----------|
| I. INTRODUCTION .....                                                                          | 1        |
| II. OVERVIEW OF THE '783 PATENT.....                                                           | 4        |
| III. GROUND 1: NOVELTY OVER LEY .....                                                          | 9        |
| A. Claim 1 .....                                                                               | 9        |
| 1. Limitation 1(a) .....                                                                       | 10       |
| a) Claim construction of “variable portion” and<br>“fixed portion” .....                       | 11       |
| b) Ley does not expressly or inherently teach a<br>variable portion or fixed portion.....      | 13       |
| 2. Limitation 1(b) .....                                                                       | 18       |
| 3. Limitation 1(c) .....                                                                       | 19       |
| a) Claim construction of “to identify” .....                                                   | 19       |
| b) Ley does teach limitation 1(c) under the<br>appropriate construction of “to identify” ..... | 20       |
| 4. Limitation 1(d) .....                                                                       | 23       |
| a) Claim construction of limitation 1(d) .....                                                 | 23       |
| b) Ley does not teach limitation 1(d) .....                                                    | 25       |
| B. Claim 15 .....                                                                              | 25       |
| C. Claims 3, 8, 16, and 22 .....                                                               | 26       |
| IV. GROUND 2: NONOBVIOUSNESS OVER LEY .....                                                    | 26       |

|    |                                                                                                             |    |
|----|-------------------------------------------------------------------------------------------------------------|----|
| A. | Claim 1 .....                                                                                               | 27 |
| 1. | Limitation 1(a) .....                                                                                       | 27 |
| a) | Ley counsels against Foresight’s modification,<br>which is confirmed by Dr. Quackenbush’s<br>testimony..... | 28 |
| b) | Adding more PCR primers would complicate<br>the assay.....                                                  | 31 |
| c) | Ley’s mutations had unknown clinical<br>relevance .....                                                     | 32 |
| 2. | Limitation 1(b) .....                                                                                       | 35 |
| 3. | Limitation 1(c) .....                                                                                       | 36 |
| 4. | Limitation 1(d) .....                                                                                       | 37 |
| 5. | No motivation to modify Ley .....                                                                           | 39 |
| B. | Claims 3, 8, 15, and 16.....                                                                                | 39 |
| C. | Claim 22 .....                                                                                              | 40 |
| V. | GROUND 3: NONOBVIOUSNESS OVER FORSHEW AND<br>DAWSON.....                                                    | 46 |
| A. | Claim 1 .....                                                                                               | 46 |
| 1. | Limitation 1(a) .....                                                                                       | 46 |
| a) | Forshew does not teach the claimed “variable<br>portion” .....                                              | 47 |
| b) | No suggestion for the claimed “variable<br>portion” .....                                                   | 48 |
| c) | No motivation to combine “variable portion”<br>and “fixed portion” .....                                    | 49 |

|      |                                           |    |
|------|-------------------------------------------|----|
| 2.   | Limitation 1(d) .....                     | 55 |
| 3.   | No motivation to arrive at claim 1 .....  | 59 |
| B.   | Claim 22 .....                            | 59 |
| VI.  | OBJECTIVE INDICIA OF NONOBVIOUSNESS ..... | 62 |
| A.   | Nexus .....                               | 62 |
| B.   | Industry Praise .....                     | 62 |
| C.   | Skepticism .....                          | 64 |
| VII. | CONCLUSION.....                           | 65 |

## TABLE OF AUTHORITIES

### Page No(s).

|                                                                                                                    |                |
|--------------------------------------------------------------------------------------------------------------------|----------------|
| <i>Arctic Cat Inc. v. Bombardier Recreational Prod. Inc.</i> ,<br>876 F.3d 1350 (Fed. Cir. 2017) .....             | 62             |
| <i>CFMT, Inc. v. YieldUp Int’l Corp.</i> ,<br>349 F.3d 1333 (Fed. Cir. 2003) .....                                 | 27             |
| <i>Cheese Systems, Inc. v. Tetra Pak Cheese and Powder Systems, Inc.</i> ,<br>725 F.3d 1341 (Fed. Cir. 2013) ..... | 59             |
| <i>Crocs, Inc. v. Int’l Trade Comm’n</i> ,<br>598 F.3d 1294 (Fed. Cir. 2010) .....                                 | 62             |
| <i>Crown Operations Intern., Ltd. v. Solutia Inc.</i> ,<br>289 F.3d 1367 (Fed. Cir. 2002) .....                    | 15             |
| <i>Fox Factory, Inc. v. SRAM, LLC</i> ,<br>944 F.3d 1366 (Fed. Cir. 2019) .....                                    | 62             |
| <i>Luminara Worldwide, LLC v. Liown Elecs. Co.</i> ,<br>814 F.3d 1343 (Fed. Cir. 2016) .....                       | 20             |
| <i>Par Pharm., Inc. v. TWI Pharms. Inc.</i> ,<br>773 F.3d 1186 (Fed. Cir. 2014) .....                              | 14, 17, 26     |
| <i>Phillips v. AWH Corp.</i> ,<br>415 F.3d 1303 (Fed. Cir. 2005) (en banc) .....                                   | 11, 12, 13, 20 |
| <i>Polaris Indus., Inc. v. Arctic Cat, Inc.</i> ,<br>882 F.3d 1056 (Fed. Cir. 2018) .....                          | 62             |
| <i>Praxair Distribution, Inc. v. Mallinckrodt Hospital Products IP</i> ,<br>890 F.3d 1024 (Fed. Cir. 2018) .....   | 23, 24         |
| <i>Verdegaal Bros. Inc. v. Union Oil Co. of California</i> ,<br>814 F.2d 628 (Fed. Cir. 1987) .....                | 10             |

Foresight Diagnostics Inc. v. Personalis, Inc.  
IPR2023-00545

|                                                                          |    |
|--------------------------------------------------------------------------|----|
| <i>WBIP, LLC v. Kohler Co.</i> ,<br>829 F.3d 1317 (Fed. Cir. 2016) ..... | 64 |
|--------------------------------------------------------------------------|----|

## EXHIBIT LIST

| Exhibit No. | Description                                                                                                                                                                                                                         |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2001        | The Scientist Staff, “2022 Top 10 Innovations,” Dec. 12, 2022, available at <a href="https://www.the-scientist.com/features/2022-top-10-innovations-70792">https://www.the-scientist.com/features/2022-top-10-innovations-70792</a> |
| 2002        | Swanton, C., “Plasma-Derived Tumor DNA Analysis at Whole-Genome Resolution,” <i>Clinical Chemistry</i> 59:1 6-8 (2013)                                                                                                              |
| 2003        | Exemplary Embodying Product Claim Chart for U.S. Patent No. 11,299,783                                                                                                                                                              |
| 2004-2009   | RESERVED                                                                                                                                                                                                                            |
| 2010        | <i>Curriculum Vitae</i> of Dr. Henry Morrice Furneaux                                                                                                                                                                               |
| 2011-2034   | RESERVED                                                                                                                                                                                                                            |
| 2035        | Declaration of Dan Norton                                                                                                                                                                                                           |
| 2036-2150   | RESERVED                                                                                                                                                                                                                            |
| 2151        | Foresight Diagnostics, About, <a href="https://foresight-dx.com/about">https://foresight-dx.com/about</a>                                                                                                                           |
| 2152        | RESERVED                                                                                                                                                                                                                            |

| Exhibit No. | Description                                                                                                                                                                           |
|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2153        | “Personalis MRD Assays to Support UK’s TRACERx ctDNA Monitoring Study,” Precision Medicine Online, April 5, 2023                                                                      |
| 2154        | “Personalis, AstraZeneca Extend Collaboration Around Residual Cancer Detection Test,” GenomeWeb, March 7, 2023                                                                        |
| 2155        | RESERVED                                                                                                                                                                              |
| 2156        | Labrousse, “MATRIX plasma-in-plasma contrived samples assessment and detection of MRD using the Personalis NeXT Personal assay,” American Society of Clinical Oncology, e15056, 2023. |
| 2157-2162   | RESERVED                                                                                                                                                                              |
| 2163        | Transcript of the deposition of John Quackenbush, Ph.D., taken on October 20, 2023.                                                                                                   |
| 2164        | Bratman and Alizadeh and Diehn, Expert Rev Mol Diagn 15:715-719 (2015)                                                                                                                |
| 2165        | Chaudhuri and Alizadeh and Diehn et al., Semin Radiat Oncol 25:305-312 (2015)                                                                                                         |
| 2166        | Dudley and Diehn, Annu. Rev. Pathol. Mech. Dis. 16:199-222 (2021)                                                                                                                     |
| 2167        | Forsheiw Supplemental Information, EX1032, from related <i>Foresight Diagnostics Inc. v. Personalis, Inc.</i> , IPR2023-00317                                                         |

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                               |
|--------------------|----------------------------------------------------------------------------------------------------------------------------------|
| 2168               | Quackenbush Declaration, EX1061, from related <i>Foresight Diagnostics Inc. v. Personalis, Inc.</i> , IPR2023-00546              |
| 2169               | Declaration of Henry Morrice Furneaux                                                                                            |
| 2170               | American Heritage Dictionary definition of “identify”                                                                            |
| 2171               | RESERVED                                                                                                                         |
| 2172               | Lewin, “Genes V,” Oxford University Press, 1994.                                                                                 |
| 2173-2176          | RESERVED                                                                                                                         |
| 2177               | Sholl, Institutional implementation of clinical tumor profiling on an unselected cancer population,” JD Insight. 1:e87062 (2016) |

Patent Owner Personalis Inc. (“Personalis”) submits this Response to the Petition filed by Foresight Diagnostic Inc. (“Foresight”) regarding U.S. 11,299,783 (“the ’783 patent”).

## **I. INTRODUCTION**

Personalis is recognized as an undisputed leader in developing innovative personalized genomic assays. The ’783 patent claims recite a novel and nonobvious process for personalized genetic testing that uses sequence data from a subject’s biological sample to identify and obtain personalized probe sets to genetic variants, including a variable portion from said sequence data and a fixed portion independent of said sequence data, then using the personalized probe sets on an additional biological sample to enrich or amplify and sequence only the genetic variants, followed by generating a report identifying the presence or absence of a health condition or disease and genetic variants which inform further therapy.

Personalis’ NeXT Personal<sup>®</sup> detection and monitoring assay practices the ’783 patent and has been hailed by *The Scientist* magazine as the top scientific innovation in 2022. EX2001 1-2. The claimed process provides a dramatic reduction in the amount of sequencing, making it much more affordable than prior art processes. By using the claimed process, Personalis has pioneered new frontiers in techniques for detecting and monitoring disease with utmost sensitivity. The personalized nature

of this approach has a number of useful applications, including for diagnosing Mendelian diseases and detecting and monitoring a subject's cancer.

Personalis' successful approach has been adopted by Foresight. EX1010 ¶¶46-51; EX1072. Foresight seeks to avoid liability for infringing the claimed invention through the following three patentability challenges it raised in this proceeding: (1) alleged anticipation by the Ley reference, (2) alleged obviousness based on Ley, and (3) alleged obviousness based on the Forshew and Dawson references.

The Ley grounds do not render the claimed invention unpatentable. Ley discloses an assay that is nothing like the claimed invention because it fails to teach or suggest all four limitations recited by claim 1. Specifically, Ley fails to teach or suggest:

- the personalized probe set comprising nucleic acid probe molecules having oligonucleotide-directed genomic content comprising “(i) at least one variable portion from a result of said sequence data and (ii) at least one fixed portion independent of said result of said sequencing data” required by limitation 1(a),
- the “additional biological sample from said subject” required by limitation 1(b),

- “subjecting said sequencing library to sequencing to identify a presence or absence of at least a subset of said set of genetic variants” as required by limitation 1(c), and
- “generating a report identifying (i) a presence or absence of a health condition or disease of the subject in said biological sample based on said identified at least a subset of (c) and (ii) genetic variants which inform a therapy choice or a change in therapy for the subject” as required by limitation 1(d).

Foresight’s anticipation and obviousness challenges are not supported by the teachings of Ley, and they are undermined by testimony from its own expert witness (Dr. Quackenbush), its own exhibits, and statements by its own founders.<sup>1</sup> The Board should reject Foresight’s petition-inspired arguments that are at odds with the rest of the record.

Foresight’s remaining challenge based on Forshew and Dawson fails to teach or suggest at least limitations 1(a) and 1(d). Foresight’s obviousness challenge is not supported by the teachings of Forshew and Dawson, and belied by testimony

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<sup>1</sup> Foresight was founded by Ash Alizadeh, Maximilian Diehn, David Kurtz, and Jake Chabon. EX2151.

from Dr. Quackenbush as well as Foresight’s own exhibits and statements by its own founders.

Claim 22 depends from claim 1 and requires that the “personalized probe set comprises hybrid capture probes.” Foresight has not proven this claim to be unpatentable for several additional and independent reasons. All three references relied upon by Foresight are directed to PCR-based assays that do not use hybrid capture probes. Foresight’s own exhibits provide numerous reasons why a person of ordinary skill in the art (POSA) would not have been motivated to abandon the core reaction principle of the PCR-based assays disclosed by Ley, Forshew, and Dawson to instead use capture probes.

The patentability of Personalis’ claims is further confirmed by objective indicia of nonobviousness including industry praise and skepticism in the field. After considering all of the relevant evidence, there is only one reasonable conclusion—the challenged claims of the ’783 patent were not anticipated or obvious at the time of the invention.

## **II. OVERVIEW OF THE ’783 PATENT**

The ’783 patent relates to “systems and methods for sample processing and data analysis,”—including “method[s] for personalized genetic testing”—for use in the diagnosis, monitoring, treatment, and prevention of diseases. EX1001 Abstract, 72:19. Claim 1 is the only independent claim and it recites:

1. A method for personalized genetic testing, comprising:

(a) obtaining a personalized probe set for a subject, which personalized probe set comprises a plurality of nucleic acid probe molecules having a plurality of nucleic acid sequences or complements thereof, wherein said plurality of nucleic acid probe molecules are configured to selectively enrich or amplify sequences comprising a set of one or more genetic variants over other sequences in at least one biological sample of said subject, wherein said set of genetic variants are identified in sequence data for said at least one biological sample, further wherein said personalized probe set comprises nucleic acid probe molecules having oligonucleotide-directed genomic content comprising: (i) at least one variable portion from a result of said sequence data and (ii) at least one fixed portion independent of said result of said sequencing data;

(b) using said personalized probe set to selectively enrich or amplify sequences comprising said set of genetic variants over other sequences in at least an additional biological sample from said subject, to generate a sequencing library;

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

(d) generating a report identifying (i) a presence or absence of a health condition or disease of the subject in said additional biological sample based on said identified at least a subset of (c) and (ii) genetic

variants which inform a therapy choice or a change in therapy for the subject.

EX1001 Claim 1.

The specification explains that high costs previously limited “clinical adoption of exome-scale sequencing,” and that “[t]his problem is even worse in cancer, where the depth of deoxynucleic acid (DNA) sequencing required can be much higher (e.g., >500×) than that for inherited diseases (e.g., 30-100×).” *Id.* 4:30-32; 4:33-36. And “[w]hile array-based DNA synthesis is now widely used to capture ... application-specific subsets of exomes (e.g., the genes involved with a specific Mendelian disease), a limitation of the field, as recognized herein, is the potential to leverage array synthesis of DNA in a personalized manner.” *Id.* 4:37-42. Instead, “[t]he field has largely used array-based synthesis to develop standard products which are broadly applicable across a whole set of human patients and/or research subjects.” *Id.* 4:42-45; *see also id.* 4:45-47 (“Even where custom array synthesis is proposed, it is to sequence regions of the genome defined independent of a specific sample.”). Sequencing costs remained high, and personal assay synthesis generally remained “unattractive” due to uncertainty caused by variations based on “conditions of the nucleic acid sequence (e.g., % GC, alignment degeneracy, primer-dimer formation).” *Id.* 39:43-45.

The claimed method, however, is directed to a method for “personalized genetic testing.” The claimed method first requires obtaining a personalized probe set, which can “include probes to a genomic region or a panel comprising multiple genomic regions” and “can be amplification based or capture hybridization-based.” *Id.* 29:17-19. A probe “generally refer[s] to a nucleic acid molecule comprising a single-stranded portion capable of hybridizing to a complementary nucleic acid sequence,” and “can be used for detection or enrichment of [said] nucleic acid molecules.” *Id.* 29:5-9. “A probe may be included in a set, or plurality, of probes.” *Id.* 29:14-15. The claimed probe set includes probes that are complementary to and thereby configured to enrich or amplify the identified genetic variants. *Id.* 29:4-9; *see also generally id.* Example 7 (describing exemplary methods to synthesize probes). Further, the claimed method requires a personalized probe set comprising nucleic acid probe molecules having oligonucleotide-directed genomic content comprising (i) at least one variable portion from a result of said sequence data and (ii) at least one fixed portion independent of said result of said sequencing data.

Second, the personalized probe set is then applied to an “additional biological sample” to selectively enrich or amplify sequences comprising the genetic variants. *Id.* 11:3-7. The additional biological sample may be a sample of the same tissue from the same subject taken at a later time point, a sample of different tissue from the same subject, or a sample from a biological relative of the subject, for example.

*See, e.g.*, EX1001 Example 1; *id.* 5:4-10. The enriched or amplified sequences of the genetic variants generate a sequencing library. *Id.* 42:52-62.

Third, the sequencing library is sequenced to identify a presence or absence of the genetic variants in the additional biological sample. The sequencing footprint of this step is less than the sequencing footprint of the sequencing data used to generate the personalized probe set in the first step. For example, to test for 500 variants this lower footprint sequencing step may require synthesis of about “175,000 bases...[c]ompared to [sequencing] an exome, where the footprint assay is typically at least 35 million bases, [] may result in 200x less sequencing.” *Id.* 63:17-20. This allows for a “dramatic reduction” in required sequencing and allows sequencing to be more affordable for family members. *Id.* 63:20-24. With the reduction in sequencing footprint, the sequencing depth can be greater than the depth of the first sequencing step without being cost prohibitive. *See, e.g., id.* 64:41-52 (“To increase the confidence of detecting a potentially mosaic variant in the parents, they will need to be sequenced at greater depth than the child. If the assay for additional members of a family pedigree is exome sequencing, it may be cost prohibitive to sequence at that depth. Using method provided herein, the footprint of the assay for incremental family members is much smaller (e.g., 175,000 bases vs 35 million bases, as discussed above). This smaller footprint makes it affordable to

sequence the incremental samples at much greater depth, thus improving the sensitivity for detection of mosaic variants in the parents.”).

Finally, a report is generated which identifies both (i) whether a health condition or disease state is present based on identification of genetic variants tested in the third step from the additional biological sample, and (ii) genetic variants which inform therapy choices or changes in therapy for the patient. This report may vary based on the type of medical conditions being examined. *See, e.g., id.* 8:36-39 (reports may identify “genetic variants shared by family members of the same family pedigree”); *id.* 8:40-46 (reports may be “generated based at least in part on a possibility that one or more genetic variants of the subject are mosaic and included in the ectodermal lineage of the subject”); *id.* 8:47-52 (reports may be generated “in part on a possibility that one or more of the genetic variants are gonadal mosaic in a father of the subject”).

### **III. GROUND 1: NOVELTY OVER LEY**

Ley does not anticipate independent claim 1, and therefore fails to anticipate any of the challenged dependent claims. Ley further fails to anticipate dependent claim 15 for additional reasons discussed herein.

#### **A. Claim 1**

“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.”

*Verdegaal Bros. Inc. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Ley fails to anticipate claim 1 because it does not teach any of the four limitations required by the claim. Specifically, Ley fails to teach:

- “(i) at least one variable portion from a result of said sequence data and (ii) at least one fixed portion independent of said result of said sequencing data” as required by limitation 1(a),
- an “additional biological sample from said subject” as required by limitation 1(b),
- “subjecting said sequencing library to sequencing to identify a presence or absence of at least a subset of said set of genetic variants” as required by limitation 1(c), and
- “generating a report identifying (i) a presence or absence of a health condition or disease of the subject in said biological sample based on said identified at least a subset of (c) and (ii) genetic variants which inform a therapy choice or a change in therapy for the subject” as required by limitation 1(d).

**1. Limitation 1(a)**

Ley does not teach a personalized probe set comprising nucleic acid probe molecules having oligonucleotide-directed genomic content comprising “(i) at least one variable portion from a result of said sequence data and (ii) at least one fixed

portion independent of said result of said sequencing data” as required by limitation 1(a). Foresight failed to proffer a construction of the recited “variable portion” and “fixed portion.” Petition 14-18. Ley does not teach the claimed personalized probe set of limitation 1(a) under the appropriate construction of these terms.

**a) Claim construction of “variable portion” and “fixed portion”**

The recited “variable portion” and “fixed portion” do not have a plain meaning to a POSA.<sup>2</sup> EX2169 ¶¶50-51. Here, the specification provides the relevant information for understanding the claim terms. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (en banc) (“[T]he specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.”). Dr. Quackenbush agrees that “what is important in interpreting these claims is what the patentee teaches us they mean by variable portion and fixed portion. So, the best place I can turn to understand what that, the patent owner means is to look at what is disclosed in the written description of the patent.” EX2163 94:7-96:7.

The specification provides an express definition of “variable portion” and “fixed portion” as follows:

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<sup>2</sup> For purposes of the trial phase of this proceeding only, Personalis does not contest Foresight’s description of a POSA. Institution Decision (“Decision”) 18-19.

In some applications, it may be desirable for the oligo-directed genomic content of the personalized assay to contain both *a variable portion (defined based on the genetic characteristics originally determined for the individual subject) and at least one fixed portion (which does not change from one subject to another)*.

EX1001 41:45-50.<sup>3</sup> The variable portion changes from subject to subject because it is “defined based on the genetic characteristics originally determined for the individual subject,” whereas the fixed portion “does not change from one subject to another.” *Id.*; *see also id.* 66:36-39 (“Thus, as discuss[ed] above, the genomic content of a personalized genetic assay may include *a portion which is variable subject to subject, and another portion which is fixed.*”). The title of the section describing variable and fixed content is entitled “Combinations of *Fixed and Variable (Personal)* Genomic Content in the Array-Synthesized Nucleic Acids.” *Id.* 41:40-41. The variable portion is “personal” to the subject, whereas the fixed portion does not change from subject to subject. Because the specification provides an express definition of “variable portion” and “fixed portion,” that definition governs the interpretation of these terms. *See Phillips*, 415 F.3d at 1316 (“[T]he inventor’s lexicography governs.”).

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<sup>3</sup> All emphases supplied unless otherwise noted.

Limitation 1(a) provides further clarification regarding the “variable portion” and “fixed portion” by specifying that the variable portion is “from a result of said sequence data” and the fixed portion must be “independent of said result of said sequencing data.” EX1001 72:32-35. This clarifying claim language “provide[s] substantial guidance as to the meaning of particular claim terms.” *Phillips*, 415 F.3d at 1314.

Based on the definition in the specification and the claim language that provides further clarification on the meaning of “variable portion” and “fixed portion” within the context of the claimed invention, *the “variable portion” recited by limitation 1(a) should be construed to refer to a portion “which changes from one subject to another and results from said sequence data,” and the “fixed portion” should be construed to refer to a portion “which does not change from one subject to another and is independent of said result of said sequencing data.”* EX2169 ¶¶51-53.

**b) Ley does not expressly or inherently teach a variable portion or fixed portion**

Foresight does not assert that Ley *expressly* teaches the use of a personalized probe set comprising nucleic acid probe molecules having oligonucleotide-directed genomic content comprising “(i) at least one variable portion from a result of said sequence data and (ii) at least one fixed portion independent of said result of said sequencing data” as required by limitation 1(a). Petition 24-30. Instead, Foresight’s

petition requires Ley to *inherently* teach this limitation. Specifically, Foresight relies on Ley inherently disclosing PCR primers that allegedly meet the claimed “variable portion” and “fixed portion.” *Id.* There is a “high standard” for Foresight to prove anticipation because inherency requires that the limitation at issue “necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art.” *Par Pharm., Inc. v. TWI Pharms. Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014). Foresight has not met that high standard for at least three reasons.

First, Dr. Quackenbush admitted in his declaration that “Ley does not provide the primer sequences or the exact exons that were analyzed.....” EX1020 ¶124. The word “primer” appears nowhere in Ley (EX1012) or Ley’s Supplemental Materials (EX1042). During deposition, Dr. Quackenbush repeatedly admitted that Ley is devoid of any information about the primer design and PCR protocol that Foresight relies upon to allege that Ley inherently anticipates limitation 1(a). For example, he admitted that “Ley does not disclose the PCR protocol that was used” and “Ley doesn’t disclose the parameters used for the PCR primer design.” EX2163 250:4-14. He further admitted “[s]o, again, Ley doesn’t describe here the primer design methodology that was used.” *Id.* 248:11-249:3. He conceded “[a]nd, yes, we don’t know the exact primers that Ley used.” *Id.* 232:17-22. He further conceded that “[a]gain, Ley doesn’t disclose the PCR protocol that was used. So, sitting here today,

I can't tell you what method Ley might have used" and "I can't speculate on what Ley did or did not do." *Id.* 261:2-18.

Given the complete lack of any details in Ley regarding PCR primers, Foresight cannot prove that Ley inherently discloses PCR primers that meet the claimed "variable portion" and "fixed portion" of limitation 1(a). Foresight is left with merely "assumption[s] and its own contentions" about what the content of Ley's PCR primers might have been, which fails to prove inherent anticipation. *Crown Operations Intern., Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1378 (Fed. Cir. 2002).

Second, Foresight asserts that Ley inherently discloses PCR primers "for known mutations of the BRCA2 and TP53 genes" that supposedly meet the "fixed portion" of limitation 1(a). Petition 30. This assertion does not withstand scrutiny. As discussed above, Dr. Quackenbush admitted that there are no details in Ley regarding the use of any PCR primers, much less PCR primers that meet the claimed "fixed portion." In addition, Ley merely reports that the *protein* sequence resulting from the BRCA2 mutation changed from asparagine to histidine (N372H). EX1012, Table 3. There are two possible codons in the BRCA2 gene that could code N372H. Ley also reports that the *protein* sequence resulting from the TP53 mutation changed from proline to arginine (P72H). *Id.* There are six possible codons in the TP53 gene that could code P72H. EX2169 ¶¶55-57; EX2172 172. Thus, Ley's subject could have had any of two codons in the BRCA2 gene, and any of six codons in the TP53

gene. Ley does not disclose which of these possible codons were present in the subject. Dr. Quackenbush's assertion that Ley's subject had "known mutations" of the BRCA2 and TP53 genes does not answer whether the oligonucleotide-directed genomic content of Ley's PCR primers might have changed from one subject to another to accommodate the several potential codons that Ley's subject may have had. If the oligonucleotide-directed genomic content of Ley's PCR primers changes from one subject to another, then they would not meet the "fixed portion" recited by limitation 1(a) because the "fixed portion" must "not change from one subject to another" under the appropriate construction of that term. Thus, Foresight has not demonstrated that Ley inherently teaches the "fixed portion" required by limitation 1(a).

Third, if Foresight belatedly argues for the first time in its Reply that the undisclosed PCR primers for the BRCA2 and TP53 mutations in Ley's subject meet the claimed "fixed portion" because they do not change from one subject to another, then Petitioner would have to explain how the undisclosed PCR primers for the other eight mutations from Ley that Foresight alleges meet the claimed "variable portion," Petition 29, do not constitute "fixed portions" that must not change from one subject to another. The other eight mutations were located in a patient with "a *typical* acute myeloid leukaemia genome," rather than an atypical genome. EX1012 66. Ley explains that specific patient being studied, UPN 933124, was selected precisely

because she had “[t]ypical features of M1 AML” that was “*representative of most patients* with M1 AML.” EX1042 1. Ley “required a gene expression profile *typical* of M1 AML with *normal cytogenetics*, to assure that the sample was *not an outlier* for this subtype.” *Id.* Because Ley’s patient was selected to be typical and representative of most patients with M1 AML, the PCR primers used by Ley to generate amplicons for the other eight mutations that Foresight relies upon to supposedly meet the “variable portion” could very well *not* change from one subject to another. The genomic content of Ley’s undisclosed PCR primers is simply unknown. EX2169 ¶58. As discussed above, Dr. Quackenbush admitted that “Ley doesn’t disclose the PCR protocol that was used” and he “can’t speculate on what Ley did or did not do.” EX2163 250:4-14, 261:2-18.

Foresight’s anticipation challenge is founded upon nothing more than speculation about probabilities and possibilities as to the genomic content that might have been present in Ley’s undisclosed PCR primers. Foresight’s speculation does not prove anticipation because inherency cannot be established “by probabilities or possibilities.” *Par Pharm.*, 773 F.3d at 1196. For at least these reasons, Petitioner has not demonstrated that Ley inherently discloses PCR primers meeting the claimed “variable portion” and “fixed portion” of limitation 1(a).

**2. Limitation 1(b)**

Limitation 1(b) requires an “additional biological sample from said subject.” Foresight, however, relies on the *same* biological samples from Ley to supposedly meet the “at least one biological sample of said subject” required by limitation 1(a) and the “additional biological sample from said subject” required by limitation 1(b).

Specifically, Foresight relies on the “the primary tumor, skin sample, and relapse tumor sample” from Ley to allegedly meet the “at least one biological sample of said subject” of limitation 1(a). Petition 27. Foresight’s arguments regarding dependent claim 2 emphasize that *it relies on all three samples* from Ley to meet limitation 1(a). Claim 2 depends from claim 1 and recites that the “at least one biological sample” from limitation 1(a) comprises “a plurality of biological samples.” Petitioner relies on “the primary tumor sample, the relapse tumor sample, and the skin biopsy sample” from Ley to allegedly meet the “at least one biological sample” recited by claim 2. Petition 35. Foresight’s position is crystal clear—it relies on all three samples from Ley to allegedly meet the “at least one biological sample of said subject” of limitation 1(a).

Because Foresight relies on the relapse tumor and skin biopsy sample to allegedly meet the “at least one biological sample of said subject” of limitation 1(a) (and also claim 2), there are no additional samples left in Ley to meet the “additional biological sample from said subject” required for limitation 1(b). EX2169 ¶¶60-63.

Foresight relies on *the same* “relapse tumor” and “skin biopsy” samples that it alleges meet the “at least one biological sample of said subject” for limitation 1(a), *see* Petition 27, to also allegedly meet the “additional biological sample from said subject” for limitation 1(b), *see* Petition 31. Foresight’s petition improperly double counts Ley’s relapse tumor and skin biopsy samples to disguise important differences between Ley’s assay and the claimed invention. Foresight fails to prove that Ley anticipates the claims for at least this reason.

### 3. **Limitation 1(c)**

Limitation 1(c) requires “subjecting said sequencing library to sequencing *to identify* a presence or absence of at least a subset of said set of genetic variants.” Ley does not teach limitation 1(c) under the appropriate construction of the term “to identify.”

#### a) **Claim construction of “to identify”**

The Board preliminarily determined that “step 1(c) is silent as to whether a genetic variant is identified *de novo* in an unknown sample, or identified in a previously tested sample for some validating or confirmatory purpose.” Decision 29. The Board also preliminarily determined that “[i]n showing that 10 variant alleles were present in both primary and relapse tumor samples, Ley Figure 3 satisfies claim step 1(c) by ‘identifying a presence of at least a subset of said set of genetic variants’ in a patient sample.” *Id.* The Board’s preliminary determinations

do not comply with how a POSA would have understood the plain meaning of “to identify” as recited by limitation 1(c).

Foresight failed to explain its interpretation of what it means “to identify” within the context of limitation 1(c). Petition 31-33, 14-18. Dr. Quackenbush was unable to provide a construction for this term, although he was provided ample opportunity to do so during deposition. EX2163 103:12-117:10.

The specification does not define “to identify.” This term should therefore be accorded its plain and ordinary meaning. *See Luminara Worldwide, LLC v. Liown Elecs. Co.*, 814 F.3d 1343, 1353 (Fed. Cir. 2016) (“Absent lexicography or disavowal, we do not depart from the plain meaning of claims.”); *Phillips*, 415 F.3d at 1312-16.

The plain meaning of “to identify” is “*to establish the identity of.*” *See* EX2170 871; EX2169 ¶¶65-69. This construction stays true to the plain meaning of “to identify” and should be adopted in this proceeding.

**b) Ley does teach limitation 1(c) under the appropriate construction of “to identify”**

Foresight readily admits that Ley performs separate steps of identification and validation. Foresight explains that “[o]nce the variants of interest, i.e., the ‘putative variants,’ *were identified, Ley then describes ‘validation* using custom PCR and capillary sequencing’ as well as sequencing of ‘validated somatic mutations’ ‘by Roche/454 sequencing of PCR-generated amplicons made from primary genomic

DNA.” Petition 25. Thus, Ley initially identifies variants of interest, and then separately validates the variants of interest by sequencing. *Id.*; EX1020 ¶109; EX2169 ¶70.

Ley’s identification step uses sequencing data to establish the identity of somatic mutations in the typical AML genome. *See* EX1012 68-69 (section of Ley entitled “Identification of somatic mutations in coding sequences”). For this identification, Ley sequenced PCR-generated amplicons to “determine[] 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).” *Id.* 69; EX2169 ¶71.

The “validation” protocol from Ley that Foresight relies upon to allegedly meet limitation 1(c) is a separate protocol from Ley’s identification step. The validation protocol merely quantifies the amount of the variants that are present in Ley’s subject. For example, Foresight relies on Ley Figure 3, *see* Petition 31-33, which quantifies the amount of genetic variants present in Ley’s subject via readcount data:

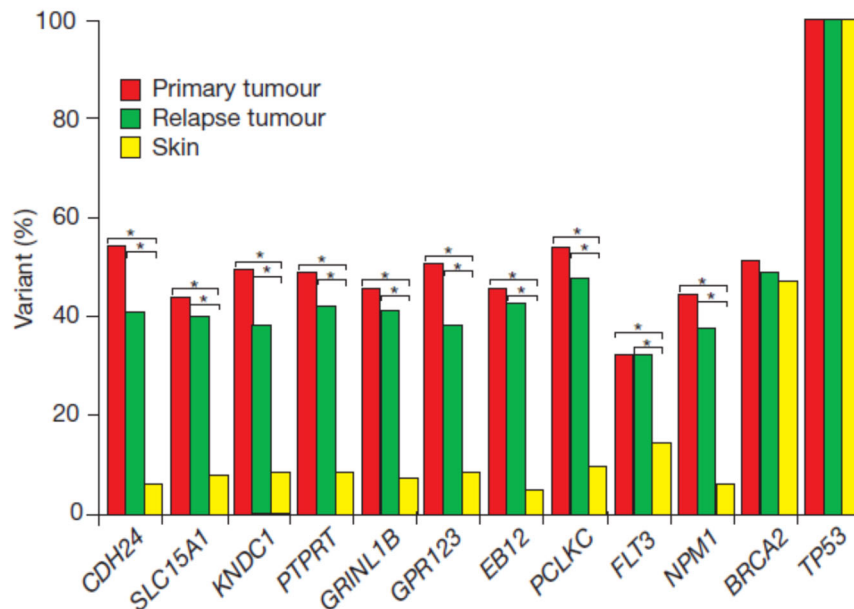


**Figure 3 | Summary of Roche/454 FLX readcount data obtained for ten somatic mutations and two validated SNPs in the primary tumour, relapse tumour and skin specimens.** The readcount data for the variant alleles in the primary tumour sample and relapse tumour sample are statistically different from that of the skin sample for all mutations ( $P < 0.000001$  for all mutations, Fisher's exact test, denoted by a single asterisk in all cases). Note that the normal skin sample was contaminated with leukaemic cells containing the somatic mutations. The patient's white blood cell count was 105,000 (85% blasts) when the skin punch biopsy was obtained.

The mutation frequencies are merely quantified during the validation protocol by tallying readcounts. The identity of the mutations was established in the preceding (and separate) protocol described in the section entitled “Identification of somatic mutations in coding sequences” on pages 68-69 of Ley. EX2169 ¶72.

Foresight's anticipation challenge relies on a POSA conflating Ley's validation protocol with the claimed “to identify” step of limitation 1(c). A POSA would not have confused these two steps as confirmed by Foresight's admission that “[o]nce the variants of interest, i.e., the ‘putative variants,’ *were identified, Ley then*

*describes ‘validation using custom PCR and capillary sequencing’ as well as sequencing of ‘validated somatic mutations’ ‘by Roche/454 sequencing of PCR-generated amplicons made from primary genomic DNA.’”* Petition 25. The result of Ley’s validation step is the quantification of variant frequencies by tallying readcount sequencing data rather than establishing the identity of a presence or absence of variants as claimed. EX2169 ¶73.

#### 4. Limitation 1(d)

Limitation 1(d) requires “generating a report identifying (i) a presence or absence of a health condition or disease of the subject in said biological sample based on said identified at least a subset of (c) and (ii) genetic variants *which inform a therapy choice or a change in therapy for the subject.*” Ley does not teach limitation 1(d) under the appropriate construction of this limitation.

##### a) Claim construction of limitation 1(d)

The Board made a preliminary determination that limitation 1(d) is directed to printed matter and a mental step and therefore accorded no patentable weight to the limitation. Decision 23-25. The Board recognized, however, that Personalis did “not presently address the printed matter argument” during the preliminary phase of this proceeding. *Id.* 23. Personalis addresses that argument now.

“Printed matter that is functionally related to its substrate is given patentable weight.” *Praxair Distribution, Inc. v. Mallinckrodt Hospital Products IP*, 890 F.3d

1024, 1032 (Fed. Cir. 2018). A claim that requires “a specific action” can “suffice[] to create a functional relationship.” *Id.* 1035. The claim at issue in *Praxair* that interrelated “claimed information regarding correlations between nitric oxide, LVD, and pulmonary edema with the concrete step of discontinuing treatment because of information” was determined to have a functional relationship to the substrate and was given patentable weight. *Id.*

Just like that claim at issue in *Praxair*, here, limitation 1(d) is entitled to patentable weight. Claim 1 of the '783 patent interrelates the claimed information in the report regarding the identification of genetic variants with the concrete step of “inform[ing] a therapy choice or a change in therapy for the subject.” EX1001 72:48-53 (limitation 1(d)). Limitation 1(d) requires a specific action (i.e., informing a therapy choice or a change in therapy for the subject) as a result of the information in the report that identifies genetic variants. EX2169 ¶¶75-76. Limitation 1(d) is not directed to a mere mental step because it requires a therapy choice or a change in therapy to be made for the subject, and that therapy choice or change in therapy must be informed by the genetic variants identified in the report. *Id.* Thus, limitation 1(d) creates a functional relationship between the printed matter (that is, the information in the report that identifies genetic variants) and the concrete step of informing a therapy choice or a change in a therapy for the subject. This functional relationship warrants patentable weight. *See Praxair*, 890 F.3d at 1035.

**b) Ley does not teach limitation 1(d)**

Foresight asserts that Ley Figure 3 “informs a therapy choice or a change” for the subject. Petition 34-35. Foresight’s assertion is wrong.

Ley fails to inform a therapy choice or a change in therapy for the subject because the subject of Ley’s assay *was deceased* at the time when Ley’s assay was performed. The subject of Ley’s assay (UPN 933124) had “*expired* 24 months after her initial diagnosis” and “[i]nformed consent for whole genome sequencing *was subsequently obtained* from her next of kin and family members.” EX1042 2. “*Subsequent to the death of patient 933124*, the WU HSC [Washington University Human Studies Committee] approved an amendment to the protocol that incorporated language specifically permitting the use of banked DNA for whole genome sequencing, to which her husband consented.” *Id.* 3. It is self-evident that there is no therapy choice or change in therapy to make for a deceased subject. EX2169 ¶78. Foresight fails to explain how Ley’s assay (which was performed after the death of the patient) involves a therapy choice or change in therapy for the deceased subject. Ley fails to anticipate limitation 1(d).

**B. Claim 15**

Claim 15 depends from claim 1 and requires that said additional biological sample “is a blood sample.”

Foresight relies on Ley's "relapse tumor sample" to supposedly meet claim 15. Foresight, however, concedes that Ley's relapse tumor sample is a tissue sample—not a blood sample. For example, Foresight concedes that "Ley discloses collecting samples *from tissue samples*, specifically a tumour sample." Petition 49; *see also id.* 51 ("Ley discloses collecting samples from tissue samples, specifically a tumor sample.").

Further Foresight does not provide any plausible mechanism to obtain an additional blood sample from the deceased patient. Anticipation cannot be established "by probabilities or possibilities." *Par Pharm.*, 773 F.3d at 1196.

**C. Claims 3, 8, 16, and 22**

Foresight does not allege that any of claims 3, 8, 16 and 22 are anticipated by Ley. Ley fails to demonstrate obviousness of these claims for reasons discussed, *infra*, regarding Ground 2.

**IV. GROUND 2: NONOBVIOUSNESS OVER LEY**

Ley does not render obvious independent claim 1, and therefore fails to render obvious any of dependent claims 2-9, 13-19, and 21-29. Ley further fails to render obvious dependent claims 3, 8, 15, 16, and 22 for additional reasons discussed herein.

**A. Claim 1**

A petition based on “obviousness requires a suggestion of all limitations in a claim.” *CFMT, Inc. v. YieldUp Int’l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003). Ley fails to render claim 1 obvious because it does not suggest any of the four limitations required by the claim.

**1. Limitation 1(a)**

Foresight’s obviousness theory requires a POSA to have been motivated to modify Ley’s assay to include “probes targeted to [1] genetic variants involved in the pharmacogenomics of cancer drugs, i.e., genetic variants that were known to have companion diagnostics, as well as to [2] tumor-driver mutations that were known in the art” to allegedly meet the “fixed portion” of limitation 1(a). Petition 43-46. This obviousness ground only serves to highlight Foresight’s lack of belief in its anticipation ground. Ley fails to teach the “variable portion” and “fixed portion” of limitation 1(a) for reasons discussed above. *Supra* Section III.A.1.

Foresight asserts that Ley’s assay inherently included twelve PCR primer pairs. Petition 25 (alleging ten pairs for “non-synonymous” mutations and two pairs for “control” mutations). As discussed above, Ley is devoid of any information about the primer design and PCR protocol that was used. Assuming, *arguendo*, that Ley’s assay did include twelve PCR primer pairs, there are at least three reasons why a POSA would not have been motivated to further complicate Ley’s assay with even

more PCR primer pairs directed to genetic variants involved in the pharmacogenomics of cancer drugs and tumor-driver mutations that were known in the art. Each of the three reasons are discussed in a separate subsection below.

**a) Ley counsels against Foresight's modification, which is confirmed by Dr. Quackenbush's testimony**

First, Ley teaches “[o]ur results strongly support the notion that hypothesis-driven (for example, candidate gene-based) examination of tumour genomes by PCR-directed” methods “is inherently limited, and will miss key mutations.” EX1012 70. Foresight’s obviousness theory requires a POSA to add more PCR primer pairs to Ley’s assay, with the additional PCR primer pairs directed to (1) genetic variants involved in pharmacogenomics of cancer drugs and (2) tumor-driver mutations known in the prior art. Adding PCR primer pairs directed to genetic variants involved in pharmacogenomics of cancer drugs and tumor-driver mutations known in the prior art are precisely the type of “hypothesis-driven” examination of tumor genomes by PCR-directed methods that Ley strongly counsels are inherently limited and will miss key mutations. EX2169 ¶84. Thus, Ley itself would dissuade a POSA from pursuing Foresight’s obviousness theory.

Rather than increase the number of PCR primers, a POSA would have instead sought to *decrease* the number of PCR primers for reasons admitted by Dr. Quackenbush during deposition. Dr. Quackenbush testified that a POSA would have been motivated by four factors when designing assays related to tumors: (1) the

desirability of increasing accuracy for an assay, EX2163 17:19-20:1, 21:12-23:10, (2) the desirability of reducing the cost of an assay, *id.* 27:15-30:22, (3) the desirability of simplifying an assay, *id.* 36:7-21, and (4) the desirability of simplifying the computational analysis for data generated by an assay, *id.* 41:18-44:17. He explained that all four of these motivations were important to a POSA. *Id.* 45:2-49:11. Foresight's proposal to increase the number of PCR primers used by Ley's assay is counterproductive to each of these four motivations. EX2169 ¶¶85-89.

For example, increasing the number of PCR primers would decrease the accuracy of the assay due to amplification issues that are discussed in the very next subsection of this Response.

Increasing the number of PCR primers also would increase the cost of the assay by requiring the design and synthesis of more PCR primers (as well as increasing costs due to issues with potential complications associated with adding more PCR primers to an assay that are discussed in the next subsection of this Response). Dr. Quackenbush explained elsewhere on behalf of Foresight that a POSA actually would have been motivated to use "fewer oligonucleotide probes" to "reduce sequencing costs." EX2168 ¶167. He further explained during his deposition that cost was "really driving some of the science" because "[i]f the assay

was simply too expensive, then one could not effectively run this assay.” EX2163  
29:19-30:10; *id.* 27:15-30:22.

Adding PCR primers to Ley’s assay would complicate the assay rather than simplify it. Dr. Quackenbush confirmed during deposition that a POSA would have sought “ways of simplifying assays to be as informative and as cost effective as possible.” *Id.* 36:7-21.

Adding PCR primers to Ley’s assay would generate more data, which would complicate the computational analysis for the assay. Dr. Quackenbush admitted during deposition that the desire to simplify computational analysis is significant because it applies “to the entire process” including “[p]rocessing the sequencing data, mapping that sequence data back to a reference,” as well as many other aspects that “were well known in the art.” *Id.* 43:15-44:19.

Foresight’s obviousness theory that requires adding more PCR primers to Ley’s already complicated assay contradicts each of the four motivations that Dr. Quackenbush testified were important for a POSA to consider when designing assays related to tumors. Foresight fails to provide a reasoned analysis why a POSA would have been motivated to ignore the significant evidence counseling against making further complications to Ley’s assay. As a result, Foresight has not proven that a POSA would have been motivated to modify Ley’s assay by adding more PCR

primers directed to (1) genetic variants involved in pharmacogenomics of cancer drugs and (2) tumor-driver mutations known in the prior art.

**b) Adding more PCR primers would complicate the assay**

Second, a POSA would not have been motivated to add even more PCR primer pairs to Ley's assay (which supposedly already had twelve PCR primer pairs) because it would complicate the assay. For example, Foresight's Mamanova exhibit states that "PCR is difficult to multiplex to any useful degree: the simultaneous use of many primer pairs can generate a high level of nonspecific amplification, caused by interaction between the primers, and more-over amplicons can fail to amplify." EX1007 112. Foresight's Mertes exhibit teaches that PCR "does not scale easily, in any format" and "any significant extent of parallelized singleplex or multiplex PCR would need to be supported by the use of automated robotics" and the products "need to be carefully normalized to equivalent molarities when pooling in advance of NGS (so that the final coverage of the total region of interest is as even as possible)." EX1006 379; EX2169 ¶¶90-91.

Foresight's position in this litigation that a POSA would have been motivated to add more PCR primers to Ley's already-complicated assay is exactly the opposite of what Foresight previously told the rest of the world in its scientific writings. For

example, Foresight’s founders<sup>4</sup> wrote that “technical limitations related to multiplexing of PCR assays have to date limited the number of genomic positions that can be interrogated” and that PCR assays can only use a “small combination of amplicons.” EX2164 716. They elsewhere wrote that the “[l]imitations of [PCR-based] approaches include interrogation of relatively few genomic loci owing to difficulties related to multiplexing of PCR assays.” EX2165 307-308. In 2021—years after the filing of the ’783 patent—they wrote that “PCR-based assays have limited multiplexability.” EX2166 202.

**c) Ley’s mutations had unknown clinical relevance**

Third, Foresight relies on Ross (EX1014) and Burell (EX1071) to supposedly motivate a POSA to add a multitude of PCR primer pairs to Ley’s assay for genetic variants involved in the pharmacogenomics of cancer drugs and tumor-driver mutations known in the prior art. Petition 43-44. Foresight ignores Ley’s explanation that the mutations identified by Ley’s assay have unknown clinical value. For example, Ley explains “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.*” EX1012 71. Ley further states

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<sup>4</sup> Foresight was founded by Ash Alizadeh, Maximilian Diehn, David Kurtz, and Jake Chabon. EX2151.

that the function of the mutations found by its assay “*is not yet known.*” *Id.* 66; EX2169 ¶92.

A POSA would not have been motivated to combine PCR primers for Ley’s mutations of unknown clinical significance with PCR primers for genetic variants and tumor-driver mutations known in the prior art because Ross teaches to avoid assays that include “abnormalities of unknown clinical importance” as follows:

Given the potential generation of ‘actionable’ gene sequence abnormalities and abnormalities of unknown clinical importance, the successful NGS-based clinical service will have a result report that is focused on the abnormalities that can lead directly to the best available therapy, direct a patient to an ongoing clinical trial, or result in some other actionable response from the treating oncologist.

EX1014 537. Ross further teaches it is not practical or feasible to test for all mutations of potentially important clinical significance in a given tumor “given the amount of tumor sample, time, and money it would take to perform so many individual tests.” *Id.*

Ross also teaches that “[c]linical applications, particularly in oncology, demand high levels of accuracy, sensitivity, and specificity for sequence-based tests focused on calling out specific genetic alterations.” *Id.* 535. Foresight’s founders wrote that “only highly sensitive detection techniques are likely to be of clinical use.” EX2165 306. Polluting Ley’s alleged set of twelve PCR primers with even

more primers would reduce accuracy, sensitivity, and specificity due to amplification issues discussed above, *supra* Section IV.A.1.b, which is something that Ross teaches to avoid. EX2169 ¶¶93-94.

Furthermore, Ley's assay used the Illumina sequencer, ABI 3730 Sanger sequencer, and the Roche/454 sequencer. EX1012 71. Ross teaches that the Illumina sequencer had "low multiplex capability." EX1014 530-31, Table 3. Ross teaches that Sanger sequencing is limited "to single-gene or hot-spot sequence analysis," *id.* 535, and was believed to be "incapable of scaling sufficiently to support the breadth of information required to manage an ever-growing arsenal of targeted anticancer drugs." *id.* 528. Ross teaches the Roche/454 sequencer had "low parallelism." *Id.* 530-31, Table 3. Thus, a POSA would not have been motivated to modify Ley's sequencing workflow to add more PCR primers as required by Foresight's obviousness theory. EX2169 ¶95.

Burell is an unrelated review paper that merely discusses genetic heterogeneity in cancer evolution. Thus, Ley's assay lacks sufficient sensitivity to be suitable to address the heterogeneity problems identified in Burell. EX2169 ¶96. The Burell reference was co-authored by Professor Charles Swanton. Dr. Swanton wrote elsewhere that "ctDNA analysis may in fact be superior to a single tumor biopsy for resolving the majority of copy number aberrations present in a single tumor." EX2002 7. Thus, Swanton instructs a POSA not to pursue a single-tumor

biopsy assay (which is the type of assay that Ley discloses), particularly in light of the genetic heterogeneity typically present in tumors but purposefully avoided by Ley’s “high sample purity.” EX1042 2. Burell is devoid of any discussion of PCR primers or how to use next generation sequencing instruments. Burell fails to rectify any of the deficiencies enumerated above concerning Foresight’s obviousness theory.

## 2. Limitation 1(b)

Limitation 1(b) requires an “additional biological sample from said subject.” As discussed above, Foresight relies on the *same* biological samples from Ley (the skin sample and relapse tumor sample) to meet the “at least one biological sample of said subject” of limitation 1(a) and the “additional biological sample from said subject” of limitation 1(b). *Supra* Section III.A.2. Because Foresight relies on the same relapse tumor and skin biopsy samples to meet the “at least one biological sample of said subject” of limitation 1(a), there are no additional samples left in Ley to meet the “additional biological sample from said subject” required for limitation 1(b).

Foresight fails to provide any motivation to modify Ley’s assay to include more samples from Ley’s patient. Adding more tumor sampling steps to Ley’s assay does not appear to be necessary for the purposes described by Ley of discovering cancer-initiating mutations. A POSA would not be motivated to obtain more

samples from Ley's patient at least because Ley's patient was deceased at the time Ley's assay was performed. EX1042 2-3; EX2169 ¶¶98-99. Even if the patient had been alive, a POSA would have known that "[b]iopsies are invasive and costly," EX1030 1, and that tumors "cannot be repeatedly sampled without invasive procedures," EX1044 2.

### 3. Limitation 1(c)

Foresight fails to provide any discussion regarding how it believes a POSA would have been motivated to modify Ley's assay to involve "subjecting said sequencing library to sequencing *to identify* a presence or absence of at least a subset of said set of genetic variants" as required by limitation 1(c). Petition 43-48. Foresight instead relies on the incorrect premise that the claimed "to identify" step and Ley's validation step are equivalent. Petition 31-33. A POSA would not conflate these distinct steps for reasons discussed above. *Supra* Section III.A.3.

Foresight readily admits that Ley performs separate steps of identification and validation by explaining that "[o]nce the variants of interest, i.e., the 'putative variants,' *were identified, Ley then describes 'validation* using custom PCR and capillary sequencing' as well as sequencing of 'validated somatic mutations' 'by Roche/454 sequencing of PCR-generated amplicons made from primary genomic DNA.'" Petition 25. Thus, Ley initially identifies variants of interest, and then separately validates the variants of interest. *Id.* The result of Ley's validation step

is the quantification of variant frequencies by tallying readcount sequencing data rather than establishing the identity of a presence or absence of variants as claimed. A POSA would not be motivated to *re*-establish the identity of mutations that had already been established. EX2169 ¶¶101-102.

Establishing the identify of a presence or absence of at least a subset of said set of genetic variants via sequencing is an innovative part of the claimed invention. There were at least three problems with prior art studies of tumor tissues that utilized sequencing: (1) short read lengths, (2) tumor heterogeneity, and (3) cost. Ley’s assay did not address these problems. Ley merely provided a short read length study that sidestepped the heterogeneity issue by using an atypical tumor sample composed of almost 100% tumor cells. EX2169 ¶¶103-104; EX1042 1-2. Typical tumor samples contain a mixture of tumor and normal cells. The normal cells tend to cause high background noise levels, which makes it difficult to establish the identity of a presence or absence of genetic variants. Further, Ley’s workflow already required significant amounts of sequencing such that there would not have been a motivation for a POSA to increase the cost and complexity of Ley’s assay by adding even more sequencing to arrive at limitation 1(c).

#### **4. Limitation 1(d)**

Ley does not suggest “generating a report identifying (i) a presence or absence of a health condition or disease of the subject in said biological sample based on said

identified at least a subset of (c) and (ii) genetic variants *which inform a therapy choice or a change in therapy for the subject*” as required by limitation 1(d) for at least two reasons.

First, the mutations identified by Ley’s assay have unknown clinical value. For example, Ley explains “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.*” EX1012 71. Ley further states that the function of the mutations found by its assay “*is not yet known.*” *Id.* 66. Because the mutations had unknown clinical value, a POSA would not have been motivated to use them to make a therapy choice or a change in therapy for Ley’s subject. EX2169 ¶106. Foresight fails to explain how a POSA would use Ley’s mutations of unknown clinical relevance to inform a therapy choice or a change in therapy for a subject.

Second, Ley’s patient was deceased at the time Ley’s assay was performed. EX1042 2-3; EX2169 ¶107. There are no therapy choices or changes in therapy to make for a deceased patient. Foresight fails to explain how a POSA would have been motivated to make a therapy choice or change in therapy for Ley’s deceased subject.

**5. No motivation to modify Ley**

As discussed above, a POSA would not have been motivated to modify Ley's assay to (1) add PCR primer pairs having a "variable portion" and "fixed portion" to meet limitation 1(a), (2) add an additional biological sample from the subject to meet limitation 1(b), (3) add a protocol to *re*-establish the identity of mutations that Ley had already been established to meet limitation 1(c), and (4) make a therapy choice or change in therapy based on mutations of unknown clinical value to a deceased patient to meet limitation 1(d). EX2169 ¶108. Foresight fails to provide a persuasive motivation for any one of these modifications, much less the complete redesign of Ley's assay that would be required to do all of them. Accordingly, Foresight failed to prove obviousness of independent claim 1 and all dependent claims.

**B. Claims 3, 8, 15, and 16**

Claims 3, 8, 15, and 16 require either a "plasma sample" or a "blood sample." Foresight asserts that a POSA would have been motivated to use Ley's assay on "cell-free tumor DNA circulating in the blood" to allegedly meet claims 3, 8, 15, and 16. Petition 49-51, 52-54.

A POSA would not have been motivated to use Ley's assay on cell-free tumor DNA with a reasonable expectation of success. Ley teaches that its assay requires "high sample purity" and that "contaminating normal cells would complicate our analysis." EX1042 2; EX2169 ¶¶113-114. In contrast to the pristine sample

required for Ley's assay, it was known that cell-free tumor DNA is incredibly impure because it is contaminated with a host of materials. Dr. Quackenbush admits that cell-free DNA is contaminated with debris from apoptosis and the death of cells that deposit "fragmented DNA, along with other parts of the cells" and waste products into the blood. EX1020 ¶86. He also admits that cell-free tumor DNA exists in the bloodstream "along with other parts of the cells," EX2163 11:16-12:19, as well as "white blood cells, red blood cells, ... additional proteins and nucleic acid," *id.* 12:20-14:9.

Foresight provides no explanation as to what modifications a POSA would have been needed to make to Ley's assay for there to be a reasonable expectation it would work on cell-free tumor DNA circulating in the blood in view of Ley's express teaching its assay requires "high sample purity" and the admissions by its own expert that such circulating DNA is highly impure and contaminated with a host of debris, cells, parts of cells, proteins, nucleic acids, and waste products.

Also, Claims 8, 15, and 16 require the "additional biological sample" to be a "blood sample." Foresight does not provide any plausible mechanism to obtain an additional blood sample from the deceased patient.

**C. Claim 22**

Claim 22 depends from claim 1 and requires the "personalized probe set comprises hybrid capture probes."

Foresight alleges that a POSA would have found it obvious to modify Ley's assay by replacing its undisclosed PCR primers with hybrid capture probes because they were "relatively interchangeable" and could be obtained "out of the box." Petition 54-55. Foresight provides almost no explanation as to why it believes a POSA would make such a drastic modification to Ley's assay.

Foresight incorrectly treats capture probes and PCR primers as being interchangeable. Foresight's Mertes exhibit teaches that capture probes and PCR are two different enrichment techniques that are "categorized according to the nature of their *core reaction principle*." EX1006 375. The core reaction principle of capture probes involves hybridizing to "targeted regions of interest, either in solution or on a solid support, so that one can physically capture and isolate the sequences of interest." *Id.* In contrast, the core reaction principle of PCR primers is "amplification" of targeted regions by a "polymerase chain reaction (PCR)" that copies target regions. *Id.*; *see also id.* 376, Fig. 1; EX2169 ¶¶116-117. Dr. Quackenbush's colleagues at the Dana-Farber Cancer Institute wrote that PCR and capture probe arrays are "orthogonal technologies." EX2177 23-24.

Foresight's founders criticized "hybrid capture-based workflows" as being limited because they "typically have longer turnaround times, since the target enrichment process often takes days (instead of hours with PCR), and are more expensive, since they involve sequencing a larger genomic space," which "may

provide diminishing additional value.” EX2166 203. They further wrote that hybrid capture assays are limited because they “can only detect alterations in genomic regions that are covered” by the capture probes. EX2165 308.

Foresight’s exhibits go to great lengths to describe the different benefits and drawbacks of these different techniques. Foresight’s Mertes exhibit has entirely different sections discussing “enrichment by hybrid capture” and “enrichment by PCR” with primers, EX1006 378-80, and explains that *“[g]iven the operational characteristics of these different targeted enrichment methods, they naturally vary in their suitability for different fields of application,” id.* 375. Mertes demonstrates “how very divergent the results of” hybrid capture and PCR primer amplification can be, as they “produce very different average coverage, evenness and specificity.” EX1006 383. Similarly, Mamanova identifies numerous differences between “PCR,” “[o]n-array hybrid capture,” and “[i]n-solution hybrid capture.” EX1007 114, Table 1.

Based on the differences in core reaction principles of the techniques, Foresight’s exhibits explain that there are many factors that a POSA must weigh when selecting either capture probes or PCR primers for a given experiment. Mamanova teaches “[t]here are several enrichment approaches, each with unique advantages and disadvantages” such that a user must “find the best compromise between sensitivity, specificity and uniformity for their particular project.” EX1007

111. Mamanova further teaches that there are **seven** “parameters” by which a POSA should evaluate capture probes or PCR primers before selecting one over the other:

- (i) sensitivity, or the percentage of the target bases that are represented by one or more sequence reads;
- (ii) specificity, or the percentage of sequences that map to the intended targets;
- (iii) uniformity, or the variability in sequence coverage across target regions;
- (iv) reproducibility, or how closely results obtained from replicate experiments correlate;
- (v) cost;
- (vi) ease of use; and
- (vii) amount of DNA required per experiment, or per megabase of target.

*Id.*

Similarly, Mertes teaches that a POSA must “rationally decide which technologies are most suitable when designing a research project” by weighing the following **seven** “series of metrics” to evaluate each “method’s innate enrichment capability” for each experiment:

- (i) Region of interest (size): ROI;
- (ii) Average read depth (in ROI): D;
- (iii) Fraction of ROI sufficiently covered (at a specified D): F;
- (iv) Specificity (fraction of reads in ROI): S;
- (v) Enrichment Factor (D for ROI versus D for rest of genome): EF;

- (vi) Evenness (lack of bias): E and
- (vii) Weight (input DNA requirement): W.

EX1006 380. Further, PCR cannot truly “capture” DNA, it can only copy it. For example, PCR cannot “capture” methylated cytosine, but capture probes can. EX2169 ¶¶118-120. Therefore, a POSA would understand that capture probes and PCR primers are different enrichment techniques, and selecting one or the other is a compromise that involves evaluating numerous parameters/metrics for each experimental design.

Foresight provides no reason why a POSA would have been motivated to reconfigure Ley’s PCR-based assay to use hybridization capture probes. As discussed above, a POSA would have needed to evaluate seven parameters and seven metrics associated with the disadvantages of capture probes before discarding the core reaction principle of Ley’s PCR assay and replacing it with capture probes. The vast majority of these parameters would have counseled a POSA to avoid attempting to redesign Ley’s experiment. For example, Mamanova teaches that “[t]he *specificity* of PCR will almost certainly always exceed that of hybrid capture, and its *uniformity* may never be matched by either hybrid capture or MIPs.” EX1007 117. Further, Mamanova teaches that PCR has higher *reproducibility* of “up to 100%” than capture probes. *Id.* Table 1. Ley already had a working assay, so switching the core reaction principle to capture probes would entail more *costs*

for redesigning the experiment, and risk making the assay *harder to use*. EX2169 ¶121. Dr. Quackenbush explained that cost was “really driving some of the science” because “[i]f the assay was simply too expensive, then one could not effectively run this assay.” EX2163 29:19-30:10; *id.* 27:15-30:22. The *sensitivity* and *amount of DNA required* are parameters that would, at best, be considered neutral; but the risks associated with modifying Ley’s already-working assay could very well cause the assay to lose sensitivity or, even worse, not work at all.

Further, Foresight failed to describe what the workflow of Ley’s PCR assay would look like if a POSA were to somehow have been motivated to use capture probes instead of PCR. Foresight leaves the Board and Personalis guessing as to which portion of Ley’s PCR-based workflow a POSA would have been motivated to change to capture probes, and which steps in Ley’s workflow would need to be kept, jettisoned, or rearranged to accommodate such a change in the core reaction principle of Ley’s assay with a reasonable expectation of success.

If a POSA were to obtain hybrid capture probes “out of the box,” Petition 54-55, then the genomic content of such probes would not meet the claimed “variable portion” which must change from one subject to another and result from sequencing data for a biological sample from the subject. EX2169 ¶¶122-123. Foresight fails to prove that a POSA would have been motivated to modify Ley’s assay to use hybrid capture probes, and therefore fails to prove obviousness of claim 22.

## **V. GROUND 3: NONOBVIOUSNESS OVER FORSHEW AND DAWSON**

The combination of Forshew and Dawson fails to render obvious independent claim 1, and therefore fails to render obvious any of dependent claims 1-9, 13-19, and 21-29. These references further fail to render obvious dependent claim 22 for additional reasons discussed herein.

### **A. Claim 1**

Forshew and Dawson fail to render claim 1 obvious because it does not teach or suggest at least two limitations of the claim:

- “(i) at least one variable portion from a result of said sequence data and (ii) at least one fixed portion independent of said result of said sequencing data” as required by limitation 1(a), and
- “generating a report identifying (i) a presence or absence of a health condition or disease of the subject in said biological sample based on said identified at least a subset of (c) and (ii) genetic variants which inform a therapy choice or a change in therapy for the subject” as required by limitation 1(d).

#### **1. Limitation 1(a)**

Limitation 1(a) requires “at least one variable portion” and “at least one fixed portion.” Foresight’s obviousness theory for this limitation is hopelessly vague and defies logic.

**a) ForsheW does not teach the claimed “variable portion”**

Petitioner asserts that ForsheW “expressly discloses the use of a variable portion” based on a set of 10 PCR primers for ForsheW’s breast cancer patient that supposedly meets the “variable portion” of limitation 1(a). Petition 64. ForsheW makes no such express disclosure because it does not disclose the sequences of the PCR primers used for its breast cancer patient.

Dr. Quackenbush confessed during deposition that “the details of how ForsheW designed his primers isn’t provided in the main text.” EX2163 147:22-148:2. The details aren’t in the main text or the supplemental materials. EX2169 ¶¶128-129. Dr. Quackenbush admitted that the PCR primers for ForsheW’s breast cancer patient “could very well represent a standard probe set that he purchased off the shelf.” EX2163 155:5-157:16; *id.* (“what ForsheW is telling us is that these may have been standard primers that could have been purchased”). Faced with the lack of details provided by ForsheW, Dr. Quackenbush speculated that “ForsheW may have been using a commercially available set of probes that targeted individual exons. In reading this, that may, in fact, be what ForsheW is referring to.” *Id.* 153:16-155:3.

If ForsheW used a standard probe set that he purchased off the shelf (in accordance with Dr. Quackenbush’s speculation), then such a probe set would not constitute the “variable portion” of limitation 1(a). The appropriate construction of

“variable portion” requires that the portion “changes from one subject to another and results from said sequence data.” *Supra* Section III.A.1.a. First, a standard probe set purchased off the shelf would not change from one subject to another. Second, a standard probe set would not “result from said sequence data” from “at least one biological sample” as required by limitation 1(a) because the standard probe set would be the result of extraneous criteria applied by the manufacturer of the standard probe set. EX2169 ¶129. Foresight has not proven that Forshew’s undisclosed PCR primers for the breast cancer patient constitute the “variable portion” required by the limitation 1(a).

**b) No suggestion for the claimed “variable portion”**

Forshew does not suggest using PCR primers that would meet the claimed “variable portion.” Forshew teaches that its TAm-Seq assay should be used “without requiring any specially designed probes” because “custom-designed probes” are “expensive” and are “difficult to implement on a routine basis.” EX1030 10. In view of Forshew’s teaching to avoid custom-designed probes, a POSA would have been dissuaded from using the claimed personalized probe set recited by limitation 1(a) comprising nucleic acid probe molecules having oligonucleotide-directed genomic content comprising at least one variable portion that changes from one subject to another and results from said sequenced data. EX2169 ¶130.

Dawson also fails to suggest using PCR primers that would meet the claimed “variable portion.” Dawson contrasts the TAm-Seq assay with digital PCR. EX1070 1207 (“Here we have demonstrated the use of two strategies to quantify circulating tumor DNA: digital PCR assay and targeted deep sequencing [TAm-Seq].”). Dawson teaches that TAm-Seq is desirable over digital PCR because digital PCR “requires the design of personalized assays, an expensive and rate-limiting step.” *Id.* Dawson teaches that targeted deep sequencing is “a cost-effective alternative” to digital PCR. *Id.*; EX2169 ¶131. In view of Dawson’s teaching to avoid personalized assays because they are expensive and rate-limiting, a POSA would have been dissuaded from using the claimed personalized probe set recited by limitation 1(a) comprising nucleic acid probe molecules having oligonucleotide-directed genomic content comprising at least one variable portion that changes from one subject to another and results from said sequenced data.

**c) No motivation to combine “variable portion” and “fixed portion”**

If the Board were to accept Petitioner’s theory that Forshe’s undisclosed PCR primers for the breast cancer patient constitute a “variable portion” as recited by limitation 1(a)—which it should not for reasons discussed above—Forshe still fails to teach or suggest combining a “variable portion” with a “fixed portion” in a personalized probe set as required by limitation 1(a).

Foresight readily admits that Forshew did not teach combining a “variable portion” with a “fixed portion” in a personalized probe set as required by limitation 1(a). Petition 64. Foresight therefore asserts that a POSA would have been motivated to convolute Forshew’s TAm-Seq assay that already included a set of 10 PCR primer pairs for a breast cancer patient with even more PCR primer pairs for variants in tumor suppressor gene TP53 mutations for ovarian cancer. Petition 64-65.

As a threshold matter, Foresight has not established that the undisclosed PCR primer pairs that Forshew used for its breast cancer patient constitute the claimed “variable portion” for reasons discussed above. Thus, even if a POSA had been motivated to combine Forshew’s undisclosed PCR primers for its breast cancer patient with PCR primers to detect TP53 mutations for ovarian cancer, Foresight would still not have established that such a combination would result in a “variable portion” and a “fixed portion” in a personalized probe set as required by limitation 1(a).

In addition, a POSA would not have been motivated to redesign Forshew’s TAm-Seq assay in the manner proposed by Foresight. According to Foresight, Forshew’s TAm-Seq assay already included a set of 10 PCR primer pairs for the breast cancer patient. Petition 64. It would take over 1,000 PCR primers to cover the TP53 gene. EX2169 ¶135. A POSA would not have been motivated to

complicate Forshew's TAm-Seq assay that already included a set of ten PCR primer pairs for breast cancer with over 1,000 additional PCR primer pairs for TP53 for several reasons.

First, Forshew expressly teaches that whatever the undisclosed PCR primer pairs were for the breast cancer patient, they definitely were "not included in the other sets of samples analyzed." EX1030 7, Fig. 4(D). Thus, we know that Forshew did not combine the breast cancer patient PCR primers with PCR primer pairs for TP53 in the manner proposed by Foresight. EX2169 ¶136.

Second, Dr. Quackenbush testified that a POSA would consider at least four motivations in designing assays related to tumors: (1) it was desirable to increase the accuracy of an assay, EX2163 17:19-20:1, 21:12-23:10, (2) it was desirable to reduce the cost of an assay, *id.* 27:15-30:22, (3) it was desirable to simplify an assay, *id.* 36:7-21, and (4) it was desirable to simplify computational analysis for data generated by an assay, *id.* 41:18-44:17. He explained that all four of these motivations were important to a POSA. *Id.* 45:2-49:11. Foresight's proposal to rework Forshew's TAm-Seq assay that already included a set of ten PCR primer pairs for breast cancer to include 1,000 additional PCR primer pairs for TP53 is contrary to each of these four motivations.

For example, Foresight's proposal to add more PCR primer pairs to Forshew's set of ten PCR primer pairs for breast cancer would have been avoided by a POSA

because it was expected to decrease accuracy and complicate the assay with amplification issues. Foresight's founders explained that Forshew's assay already suffered from "technical limitations related to multiplexing of PCR assays [that] have to date limited the number of genomic positions that can be interrogated," and explained that Forshew's methods can only use a "small combination of amplicons." EX2164 716 (Reference 15 is Forshew). Foresight's founders explained that Forshew's existing assays were limited to the "interrogation of relatively few genomic loci owing to difficulties related to multiplexing of PCR assays." EX2165 307-308. Foresight's founders admitted that in 2021 it remained true that "PCR-based assays have limited multiplexability." EX2166 202. Foresight's Mamanova exhibit states that "PCR is difficult to multiplex to any useful degree: the simultaneous use of many primer pairs can generate a high level of nonspecific amplification, caused by interaction between the primers, and more-over amplicons can fail to amplify." EX1007 112. Foresight's Mertes exhibit teaches that PCR "does not scale easily, in any format" and "any significant extent of parallelized" multiplex PCR "would need to be supported by the use of automated robotics" and multiplex products "need to be carefully normalized to equivalent molarities when pooling in advance of NGS (so that the final coverage of the total region of interest is as even as possible)." EX1006 379; EX2169 ¶¶137-140.

In addition, Forshew used the Illumina GAIIx sequencer (EX1030 3; EX2167 19) and an ABI 3730 Sanger sequencer (EX2167 1). Foresight's Ross exhibit teaches that the Illumina sequencer had "low multiplex capability." EX1014 530-31, Table 3. Ross teaches that Sanger sequencing is limited "to single-gene or hot-spot sequence analysis," *id.* 535, and was believed to be "incapable of scaling sufficiently to support the breadth of information required to manage an ever-growing arsenal of targeted anticancer drugs." *id.* 528; EX2169 ¶141. Foresight provides no analysis as to how the undisclosed set of 10 PCR primer pairs would have been expected to be compatible with PCR primer pairs for the TP53 in the convoluted assay that it proposes.

The Editor's Summary of Forshew criticizes the TAm-Seq assay as "need[ing] to achieve a more sensitive detection limit (<2% allele frequency) to identify mutations in the plasma of patients with less advanced cancers." EX1030 (Editor's Summary). Foresight's Ross exhibit teaches that "[c]linical applications, particularly in oncology, demand high levels of accuracy, sensitivity, and specificity for sequence-based tests focused on calling out specific genetic alterations." EX1014 535. Foresight's founders wrote that "only highly sensitive detection techniques are likely to be of clinical use." EX2165 306. Adding PCR primer pairs for TP53 to the undisclosed set of 10 PCR primers that Forshew used for breast cancer would have been undesirable because it would have been expected

to reduce accuracy, sensitivity, and specificity due to amplification complications discussed above. EX2169 ¶142. Such a reduction in accuracy, sensitivity, and specificity is exactly what The Editor's Summary of Forshew and Ross teach a POSA would want to avoid.

Nothing in Dawson corrects the numerous issues with Foresight's proposal to sully Forshew's breast cancer assay with even more PCR primers. Dawson uses the same TAm-Seq assay as Forshew. EX1070 1200. Foresight's founders criticize Forshew and Dawson's TAm-Seq assay because it lacked sensitivity:

Previously published methods employing amplicon<sup>8,10,11</sup>, whole exome<sup>12</sup>, or whole genome<sup>9,32,33,24</sup> sequencing would not be sensitive enough to detect ctDNA in most patients with NSCLC, even at 10-fold or greater sequencing costs (Fig. 1d and Supplementary Fig. 8).

EX1044 7 (Reference 8 is Forshew and Reference 11 is Dawson). They repeat their criticisms of Forshew and Dawson as being limited due to, *inter alia*, modest sensitivity and cost:

Recently, approaches employing massively parallel sequencing have been used to detect ctDNA<sup>5-12</sup>. However, the methods reported to date have been limited by modest sensitivity<sup>13</sup>, applicability to only a minority of patients, the need for patient-specific optimization, and/or cost.

*Id.* 2 (Reference 8 is Forshew and Reference 11 is Dawson); EX2169 ¶143. As discussed above, adding more PCR primers for TP53 to Forshew's existing assay

that already uses a set of 10 undisclosed PCR primers for breast cancer would have been expected to decrease the sensitivity of the assay and increase its cost.

In summary, Foresight's founders and exhibits teach that a POSA would have avoided convoluting Forshew's TAm-Seq assay that already included a set of ten PCR primer pairs for breast cancer with 1,000 additional PCR primer pairs for TP53 because it would have been expected to decrease the accuracy of the assay, increase the cost of the assay, complicate the assay, and complicate the computation analysis for the data generated by the assay. Foresight's obviousness assertion contradicts each of the four motivations that Dr. Quackenbush testified were important for a POSA to consider when designing assays related to tumors. Foresight fails to provide a reasoned analysis why a POSA would have been motivated to make its proposed modifications to Forshew's assay in the face of its own evidence counseling against making such a modification.

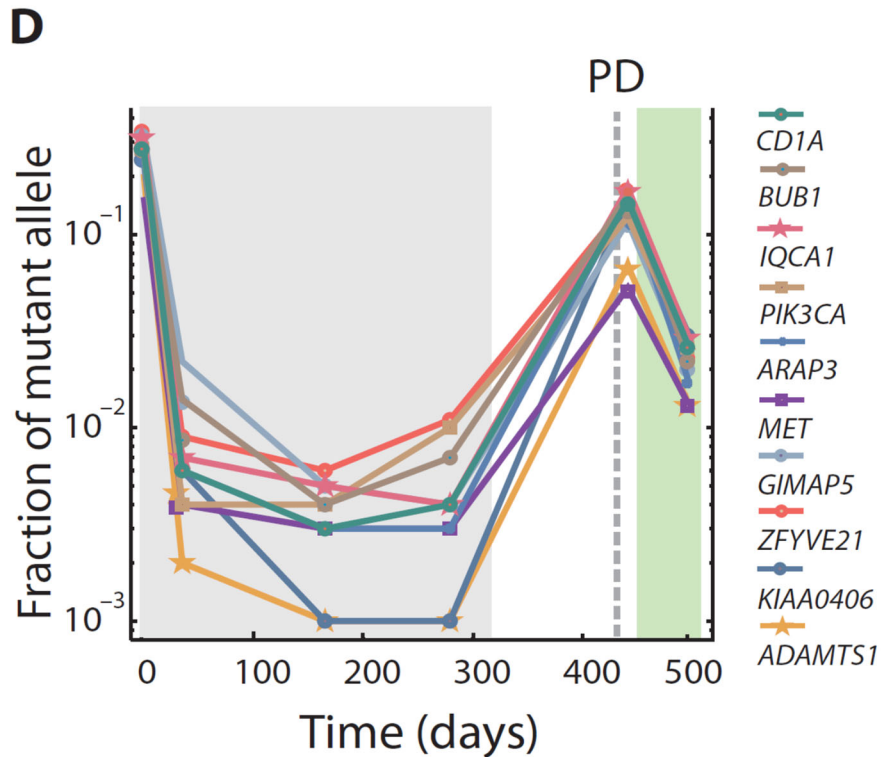
## **2. Limitation 1(d)**

Limitation 1(d) requires "generating a report identifying (i) a presence or absence of a health condition or disease of the subject in said biological sample based on said identified at least a subset of (c) and (ii) genetic variants *which inform a therapy choice or a change in therapy for the subject.*" Limitation 1(d) warrants patentable weight for reasons discussed above. *Supra* Section III.A.4.a.

Foresight asserts that Figure 4(D) of “Forshew shows a report depicting the fraction of the various mutant alleles over time, including in response to therapy.” Petition 69. Figure 4(D), however, does not constitute a report that informs a therapy choice or a change in therapy for the subject based on Forshew’s TAM-Seq assay for at least four reasons.

First, neither Forshew nor Dawson teaches or suggests the claimed steps of the method at least because it fails to teach or suggest limitation 1(a). *Supra* Section V.A.1. Thus, Figure 4(D) in Forshew does not teach or suggest generating a report based on the claimed method.

Second, Forshew explains that the breast cancer patient was treated with two phases of chemotherapy. EX1030 9. In the first chemotherapy phase, “[t]he patient was treated with a single-agent epirubicin (gray-shaded region).” *Id.* The patient was treated with epirubicin from time zero to a few days after day 300, as shown by the gray-shaded region in Figure 4(D):



*Id.* 7, Fig. 4(D). Forshew does not teach that the patient was treated with epirubicin for this period of time due to any aspect of the TAm-Seq assay. Rather, the patient was treated with epirubicin based on her having breast cancer (which was known *before* the fraction of her mutant allele was tracked using the TAm-Seq assay). In the second chemotherapy phase, “[a]fter 4 months off treatment, *a CT scan* showed *progressive disease* and the patient commenced further treatment with paclitaxel therapy.” *Id.* 9. Further evidence of this includes “PD” in Figure 4(D), which refers to “progressive disease,” which was based on the CT scan. *Id.* Thus, the patient received paclitaxel therapy based on *a CT scan*, not based on any result from the TAm-Seq assay. The change in therapy for Forshew’s patient that Foresight relies

upon was not based on the results of TAm-Seq assay from Figure 4(D). EX2169 ¶¶145-146. Foresight's obviousness position is based on a misrepresentation of Forshew's Figure 4(D) and fails to prove obviousness.

Third, the Editor's Summary of Forshew cautions that the TAm-Seq assay must be further "optimized" before it can "inform clinical decision-making on an individual basis." EX1030 (Editor's Summary). Forshew further cautions that its TAm-Seq assay will require faster and more accurate sequencing technologies or amplification strategies before it can even potentially be considered for use in with patients at the point of care. *Id.* 2 ("Combined with faster, more accurate sequencing technologies or rare allele amplification strategies, this approach could potentially be used for personalized medicine at point of care."). Based on these express cautions, a POSA would not have believed that the TAm-Seq assay was ready to be used to inform a therapy choice or a change in therapy for a patient. EX2169 ¶¶147-148.

Fourth, Foresight fails to account for the expected delay in obtaining data from Forshew's TAm-Seq assay due to the length of time it would take to perform the assay and process the resulting data. Foresight does not articulate how a POSA would obtain data from Forshew's TAm-Seq assay within a clinically relevant timeframe for making a therapy choice or change in therapy for the Forshew's patient.

For at least the foregoing reasons, Forshew and Dawson do not teach or suggest limitation 1(d).

**3. No motivation to arrive at claim 1**

As discussed above, a POSA reading Forshew and Dawson would not have been motivated to arrive at the “variable portion” and “fixed portion” required by limitation 1(a) or to make the therapy choice or change in therapy required by limitation 1(d). Foresight fails to provide a persuasive motivation for either of these changes to Forshew and Dawson, and it did not prove that a POSA would have been motivated to make both of them to arrive at the claimed invention absent forbidden hindsight. *Cheese Systems, Inc. v. Tetra Pak Cheese and Powder Systems, Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013). Accordingly, Foresight failed to prove obviousness of independent claim 1 and all dependent claims.

**B. Claim 22**

Claim 22 depends from claim 1 and requires the “personalized probe set comprises hybrid capture probes.”

Foresight alleges that a POSA would have found it obvious to overhaul Forshew and Dawson’s TAM-Seq assay by replacing its undisclosed PCR primers for the breast cancer patient with hybrid capture probes because they were “relatively interchangeable” and could be obtained “out of the box.” Petition 75-76. Foresight

merely repeats the same arguments it previously made regarding claim 22 in Ground 2.

As discussed above, Foresight incorrectly treats capture probes and PCR primers as being interchangeable. *Supra* Section IV.C. Foresight’s Mertes exhibit teaches that capture probes and PCR are two different enrichment techniques that are “categorized according to the nature of their *core reaction principle*.” EX1006 375; EX2169 ¶151. Foresight’s Mamanova exhibit teaches that “[t]here are several enrichment approaches, each with unique advantages and disadvantages” such that a user must “find the best compromise between sensitivity, specificity and uniformity for their particular project.” EX1007 111. Mamanova teaches that a POSA would have needed to evaluate seven parameters associated with the disadvantages of capture probes before discarding the core reaction principle of the PCR-based TAm-Seq assay and replacing it with capture probes.

The vast majority of these parameters would have counseled a POSA to avoid attempting to redesign the TAm-Seq assay. For example, Mamanova teaches that “[t]he *specificity* of PCR will almost certainly always exceed that of hybrid capture, and its *uniformity* may never be matched by either hybrid capture or MIPs.” *Id.* Further, Mamanova teaches that PCR has higher *reproducibility* of “up to 100%” than capture probes. *Id.* Table 1. Forsheo already had a working assay, so switching the core reaction principle to capture probes would entail more *costs* for redesigning

the experiment (and adding a different detection mechanism), and risk making the assay *harder to use*. EX2169 ¶¶152. The *sensitivity* and *amount of DNA required* are parameters that would, at best, be considered neutral; but the risks associated with modifying Forshew's already-working assay could very well cause the assay to lose sensitivity or even worse, not work at all.

Similarly, Foresight's Mertes exhibit explains that PCR primers and capture probes have different "operational characteristics" that "naturally vary in their suitability for different fields of application." EX1006 375. Mertes demonstrates "how very divergent the results" of hybrid capture and PCR primer amplification can be, as they "produce very different average coverage, evenness and specificity." *Id.* 383. Mertes teaches that a POSA would have needed to evaluate seven metrics associated with the disadvantages of capture probes before forsaking the already-working core reaction principle of the PCR-based TAM-Seq assay for capture probes. EX2169 ¶¶153-154. A POSA would not have been motivated to make such a drastic change to the assay's core reaction principle.

Also, if a POSA were to obtain hybrid capture probes "out of the box" as alleged in the Petition at 75-76, then the genomic content of such probes would not meet the claimed "variable portion" which must change from one subject to another and result from sequencing data for a biological sample from the subject. Foresight fails to prove that a POSA would have been motivated to modify Forshew and

Dawson to use hybrid capture probes, and therefore fails to prove obviousness of claim 22.

## **VI. OBJECTIVE INDICIA OF NONOBVIOUSNESS**

Objective indica “can be the most probative evidence of nonobviousness in the record.” *Crocs, Inc. v. Int’l Trade Comm’n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010).

### **A. Nexus**

Personalis is entitled to a presumption of nexus because, as detailed by Dr. Furneaux, Personalis’ NeXT Personal<sup>®</sup> assay embodies claim 1 of the ’783 patent. EX2169 ¶156; *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018).

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, Personalis has carried its burden.

### **B. Industry Praise**

Personalis’ assay has received industry praise due in part to its sensitivity. *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 '783 patent earned the #1 ranking. See EX2001; EX2035 ¶11.

Additional evidence of industry praise comes from an article reporting that three institutions “adopted Personalis’ NeXT Personal” for their TRACERx study due to its “highly sensitive test.” EX2153; EX2035 ¶¶14-17. Yet another article highlights the extended collaboration between Personalis and AstraZeneca regarding NeXT Personal in clinical research and drug development. EX2154; EX2156; EX2035 ¶¶18-20.

Indeed, the differences between the prior art methods and the method claimed in the '783 patent yield radically different results. Personalis’ assay can detect tumor in DNA in blood plasma at levels of about one part per million (or 0.0001%). Personalis’ assay therefore can detect allele frequencies of 0.0001%. By comparison, the Editor’s Summary of Forshew explains that the field sought allele frequency detections of less than 2%. EX1030 (Editorial Summary) (“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.”). Ley’s assay was only able to detect allele frequencies at approximately 3% for the “skin” sample. EX1012 69, Figure 3; EX2169 ¶158. Thus, Forshew and Ley were several

orders of magnitude less sensitive than the claimed method. The patented technique has been lauded by independent judges as the top scientific innovation of 2022, and by research institutions and pharmaceutical companies.

### **C. Skepticism**

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 (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." EX1030 10; *id.* 1; *see also* EX1031 (discussing "the key challenges in cancer genome sequencing"). Experts in the field were clearly skeptical of the capture probes Forshew described as "difficult to implement on a routine basis." EX1030 10.

Other references outline industry-wide problems with next-generation sequencing (NGS) at the time, which were unexpectedly solved by the methods in the '783 Patent. Anderson emphasizes that "difficult engineering challenges must be overcome before these technologies could become commercially viable." EX1004 48. Lo identifies difficulties regarding "how to handle the massive amount

of sequencing data” when utilizing NGS for profiling cancer genomes. EX1017 3;  
EX2169 ¶¶159-160.

This objective real-world evidence supports a finding that the claims of the  
'783 patent are nonobvious and, consequently, Foresight's attempt to demonstrate  
that the claims of the '783 patent are unpatentable fails.

## **VII. CONCLUSION**

For the foregoing reasons, the Board should confirm patentability of all  
challenged claims of the '783 patent. The Board should confirm patentability of  
dependent claim 22 for the additional independent reasons provided herein.

Respectfully submitted,

WEIL, GOTSHAL & MANGES LLP

Dated: November 3, 2023

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### **CERTIFICATE OF COMPLIANCE**

Pursuant to 37 C.F.R. § 42.24(d), Counsel for Patent Owner Personalis, Inc. hereby certifies that this document complies with the type-volume limitation of 37 C.F.R. § 42.24(b). This document contains approximately 13,910 words, including any statement of material facts to be admitted or denied in support, and excluding the table of contents, table of authorities, mandatory notices under § 42.8, exhibit list, certificate of service or word count, or appendix of exhibits or claim listing.

Dated: November 3, 2023

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**CERTIFICATE OF SERVICE**

I hereby certify that, pursuant to 37 C.F.R. § 42.6(e) and with the agreement of counsel for Petitioner, a true and correct copy of **PATENT OWNER RESPONSE AND EXHIBITS 2010, 2035, 2151, 2153-2154, 2156, 2163-2170, 2172, and 2177** are being served electronically on November 3, 2023, to the e-mail addresses shown below:

|                                                                                                                                                                                              |                                                                                                                                                 |
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