

UNITED STATES PATENT AND TRADEMARK OFFICE

---

BEFORE THE PATENT TRIAL AND APPEAL BOARD

---

FORESIGHT DIAGNOSTICS INC.,  
Petitioner,

v.

PERSONALIS, INC.  
Patent Owner.

---

Case IPR2023-00546  
U.S. Patent No. 10,450,611

---

**PATENT OWNER RESPONSE**

## TABLE OF CONTENTS

|                                                                                                | Page No. |
|------------------------------------------------------------------------------------------------|----------|
| I. INTRODUCTION .....                                                                          | 1        |
| II. OVERVIEW OF THE '611 PATENT.....                                                           | 4        |
| III. GROUND 1: NOVELTY OVER LEY .....                                                          | 9        |
| A. Claim 1 .....                                                                               | 9        |
| 1. Ley does not teach the required sequencing depth .....                                      | 10       |
| 2. Ley does not teach 175 kilobases or less .....                                              | 12       |
| 3. Ley does not teach sequencing “to identify” .....                                           | 14       |
| a) Claim construction of “to identify” .....                                                   | 15       |
| b) Ley does teach limitation 1(e) under the<br>appropriate construction of “to identify” ..... | 16       |
| B. Claim 5 .....                                                                               | 18       |
| 1. Claim construction of “variable portion” and “fixed<br>portion” .....                       | 19       |
| 2. Ley does not expressly or inherently teach a variable<br>portion or fixed portion .....     | 21       |
| C. Claims 10 and 28.....                                                                       | 26       |
| IV. GROUND 2: NONOBVIOUSNESS OVER LEY .....                                                    | 27       |
| A. Claim 1 .....                                                                               | 27       |
| 1. Ley does not suggest the required sequencing depth.....                                     | 28       |
| 2. Ley does not suggest 175 kilobases or less.....                                             | 30       |

# TABLE OF CONTENTS

(*cont'd*)

|                                                                                                             | <b>Page No.</b> |
|-------------------------------------------------------------------------------------------------------------|-----------------|
| 3. Ley does not suggest sequencing “to identify” .....                                                      | 31              |
| 4. No motivation to modify Ley .....                                                                        | 33              |
| B. Claim 5 .....                                                                                            | 35              |
| 1. Ley counsels against Foresight’s modification, which<br>is confirmed by Dr. Quackenbush’s testimony..... | 36              |
| 2. Adding more PCR primers would complicate the<br>assay .....                                              | 38              |
| 3. Ley’s mutations had unknown clinical relevance.....                                                      | 40              |
| C. Claim 10 .....                                                                                           | 42              |
| D. Claim 28 .....                                                                                           | 43              |
| V. GROUND 3: NOVELTY OVER NEWMAN.....                                                                       | 44              |
| A. Claim 1 .....                                                                                            | 44              |
| 1. Limitation 1(a) .....                                                                                    | 45              |
| 2. Limitation 1(d).....                                                                                     | 46              |
| 3. Limitation 1(e): said additional biological sample .....                                                 | 48              |
| 4. Limitation 1(e): coverage of 175 kilobases or less.....                                                  | 49              |
| B. Claim 5 .....                                                                                            | 50              |
| C. Claims 10 and 28.....                                                                                    | 51              |
| D. Claim 11 .....                                                                                           | 52              |

**TABLE OF CONTENTS**  
**(cont'd)**

|                                                | <b>Page No.</b> |
|------------------------------------------------|-----------------|
| VI. GROUND 4: NONOBVIOUSNESS OVER NEWMAN ..... | 52              |
| A. Claim 1 .....                               | 53              |
| 1. Limitation 1(d) .....                       | 53              |
| 2. Limitation 1(e) .....                       | 56              |
| 3. Limitation 1(a) .....                       | 57              |
| 4. Limitation 1(e) .....                       | 58              |
| 5. No motivation to modify Newman .....        | 59              |
| B. Claim 5 .....                               | 59              |
| C. Claims 10, 11, and 28 .....                 | 62              |
| VII. OBJECTIVE INDICIA OF NONOBVIOUSNESS ..... | 63              |
| A. Nexus .....                                 | 63              |
| B. Industry Praise .....                       | 63              |
| C. Skepticism .....                            | 64              |
| VIII. 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) ..... | 63             |
| <i>Bayer Schering Pharma AG v. Barr Laboratories, Inc.</i> ,<br>575 F.3d 1341 (Fed. Cir. 2009) .....   | 30             |
| <i>Belden Inc. v. Berk-Tek LLC</i> ,<br>805 F.3d 1064 (Fed. Cir. 2015) .....                           | 60             |
| <i>CFMT, Inc. v. YieldUp Int’l Corp.</i> ,<br>349 F.3d 1333 (Fed. Cir. 2003) .....                     | 27             |
| <i>Crocs, Inc. v. Int’l Trade Comm’n</i> ,<br>598 F.3d 1294 (Fed. Cir. 2010) .....                     | 63             |
| <i>Crown Operations Intern., Ltd. v. Solutia Inc.</i> ,<br>289 F.3d 1367 (Fed. Cir. 2002) .....        | 12, 23         |
| <i>DePuy Spine, Inc. v. Medtronic Sofamore Danek, Inc.</i> ,<br>567 F.3d 1314 (Fed. Cir. 2009) .....   | 55             |
| <i>In re Kahn</i> ,<br>441 F.3d 977 (Fed. Cir. 2006) .....                                             | 29             |
| <i>Luminara Worldwide, LLC v. Liown Elecs. Co.</i> ,<br>814 F.3d 1343 (Fed. Cir. 2016) .....           | 15             |
| <i>Net MoneyIN, Inc. v. VeriSign, Inc.</i> ,<br>545 F.3d 1359 (Fed. Cir. 2008) .....                   | 48, 51, 52     |
| <i>Ortho-McNeil Pharms., Inc. v. Mylan Labs., Inc.</i><br>520 F.3d 1358 (Fed. Cir. 2008) .....         | 31             |
| <i>Phillips v. AWH Corp.</i> ,<br>415 F.3d 1303 (Fed. Cir. 2005) (en banc) .....                       | 16, 19, 20, 21 |

**TABLE OF AUTHORITIES**  
**(cont'd)**

**Page No(s).**

|                                                                                                     |        |
|-----------------------------------------------------------------------------------------------------|--------|
| <i>Polaris Indus., Inc. v. Arctic Cat, Inc.</i> ,<br>882 F.3d 1056 (Fed. Cir. 2018) .....           | 63     |
| <i>Southwire Co. v. Cerro Wire LLC</i> ,<br>870 F.3d 1306 (Fed. Cir. 2017) .....                    | 28, 58 |
| <i>Verdegaal Bros. Inc. v. Union Oil Co. of California</i> ,<br>814 F.2d 628 (Fed. Cir. 1987) ..... | 9      |
| <i>WBIP, LLC v. Kohler Co.</i> ,<br>829 F.3d 1317 (Fed. Cir. 2016) .....                            | 64     |

**OTHER AUTHORITIES**

|                        |    |
|------------------------|----|
| 37 C.F.R. §42.62 ..... | 11 |
|------------------------|----|

### 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        | K.C. Allen Chan et al., “Cancer Genome Scanning in Plasma: Detection of Tumor-Associated Copy Number Aberrations, Single-Nucleotide Variants, and Tumoral Heterogeneity by Massively Parallel Sequencing,” <i>Clinical Chemistry</i> (2013)                                                                                                                                                                                                                                   |
| 2004        | Exemplary Embodying Product Claim Chart for U.S. Patent No. 10,450,611                                                                                                                                                                                                                                                                                                                                                                                                        |
| 2005        | Tim Forshew, et al., “Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA,” <i>Science Translational Medicine</i> (2012), EX1030, from related <i>Foresight Diagnostics Inc. v. Personalis, Inc.</i> , IPR2023-00545                                                                                                                                                                                                      |
| 2006        | Matthew W. Anderson & Iris Schrijver, “Next Generation DNA Sequencing and the Future of Genomic Medicine,” <i>Genes</i> (2010)                                                                                                                                                                                                                                                                                                                                                |
| 2007        | Dennis Lo, “Cancer Genome Scanning in Plasma, <i>Clinical Chemistry Journal</i> ,” Jan. 3, 2013 <a href="https://www.aacc.org/science-and-research/clinicalchemistry/clinical-chemistry-podcasts/2013/cancer-genomescanningin-plasma-detection-of-tumor-associated-copynumberaberrations">https://www.aacc.org/science-and-research/clinicalchemistry/clinical-chemistry-podcasts/2013/cancer-genomescanningin-plasma-detection-of-tumor-associated-copynumberaberrations</a> |
| 2008-2009   | RESERVED                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                                                                    |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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                                                                                                                                                                              |
| 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                                                                                                                                                                              |

| Exhibit No. | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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        | RESERVED                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 2168        | RESERVED                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 2169        | Declaration of Henry Morrice Furneaux                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 2170        | American Heritage Dictionary definition of “identify”                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 2171        | <a href="https://www.aacc.org/science-and-research/clinicalchemistry/clinical-chemistry-podcasts/2013/cancer-genomescanning-in-plasma-detection-of-tumor-associated-copynumber-aberrations">https://www.aacc.org/science-and-research/clinicalchemistry/clinical-chemistry-podcasts/2013/cancer-genomescanning-in-plasma-detection-of-tumor-associated-copynumber-aberrations</a> , EX1017, from related <i>Foresight Diagnostics Inc. v. Personalis, Inc.</i> , IPR2023-00545 |
| 2172        | Lewin, “Genes V,” Oxford University Press, 1994.                                                                                                                                                                                                                                                                                                                                                                                                                               |

| Exhibit No. | Description                                                                                                                                                                                                                |
|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2173        | Quackenbush Declaration, EX1020, from related <i>Foresight Diagnostics Inc. v. Personalis, Inc.</i> , IPR2023-00545                                                                                                        |
| 2174        | Matthew W. Anderson & Iris Schrijver, “Next Generation DNA Sequencing and the Future of Genomic Medicine,” <i>Genes</i> (2010), EX1004, from related <i>Foresight Diagnostics Inc. v. Personalis, Inc.</i> , IPR2023-00545 |
| 2175        | “No symbol” definition, <a href="https://en.wikipedia.org/wiki/No_symbol">https://en.wikipedia.org/wiki/No_symbol</a>                                                                                                      |
| 2176        | Ashford, “Dana Farber Poised to Shift ‘Profile’ Tumor Analysis Program From Research Study to Clinical Test,” <i>Genome Web</i> , September 16, 2016.                                                                      |
| 2177        | Sholl, Institutional implementation of clinical tumor profiling on an unselected cancer population,” <i>JD Insight</i> . 1:e87062 (2016)                                                                                   |

Patent Owner Personalis Inc. (“Personalis”) submits this Response to the Petition filed by Foresight Diagnostic Inc. (“Foresight”) regarding U.S. 10,450,611 (“the ‘611 patent”). The instant case is related to IPR2023-00545, where Foresight challenges U.S. Patent No. 11,299,783 (“the ‘783 Patent”).

## **I. INTRODUCTION**

Personalis is recognized as an undisputed leader in developing innovative personalized genomic assays. The ‘611 patent claims recite a novel and nonobvious personalized method that sequences a subject’s biological sample, identifying and designing probe sets to genetic variants, then applying the probe sets to an additional biological sample to enrich or amplify and sequence only the genetic variants.

Personalis’ NeXT Personal<sup>®</sup> detection and monitoring assay practices the ‘611 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 ¶¶40-45; EX1037. Foresight seeks to avoid liability for infringing the claimed

invention through the following four patentability challenges it raised in this proceeding: (1) alleged anticipation by the Ley reference, (2) alleged obviousness based on Ley, (3) alleged anticipation by the Newman reference, and (4) alleged obviousness based on Newman.

The Ley grounds do not render the claimed invention unpatentable. Specifically, Ley fails to teach or suggest at least three distinct requirements of limitation 1(e):

- “a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a),”
- “subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less,” and
- “subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less *to identify* a presence or absence of at least a subset of said set of genetic variants in said additional biological sample from said subject or said at least one biological relative.”

Foresight fails to prove that Ley inherently anticipates the “sequencing depth” and “coverage of 175 kilobases (kb) or less” required by limitation 1(e). In addition, Foresight’s anticipation and obviousness challenges regarding limitation 1(e) are not supported by the teachings of Ley. Testimony from Foresight’s own expert witness

(Dr. Quackenbush) confirms that Foresight has not proved unpatentability based on Ley for reasons discussed herein.

The Newman grounds do not render the claimed invention unpatentable. Specifically, Newman fails to teach or suggest at least four requirements of claim 1:

- “wherein said sequencing comprises sequencing 12 gigabases (GB) or more” as required by limitation 1(a),
- “an additional biological sample from said subject or at least one biological relative of said subject” as required by limitation 1(d), and
- “said additional biological sample from said subject or said at least one biological relative” as required by limitation 1(e), and
- “subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less” as required by limitation 1(e).

Foresight fails to prove that Newman inherently anticipates limitation 1(a) and limitation 1(e). In addition, Foresight’s anticipation and obviousness challenges are not supported by the teachings of Newman. Testimony from Dr. Quackenbush confirms that Foresight has not proved unpatentability based on Newman for reasons discussed herein. Further, Foresight’s proposed modification to Newman that supposedly renders obvious the “additional biological sample” required by limitation 1(d) fails because the modification is something that Newman expressly instructs a person of ordinary skill in the art (POSA) *not* to do.

Foresight fails to prove unpatentability of dependent claims 5, 10, and 28 for additional and independent reasons. Claim 5 requires a “fixed portion” and a “variable portion.” Claim 10 requires “a therapeutic intervention” and claim 28 requires “treat[ing] said subject or said at least one biological relative for a disorder.” Ley and Newman do not teach or suggest any of these limitations for reasons discussed herein.

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 ’611 patent were not anticipated or obvious at the time of the invention.

## **II. OVERVIEW OF THE ’611 PATENT**

The ’611 patent relates to “methods and systems for personalized genetic testing of as subject” for use in the diagnosis, monitoring, treatment, and prevention of diseases. EX1001 Abstract. Claim 1 is the only independent claim and it recites:

1. A method for personalized genetic testing, comprising:
  - (a) sequencing nucleic acid molecules from at least one biological sample of a subject to generate sequencing data, wherein said sequencing comprises sequencing 12 gigabases (GB) or more;
  - (b) computer processing said sequencing data to identify a plurality of nucleic acid sequences having a set of genetic variants,

wherein said set of genetic variants are identified with respect to a reference;

(c) obtaining a probe set comprising a plurality of nucleic acid probe molecules having said 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 said set of genetic variants over other sequences in said at least one biological sample;

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

(e) subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less to identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample from said subject or said at least one biological relative, wherein a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a).

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×).” EX1001 4:23-24; 4:26-29. 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.* 4:30-35. 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.* 4:35-38; *see also id.* 4:38-40 (“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.* 36:39-44.

The claimed method, however, is directed to a method for “personalized genetic testing.” First, the claimed method requires sequencing nucleic acid molecules from at least one biological sample, which can be a tissue sample, blood sample, or tumor tissue (EX1001 8:63-65, 10:7-8), to generate sequencing data of 12 gigabases (GB) or more of coverage. *See, e.g., id.* 62:31-38 (“In the standard cancer sequencing process, a deep tumor sample can be exome sequenced (e.g., 30-75 billion bases) and a germline DNA sample can be exome sequenced (e.g., 12 billion bases).... Also, a tumor RNA (e.g., 22 billion bases...) can be deep transcriptome sequenced.”).

Second, the sequencing data undergoes computer processing to identify genetic variants and their nucleic acid sequences. *See, e.g., id.* 11:46-55. Genetic variant “generally refers to an alteration, variant or polymorphism in a nucleic acid sample or genome of a subject.” *Id.* 25:4-6. The variants are identified with respect to a reference, including genomes or sequences from the same subject or another individual. *Id.* 25:6-9.

Third, the claimed method involves obtaining a probe set. 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.* 26:1-6. “A probe may be included in a set, or plurality, of probes.” *Id.* 26:11-12. The claimed probe set includes probes that are complementary to and thereby configured to enrich or amplify the identified genetic variants. *Id.* 26:1-19; *see also generally id.* Example 7 (describing exemplary methods to synthesize probes).

Fourth, the probe set is then applied to an “additional biological sample” to selectively enrich or amplify sequences comprising the genetic variants. *See, e.g., id.* 26:1-19. The additional biological sample may be a sample of the same tissue from same subject taken at a later time point, a sample of different tissue from the same subject, a sample from a biological relative of the subject, etc. *See, e.g., id.*

Example 1; *id.* 5:4-9. The enriched and amplified sequences of the genetic variants generate a sequencing library. *See, e.g., id.* 4:55-63.

Finally, the sequencing library is sequenced to identify a presence or absence of the genetic variants in the additional biological sample. The sequencing coverage of this step is 175 kilobases (kb) or less. *See* EX1001 34:65-35:3 (“As a non-limiting example, 500 variants may require the synthesis of at least about 500 sequences. The genomic region captured by each probe can be at least about 350 bases. Therefore, for at least about 500 sequences, the footprint of this assay may be about 175,000 bases.”). This is far less than the 12 GB sequenced during the first step, and, when “[c]ompared to an exome, where the footprint of the assay is typically at least 35 million bases, this may result in 200× less sequencing.” *Id.* 35:3-5. Use of targeted probes allows for a “dramatic reduction in the amount of sequencing required,” making it “much more affordable to sequence additional pedigree members” or other additional biological samples. *Id.* 35:5-9. 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.* 61:37-49 (“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.”).

### **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 claims 5, 10, and 28 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 at least three distinct requirements recited by limitation 1(e). Specifically, Ley fails to teach:

- “a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a),”
- “subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less,” and
- “subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less *to identify* a presence or absence of at least a

subset of said set of genetic variants in said additional biological sample  
from said subject or said at least one biological relative.”

**1. Ley does not teach the required sequencing depth**

Foresight does not allege that Ley *expressly* teaches “a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a)” as required by limitation 1(e). Petition 32. Instead, Foresight relies on Dr. Quackenbush to allege that Ley *inherently* discloses the “sequencing depth of said sequencing of (e).” Specifically, Foresight relies on Dr. Quackenbush adding together variant and reference read counts found in Ley’s Table 3 to allege that Ley inherently discloses sequencing depths that “ranged from 588-fold to 12,365-fold.” Petition 32 (citing EX1061 ¶¶123-125). Table 3 from Ley is reproduced below:

**Table 3 | 454 Readcount data for somatic mutations and known SNPs**

| Gene    | Consequence | Primary AML (100% blasts) |       |             | Skin    |       |             | Relapse (78% blasts) |      |             |
|---------|-------------|---------------------------|-------|-------------|---------|-------|-------------|----------------------|------|-------------|
|         |             | Variant                   | Ref   | Variant (%) | Variant | Ref   | Variant (%) | Variant              | Ref  | Variant (%) |
| CDH24   | Y590X       | 5672                      | 4890  | 53.70       | 564     | 10358 | 5.16        | 3108                 | 4599 | 40.33       |
| SLC15A1 | W77X        | 3817                      | 4962  | 43.48       | 875     | 10773 | 7.51        | 4714                 | 7173 | 39.66       |
| KNDC1   | L799F       | 4640                      | 4848  | 48.90       | 770     | 8972  | 7.90        | 3883                 | 6342 | 37.98       |
| PTPRT   | P1235L      | 998                       | 1058  | 48.54       | 126     | 1489  | 7.80        | 350                  | 493  | 41.52       |
| GRINL1B | R176H       | 2211                      | 2674  | 45.26       | 318     | 4461  | 6.65        | 1447                 | 2070 | 41.14       |
| GPR123  | T38I        | 4618                      | 4569  | 50.27       | 850     | 9751  | 8.02        | 3660                 | 6057 | 37.67       |
| EBI2    | A338V       | 12750                     | 15453 | 45.21       | 458     | 10088 | 4.34        | 2646                 | 3627 | 42.18       |
| PCLKC   | P1004L      | 992                       | 855   | 53.71       | 341     | 3153  | 9.76        | 705                  | 773  | 47.70       |
| FLT3    | ITD         | 4220                      | 7810  | 35.08       | 3475    | 23159 | 13.05       | 3870                 | 8495 | 31.30       |
| NPM1    | CATG ins    | 1550                      | 1974  | 43.98       | 143     | 2390  | 5.65        | 2303                 | 3910 | 37.07       |
| BRCA2   | N372H       | 778                       | 752   | 50.85       | 763     | 876   | 46.55       | 285                  | 303  | 48.47       |
| TP53    | P72R        | 8989                      | 1     | 99.99       | 8161    | 0     | 100.00      | 7914                 | 6    | 99.92       |

The differences between variant frequencies in primary or relapse tumour samples and skin were highly significant for all somatic mutations ( $P < 0.000001$ , Fisher’s exact test, one tailed). The BRCA2 variant is a known heterozygous SNP in this genome, and the TP53 variant is a known homozygous SNP.

EX1012 70, Table 3. This table provides “454 Readcount data for somatic mutations and known SNPs.” *Id.* Dr. Quackenbush makes a conclusory assertion that by simply “[s]umming the variant and reference read counts for each gene in each sample” shown in Table 3 “one can see that the variant loci in the additional relapse

sample (‘additional biological sample from said subject’) have been sequenced at depths ranging from 588-fold to 12,365-fold.” EX1061 ¶125.

The read counts found in Ley’s Table 3 do not provide sufficient information to calculate the sequencing depth. Dr. Quackenbush explained in the background “overview” section of his declaration that a POSA would have known that sequencing depth is calculated using the Lander/Waterman equation:

$$C=L*(N/G)$$

Where C stands for “coverage” or “sequencing depth,” G is the length of the genes being studied, L is the read length, and N is the number of reads. EX1061 ¶66.

Ley’s Table 3 only provides N, the number of reads (i.e., Ley’s “readcount”). Knowing the number of reads (N) alone does not allow a POSA to calculate the sequencing depth (C). To calculate sequencing depth (C), the POSA must also know the relevant read length (L) and the relevant length of genes being studied (G).

Dr. Quackenbush fails to indicate the relevant read length (L) or length of genes being studied (G) that a POSA would have used to calculate Ley’s sequencing depth (C). Dr. Quackenbush’s conclusory assertion that Ley’s sequencing depths ranged from 588-fold to 12,365-fold is unsupported and should be excluded because it does not disclose the underlying facts or data upon which it is based concerning read length (L) or length of genes being studied (G). 37 C.F.R. §42.62(a) (“Expert

testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.”).

Dr. Quackenbush admits that “Ley does not provide the primer sequences or the exact exons that were analyzed.” EX1061 ¶121. The primer sequences impact the read length of the resulting amplicon. EX1061 ¶¶75-78; EX2169 ¶¶175-177. Thus, Ley does not provide the read length (L). In addition, Ley does not provide the length of genes studied (G) because Ley does not provide the exact exons that were analyzed. Accordingly, Ley does not provide sufficient information to calculate the sequencing depth (C) for the experiments from Ley relied upon by Foresight to allegedly meet limitation 1(e). EX2169 ¶¶178-180. Foresight is left with merely “assumption[s] and its own contentions” about what Ley’s sequencing depth might have been. *Crown Operations Intern., Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1378 (Fed. Cir. 2002). This is insufficient to prove that the claimed sequencing depth “was necessarily present” in Ley. *Id.* Because Ley fails to disclose sufficient information to calculate Ley’s sequencing depth, Foresight has not (and indeed cannot) prove that Ley inherently discloses limitation 1(e).

**2. Ley does not teach 175 kilobases or less**

Limitation 1(e) requires “subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less.”

Ley does not *expressly* teach this requirement of limitation 1(e), and Foresight does not contend otherwise. Petition 30-31. Instead, Foresight relies on Dr. Quackenbush to allege that Ley *inherently* discloses the sequencing at a coverage of 175 kilobases or less based on his calculation that Ley sequenced, at most, 45.254 kilobases. Petition 30-31 (citing EX1061 ¶121).

Dr. Quackenbush does not prove that Ley sequenced at most 45.254 kilobases. Dr. Quackenbush first assumes an “upperbound” on the sequence coverage of Ley based on a PCR primer pair that would generate an amplicon for the entire length of each of the genes that contained a genetic variant identified by Ley as follows:

While Ley does not provide the primer sequences or the exact exons that were analyzed, *one can easily set an upper bound on the sequence coverage Ley teaches by using the entire length of the genes* that contained the genetic variant rather than the much smaller sequence of the variant-containing exon.

EX1061 ¶121.<sup>1</sup> Dr. Quackenbush then makes a second assumption that “the messenger RNA corresponding to the coding region of these ten genes” allows a POSA to “easily obtain the length of the entire coding sequence for each of the[se] genes.” EX1061 ¶121.

---

<sup>1</sup> All emphases supplied unless otherwise noted.

Dr. Quackenbush's second assumption is incorrect. Messenger RNA does not correspond to the length of the ten genes used by Ley. The length of the messenger RNA only corresponds to the length of the *exons* within Ley's genes. It is basic biology that the entire length of a gene includes both exons *and introns*. EX2172 149-150; EX2169 ¶¶182-183. The exons within a gene are interrupted by introns. In many genes, the introns are much longer than the exons. In fact, "the exome represents only approximately 1% of the genome." EX1031 690. Dr. Quackenbush explains that, while the exons for a given gene could span, for example, 1,000 bases, those exons could be distributed over tens of thousands of bases when including the introns for the gene. EX2163 33:19-22. Therefore, setting the "upper bound on the sequence coverage Ley teaches by using the entire length of the genes," EX1061 ¶121, which Dr. Quackenbush assumes is required to establish that Ley inherently teaches limitation 1(e), would actually amount to far more than 175 kilobases. EX2169 ¶183. Accordingly, Foresight fails to prove that Ley inherently discloses limitation 1(e).

**3. Ley does not teach sequencing "to identify"**

Limitation 1(e) requires "subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less *to identify* a presence or absence of at least a subset of said set of genetic variants in said additional biological sample from said

subject or said at least one biological relative.” Ley does not teach limitation 1(e) under the appropriate construction of the term “to identify.”

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

The Board preliminarily determined that “step 1(e) is silent as to whether a genetic variant is identified de novo in a previously untested ‘additional’ sample, or identified in a previously tested sample for some validating or confirmatory purpose.” Institution Decision (“Decision”) 27. The Board also preliminarily determined that “[i]n showing that variant alleles were present in both primary and relapse tumor samples, Ley’s Figure 3 satisfies claim step 1(e) by ‘identifying a presence or absence of at least a subset of said set of genetic variants in said additional biological 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(e).

Foresight failed to explain its interpretation of what it means “to identify” within the context of limitation 1(e). Petition 30-32, 16-19. 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 ¶¶185-189. This construction stays true to the plain meaning of “to identify” and should be adopted in this proceeding.

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

Foresight readily admits that Ley performs separate steps of identification and validation. Dr. Quackenbush 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.’” EX2173 ¶109. Thus, Ley initially identifies variants of interest, and then separately validates the variants of interest by sequencing. *Id.*; EX2169 ¶190.

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 ¶191.

The “validation” protocol from Ley that Foresight relies upon to allegedly meet limitation 1(e) 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 31-32, which quantifies the amount of genetic variants present in Ley’s subject via readcount data:

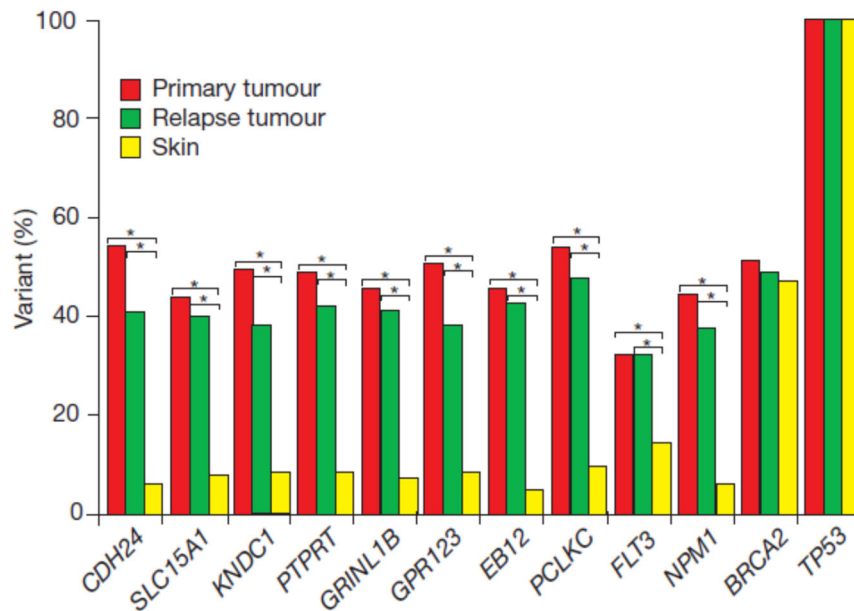


**Figure 3 | Summary of Roche/454 FLX readcount data obtained for ten somatic mutations and two validated SNPs in the primary tumour, relapse tumour and skin specimens.** The readcount data for the variant alleles in the primary tumour sample and relapse tumour sample are statistically different from 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 ¶192.

Foresight’s anticipation challenge relies on a POSA conflating Ley’s validation protocol with the claimed “to identify” step of limitation 1(e). A POSA would not have confused these two steps as confirmed by Dr. Quackenbush’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.” EX2173 ¶109. 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 ¶193.

**B. Claim 5**

Claim 5 depends from claim 1 and requires “each of said plurality of nucleic acid probe molecules includes oligonucleotide-directed genomic content comprising (i) at least one variable portion from a result of said sequencing of (a) and (ii) at least one fixed portion independent of said result of said sequencing of (a).”

Ley does not teach a probe set comprising a plurality of nucleic acid probe molecules having oligonucleotide-directed genomic content comprising “(i) at least one variable portion from a result of said sequencing of (a) and (ii) at least one fixed portion independent of said result of said sequencing of (a)” as required by claim 5. Foresight failed to proffer a construction of the recited “variable portion” and “fixed portion.” Petition 16-19. Ley does not teach the claimed plurality of nucleic acid probe molecules of claim 5 under the appropriate construction of these terms.

**1. 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 ¶¶196-197. 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

---

<sup>2</sup> For purposes of the trial phase of this proceeding only, Personalis does not contest Foresight’s description of a POSA. Decision 15-16.

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:

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 38:42-47. 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.* 63:33-36 (“Thus, as discussed 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.* 38:37-38. 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.”).

Claim 5 provides further clarification regarding the “variable portion” and “fixed portion” by specifying that the variable portion is “from a result of said sequencing of (a)” and the fixed portion must be “independent of said result of said sequencing of (a).” EX1001 69:63-67. 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 claim 5 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 ¶¶197-199.

2. **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

sequencing of (a) and (ii) at least one fixed portion independent of said result of said sequencing of (a)” as required by claim 5. Petition 36-38. 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.*, 773 F.3d at 1196. Foresight has not met that high standard for at least three reasons.

First, Dr. Quackenbush admits that “Ley does not provide the primer sequences or the exact exons that were analyzed.” EX1061 ¶121. 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 claim 5. 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 claim 5. 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 claim 5. Petition 37. 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 ¶¶201-203; 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 claim 5.

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 Foresight 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 36-37, 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 ¶204. 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 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, Foresight has not demonstrated that Ley inherently discloses PCR primers meeting the claimed “variable portion” and “fixed portion” of claim 5.

**C. Claims 10 and 28**

Claim 10 depends from claim 1 and requires “providing a therapeutic intervention at least based on said presence or absence of said at least said subset of said genetic variants identified in (e).”

Claim 28 depends from claim 1 and requires “using said presence or absence of said at least said subset of said set of genetic variants identified in (e) to treat said subject or said at least one biological relative for a disorder.”

Foresight argues that Ley discloses a therapeutic intervention and treating the subject for a disorder based on the patient’s “implication of the SLC15A1,” “positive mutation in the FLT3 and NPM1 genes,” and Ley’s Figure 3. Petition 38-40, 43-45.

Ley does not disclose a therapeutic intervention or using the presence/absence of genetic variants to treat 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 therapeutic intervention or treatment to make

for a deceased subject. EX2169 ¶208. Foresight fails to explain how Ley’s assay (which was performed after the death of the patient) could possibly involve a therapeutic intervention or treatment for the deceased subject. Ley fails to anticipate claims 10 and 28.

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

Ley does not render obvious independent claim 1, and therefore fails to render obvious any of the challenged dependent claims. Ley further fails to render obvious dependent claims 5, 10, and 28 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 at least three distinct requirements recited by limitation 1(e). Specifically, Ley fails to suggest:

- “a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a),”
- “subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less,” and
- “subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less *to identify* a presence or absence of at least a

subset of said set of genetic variants in said additional biological sample from said subject or said at least one biological relative.”

**1. Ley does not suggest the required sequencing depth**

As discussed above, Foresight relies on the incorrect premise that the claimed sequencing depth is inherently anticipated by the readcounts from Ley’s Table 3. *Supra* Section III.A.1. The Federal Circuit has cautioned that “[t]he use of inherency in the context of obviousness must be carefully circumscribed because that which may be inherent is not necessarily known and that which is unknown cannot be obvious.” *Southwire Co. v. Cerro Wire LLC*, 870 F.3d 1306, 1310–11 (Fed. Cir. 2017). For inherency to supply a missing claim limitation in an obviousness analysis, “the limitation at issue necessarily must be present.” *Id.* at 1311. Ley fails to disclose sufficient information to determine Ley’s sequencing depth, and Foresight has not (and indeed cannot) prove that Ley inherently discloses limitation 1(e). *Supra* Section III.A.1.

Foresight asserts that there was a general motivation to “achiev[e] a higher sequence depth” for the purpose of “increasing accuracy of detecting and quantifying mutations in tumors.” Petition 47. Foresight does not discuss why a POSA would have thought that the accuracy and/or quantification aspects of Ley’s assay that generated the data in Table 3 needed improvement. Therefore, Foresight fails to provide a reasoned rationale why a POSA would have been motivated to

increase the sequencing depth for Ley's assay. *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ("there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). Moreover, as discussed above, Ley did not disclose sufficient information to determine the sequencing depth for the data in Table 3. EX2169 ¶212. Without knowing Ley's sequencing depth, a POSA would have no baseline sequencing depth from which to measure whether it was desirable to achieve a higher (or lower) sequencing depth for the assay that generated Ley's Table 3.

Further, Foresight's assertion that a POSA would want to achieve a higher sequence depth to increase accuracy is counterproductive to other factors that Dr. Quackenbush explained a POSA would try to achieve when designing assays for tumors. He testified that it was desirable to reduce the cost of an assay, EX2163 27:15-30:22, that it was desirable to simplify an assay, *id.* 36:7-21, and that it was desirable to simplify computational analysis for data generated by an assay, *id.* 41:18-44:17. Increasing sequencing depth would complicate the assay with more sequencing. It would also increase the computational analysis by generating more data to analyze. And it would increase the cost of the assay by increasing the amount of sequencing and data analysis. EX2169 ¶¶213-214. Dr. Quackenbush admitted that a POSA's desire to increase accuracy was not more important than any of these other three factors. Thus, Foresight's asserted motivation does not prove

obviousness because where, as here, “the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful,” the invention would not have been obvious. *Bayer Schering Pharma AG v. Barr Laboratories, Inc.*, 575 F3d 1341, 1347 (Fed. Cir. 2009).

**2. Ley does not suggest 175 kilobases or less**

Limitation 1(e) requires “subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less.”

As discussed above, Foresight relies on the incorrect premise that the claimed coverage of 175 kilobases or less is inherently anticipated by Ley. *Supra* Section III.A.2. Foresight tries to avoid its burden of articulating a reasoned rationale as to why the claimed sequencing coverage would have been obvious by asserting that the specification does not attach any significance to the claimed coverage. Petition 46-47. This assertion is incorrect. The specification explains that the 175 kilobase limitation dramatically reduces the amount of sequencing required and makes the claimed methods much more affordable than prior art methods. EX1001 59:29-62:3 (Example 1), 34:42-35:56 (explaining that the 175 kilobase limitation results in 200x less sequencing by providing at least a 10x reduction in the sequencing footprint), 23:48-54, Figs. 3-4; EX2169 ¶217.

Foresight falls back on a generalized motivation to “target smaller genomic regions” and “reduce sequencing costs” that it believes existed at the time of the

invention. Petition 47. Foresight does not discuss why a POSA would have thought that Ley's specific assay that generated the data in Table 3 would benefit from targeting a smaller genomic region or a reduction in sequencing costs. 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. Thus, targeted examination of smaller genomic regions is the type of "hypothesis-driven" examination of genomic regions that Ley strongly counsels are inherently limited and will miss key mutations. EX2169 ¶218. Thus, Ley itself would dissuade a POSA from targeting smaller genomic regions. Foresight's obviousness position "simply retrace[s] the path of the inventor with hindsight, discount[s] the number and complexity of alternatives, and conclude[s] that the invention" was obvious. *Ortho-McNeil Pharms., Inc. v. Mylan Labs., Inc.* 520 F.3d 1358, 1364 (Fed. Cir. 2008). "[T]his reasoning is always inappropriate for an obviousness test" and should be rejected. *Id.*

**3. Ley does not suggest sequencing "to identify"**

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 at a coverage of 175 kilobases (kb) or less *to identify* a presence or absence of at least a subset of said set of genetic variants in

said additional biological sample from said subject or said at least one biological relative” as required by limitation 1(e). Petition 46-47. Foresight instead relies on the incorrect premise that the claimed “to identify” step and Ley’s validation step are equivalent. Petition 30-32. A POSA would not conflate these distinct steps for reasons discussed above. *Supra* Section III.A.3.b.

Dr. Quackenbush 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.’ EX2173 ¶109. 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 ¶¶220-221.

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 ¶¶222-223; 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(e).

**4. No motivation to modify Ley**

As discussed above, a POSA would not have been motivated to modify Ley's assay to (1) increase the undisclosed and unknown sequencing depth of Ley's assay to meet "a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a)" recited by limitation 1(e), (2) change Ley's undisclosed sequencing coverage to be performed "at a coverage to 175 kilobases (kb) or less" as required by limitation 1(e), and (3) add a protocol to *re*-establish the identity of mutations that Ley had already been established to meet the "to identify" requirement of limitation 1(e). EX2169 ¶224. Foresight fails to provide a persuasive motivation for any one of these modifications, much less the redesign of Ley's assay that would be required to do all of them.

For example, Dr. Quackenbush invoked the “Profile” study at the Dana-Farber Cancer Institute as a relevant prior art study. EX2163 27:15-29:5, 51:16-52:1. “Profile was an attempt to sequence cancer-associated genes in every patient who walked through the doors of the Dana-Farber Cancer Institute.” *Id.* It cost approximately \$6 million to run the Profile study each year, the cost of which was covered by philanthropic funds. EX2176. The cost was unlikely to be covered by insurance companies. *Id.* This highlights two very different scenarios. In the first scenario, a rare institution like Dana-Farber that was not cost constrained and could cover \$6 million in fees to run the Profile study. If such a rare laboratory had been motivated to perform the large-scale sequencing of “12 gigabases (GB) or more” required by limitation 1(a), the laboratory would not have been simultaneously motivated to reduce costs to arrive “a sequencing depth of said sequencing of (e) [that] is greater than a sequencing depth of said sequencing of (a)” as required by limitation 1(e). The second scenario concerns a typical laboratory that faced real-world cost constraints. If such a typical laboratory had been motivated to reduce costs to arrive at “a sequencing depth of said sequencing of (e) [that] is greater than a sequencing depth of said sequencing of (a),” the laboratory would not have been simultaneously motivated to arrive at the expensive large-scale sequencing of “12 gigabases (GB) or more” required by limitation 1(a). EX2169 ¶¶225-226.

Accordingly, Foresight failed to prove obviousness of independent claim 1 and all dependent claims.

**B. Claim 5**

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 claim 5. Petition 48-53. Ley fails to teach the "variable portion" and "fixed portion" of claim 5 for reasons discussed above. *Supra* Section III.B.

Foresight asserts that Ley's assay inherently included twelve PCR primer pairs. Petition 36-37 (alleging ten pairs for "non-synonymous" mutations and two pairs for "control" amplicons). 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.

1. **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 ¶230. 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, EX216317:19-20:1, 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.

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 that a POSA actually would have been motivated to use "fewer oligonucleotide probes" to "reduce sequencing costs." EX1061 ¶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. EX2169 ¶¶231-235. 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.

**2. 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 ¶236.

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>3</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

---

<sup>3</sup> Foresight was founded by Ash Alizadeh, Maximilian Diehn, David Kurtz, and Jake Chabon. EX2151.

difficulties related to multiplexing of PCR assays.” EX2165307-308. In 2021—years after the filing of the ’611 patent—they wrote that “PCR-based assays have limited multiplexability.” EX2166 202.

**3. 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 49-52. 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 that the function of the mutations found by its assay “*is not yet known.*” *Id.* 66; EX2169 ¶238.

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.B.2, which is something that Ross teaches to avoid. EX2169 ¶¶239-240.

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 ¶241.

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. EX2169 ¶242. Burell fails to rectify any of the deficiencies enumerated above concerning Foresight’s obviousness theory.

C. **Claim 10**

Foresight fails to include any discussion as to why the claimed “providing a therapeutic intervention at least based on said presence or absence of said at least

said subset of said genetic variants identified in (e)” of claim 10 is obvious over Ley. Petition 46-47. Ley fails to teach or suggest claim 10 for reasons discussed above. *Supra* Section III.C.

**D. Claim 28**

Ley does not suggest “using said presence or absence of said at least said subset of said set of genetic variants identified in (e) to treat said subject or said at least one biological relative for a disorder” as required by claim 28 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 treat a subject for a disorder. EX2169 ¶247. Foresight fails to explain how a POSA would use mutations of unknown clinical relevance to treat a subject for a disorder.

Second, Ley’s patient was deceased at the time Ley’s assay was performed. EX1042 2-3; EX2169 ¶248. There are no treatments for a disorder to make for a

deceased patient. Foresight fails to explain how a POSA would have been motivated to treat Ley's deceased subject for a disorder.

### **V. GROUND 3: NOVELTY OVER NEWMAN**

Newman does not anticipate independent claim 1, and therefore fails to anticipate any of the challenged dependent claims. Newman further fails to anticipate dependent claims 5, 10, 11, and 28 for additional reasons discussed herein.

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

Newman fails to anticipate claim 1 because it does not teach at least four requirements of the claim:

- “wherein said sequencing comprises sequencing 12 gigabases (GB) or more” as required by limitation 1(a),
- “an additional biological sample from said subject or at least one biological relative of said subject” as required by limitation 1(d), and
- “said additional biological sample from said subject or said at least one biological relative” as required by limitation 1(e); and
- “subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less” as required by limitation 1(e).

**1. Limitation 1(a)**

Newman does not teach “sequencing nucleic acid molecules from at least one biological sample of a subject to generate sequencing data, *wherein said sequencing comprises sequencing 12 gigabases (GB) or more*” as required by limitation 1(a).

Foresight does not assert that Newman *expressly* teaches sequencing that comprises 12 gigabases or more. Petition 56-58. Nor could it. Newman does not expressly disclose the number of gigabases generated.

Instead, Foresight relies on Newman’s disclosure of sequencing its GBM Relapse tumor sample or GBM PBL (peripheral blood leukocyte) germline sample to allegedly meet this limitation *inherently*. *Id.* Newman discloses that sequencing was performed using either “2 x 100 or 2 x 150 paired-end reads.” Petition 57-58; EX1043 Online Methods page 1. Newman does not disclose whether “2 x 100” or “2 x 150” was used for either of the two GBM samples. EX2169 ¶252. If 2 x 100 was used, then sequencing the 82,247,848 reads for the GBM Relapse sample would only constitute 8.2 GB (100 bp read length \* 82,247,848) and sequencing the 86,781,192 reads for the GBM PBL sample would only constitute 8.7 GB (100 bp read length \* 86,781,192). Sequencing just 8.2 or 8.7 GB does not meet the 12 GB limitation. Foresight fails to prove that Newman anticipates limitation 1(a) because inherency cannot be established “by probabilities or possibilities.” *Par Pharm.*, 773 F.3d at 1196.

**2. Limitation 1(d)**

Limitation 1(d) requires “an additional biological sample from said subject or at least one biological relative of said subject.”

To allegedly meet the “at least one biological sample of a subject” required by limitation 1(a), Foresight relies on two tissue samples from Newman: a GBM (glioblastoma) Relapse sample and a GBM PBL (peripheral blood leukocyte) sample. Petition 57. The glioblastoma samples were used by Newman to “establish the detection limit” of its CAPP-Seq assay. EX1043 551.

To allegedly meet the “additional biological sample from said subject” required by limitation 1(d), Foresight turns to a different CAPP-Seq assay. Specifically, Foresight relies on Newman’s Figure 1b to allegedly meet the additional biological sample of limitation 1(d). Petition 60. The caption for Figure 1b states that it is a “[s]chematic illustrating the potential application of CAPP-Seq to *noninvasive (biopsy-free)* genotyping and monitoring of ctDNA.” EX1043 548, Fig. 1b. Figure 1b expressly crosses out “Tissue biopsy” to emphasize that no tissue is taken in this noninvasive application of CAPP-Seq:



EX1043 Fig. 1b; EX2169 ¶¶254-255. Thus, Newman expressly teaches that the biopsy-free application of CAPP-Seq in Figure 1b is *not* used with invasively-obtained tissue samples such as the GBM Relapse and GBM PBL tissue samples.

Foresight also relies on Newman Figure 5d for limitation 1(d). Petition 61. But the sample used to generate Figure 5d isn't from the same subject or relative of the subject as the GBM patient. Glioblastoma is a type of *brain cancer*. Figure 5d concerns data from a different subject that had *lung cancer*. EX1043 553 (“We studied all NSCLC [non-small cell lung cancer] patients in our cohort.... ctDNA measurements were highly correlated (Fig. 5d, top...)... iDES continued to outperform the other methods tested (Fig. 5d, bottom).”); EX2169 ¶256. Thus, Figure 5d isn't from an additional biological sample from *the same* subject or a relative of the subject as required by limitation 1(d).

Foresight fails to establish that claim 1 is anticipated because Newman does not disclose all elements “arranged as in the claim,” “without any need for picking,

choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370-71 (Fed. Cir. 2008).

**3. Limitation 1(e): said additional biological sample**

Limitation 1(e) requires “subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less to identify a presence or absence of at least a subset of said set of genetic variants *in said additional biological sample from said subject or said at least one biological relative*, wherein a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a).”

Foresight relies on the *same* GBM Relapse and GBM PBL samples from Newman to supposedly meet the “at least one biological sample of a subject” required by limitation 1(a) and the “additional biological sample from said subject” required by limitation 1(e). Specifically, Foresight relies on Newman’s GBM Relapse and GBM PBL samples to supposedly meet the “at least one biological sample of a subject” required by limitation 1(a). Petition 57 (citing rows 286-87 of Table 2). Foresight relies on these *same* samples for limitation 1(e). *Id.* 61-62; EX2169 ¶258. By relying on the same tumor samples from Newman for both limitations 1(a) and 1(e), Foresight failed to identify the “additional biological sample” required by limitation 1(e).

**4. Limitation 1(e): coverage of 175 kilobases or less**

Limitation 1(e) requires “*subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less* to identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample from said subject or said at least one biological relative.”

Foresight relies on Newman’s “157 kb selector (capture panel) for the glioblastoma tumor” supposedly being less than the claimed 175 kilobases for limitation 1(e). Petition 61-32. Dr. Quackenbush admitted during deposition, however, that Newman does not provide information about the length of the DNA molecules that were captured by the 157 kb personalized selector that was used with the GBM tumor sample. EX216385:17-22 (“Q. Do you know the length of the DNA molecules that were captured by the 157 kilobase personalized selector that Newman used? A. I don’t think that information is provided. But the goal was to target 157,000 base pairs that contain 1,500 mutations.”).

Dr. Furneaux explains that the cell-free DNA was contacted with Newman’s 157 kb selector panel of capture probes to pull down GBM tumor DNA having sequences complementary to the capture probes on the panel. EX2169 ¶260. The length of each strand of DNA pulled down by each of the capture probes in the 157 kb panel is likely much longer than the length of the capture probe. *Id.* Dr. Furneaux determined that it is likely that the 157kb selector actually captured 544kb of DNA.

*Id.* Thus, Newman’s 157 kb selector panel likely captures much more than 175 kilobases. *Id.* Accordingly, the sequencing library generated from the use of Newman’s 157 kb selector panel likely includes much more than 175 kilobases that is subjected to sequencing. Foresight has therefore not proven that Newman inherently discloses “subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less” as required by limitation 1(e) because inherency cannot be established “by probabilities or possibilities.” *Par Pharm.*, 773 F.3d at 1196.

**B. Claim 5**

Claim 5 depends from claim 1 and requires “each of said plurality of nucleic acid probe molecules includes oligonucleotide-directed genomic content comprising (i) at least one variable portion from a result of said sequencing of (a) and (ii) at least one fixed portion independent of said result of said sequencing of (a).”

Foresight relies on the 157kb personalized selector panel of capture probes that Newman used for the GBM (glioblastoma) sample to allegedly meet the claimed “variable portion,” and the separate 175-kb NSCLC (lung cancer) selector panel of capture probes to allegedly meet the claimed “fixed portion.” Petition 64-65. Dr. Quackenbush admitted during deposition that these two selectors are distinct from each other. EX2163 221:11-223:8 (“So, the non-small cell lung carcinoma, the NSCLC selector, is distinct from the glioblastoma selector.”); EX2169 ¶266. Foresight’s proposed combination of Newman’s 157kb GBM selector panel and

NSCLC selector panel does not prove inherency because Foresight fails to establish that Newman discloses all elements “arranged as in the claim,” “without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.” *Net MoneyIN*, 545 F.3d at 1370-71.

**C. Claims 10 and 28**

Claim 10 depends from claim 1 and requires “providing a therapeutic intervention at least based on said presence or absence of said at least said subset of said genetic variants identified in (e).”

Claim 28 depends from claim 1 and requires “using said presence or absence of said at least said subset of said set of genetic variants identified in (e) to treat said subject or said at least one biological relative for a disorder.”

The mutations identified by Newman were of unknown clinical value. For example, Newman states that its assay is merely “likely to play” a role in personalized cancer therapy. EX1043 554. Newman does not teach that its assay was actually used to play a role in a therapeutic intervention or to treat a subject for a disorder. EX2169 ¶269. Being “likely to play” a role does not establish that it was actually used to provide a therapeutic intervention or to treat a subject for a disorder. Newman therefore fails to anticipate the requirement of claim 10 to provide a therapeutic intervention and the requirement of claim 28 to treat the subject for a disorder.

**D. Claim 11**

Claim 11 depends from claim 1 and recites “said at least one biological sample includes a tumor sample and said nucleic acids molecules are from cells in said tumor sample.”

Foresight relies on “*lung tumor* samples” from Newman to allegedly meet claim 11. As discussed above, Foresight relies on two GBM (glioblastoma) samples from Newman to supposedly meet the “at least one biological sample of a subject” required for limitation 1(a). Glioblastoma is a type of *brain cancer*. The lung tumor samples from Newman are from a different subject. EX2169 ¶¶272-273. Foresight fails to establish that Newman anticipates claim 11 by disclosing all elements “arranged as in the claim,” “without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.” *Net MoneyIN*, 545 F.3d at 1370-71.

**VI. GROUND 4: NONOBVIOUSNESS OVER NEWMAN**

Newman does not render obvious independent claim 1, and therefore fails to render obvious any of the challenged dependent claims. Newman further fails to render obvious dependent claims 5, 10, 11, and 28 for additional reasons discussed herein.

**A. Claim 1**

Newman fails to render claim 1 obvious because it does not suggest at least four requirements of the claim:

- “an additional biological sample from said subject or at least one biological relative of said subject” as required by limitation 1(d),
- “said additional biological sample from said subject or said at least one biological relative” as required by limitation 1(e),
- “wherein said sequencing comprises sequencing 12 gigabases (GB) or more” as required by limitation 1(a), and
- “subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less” as required by limitation 1(e).

**1. Limitation 1(d)**

As discussed above, Newman does not teach the “additional biological sample” required by limitation 1(d). *Supra* Section V.A.2. Foresight provides no explanation why a POSA would have been motivated to obtain an additional biological sample to use in Newman’s assay. Petition 70-72.

To allegedly meet the “at least one biological sample of a subject” required by limitation 1(a), Foresight relies on two tissue samples from Newman: the GBM Relapse and GBM PBL samples.

To allegedly meet the “additional biological sample from said subject” required by limitation 1(d), Foresight relies on Newman’s Figure 1b to allegedly meet the additional biological sample of limitation 1(d). Petition 60.

Newman clearly teaches away from Foresight’s proposed combination. The caption for Figure 1b states that it is a “[s]chematic illustrating the potential application of CAPP-Seq *to noninvasive (biopsy-free)* genotyping and monitoring of ctDNA.” EX1043 548, Fig. 1b. Thus, Newman expressly instructs a POSA *not* to combine the GBM tissue samples with the noninvasive biopsy-free application of CAPP-Seq described in Figure 1b. The caption for Figure 1b states that it is a “[s]chematic illustrating the potential application of CAPP-Seq *to noninvasive (biopsy-free)* genotyping and monitoring of ctDNA.” *Id.* Newman Figure 1b even includes the proverbial “prohibition sign” (also known as the “no symbol,” the “do not” symbol, the “universal no” symbol, and the “don’t do it” symbol), which consists of a red circle with a slash mark through “Tissue biopsy” as reproduced below:



EX1043, Fig. 1b; EX2175; EX2169 ¶278. Newman’s express instruction *not* to use an invasively obtained tissue sample is precisely the type of discouragement, criticism, and discrediting that constitutes a teaching away from the “additional biological sample” required by limitation 1(d). *See DePuy Spine, Inc. v. Medtronic Sofamore Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009) (“A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.”). Here, “an inference of nonobviousness is especially strong” because “the prior art’s teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined” the prior art to allegedly arrive at the claimed invention. *Id.* 1326.

Moreover, Newman is co-authored by two of Foresight’s founders. Foresight’s petition-inspired position in this litigation that that a POSA would have used Newman’s Figure 1b to arrive at the claimed “additional biological sample”

required by limitation 1(d) is directly contradicted by what its Founders previously told the rest of the world through the Newman reference itself. Foresight's position in this litigation lacks credibility and should be rejected.

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

As discussed above, Newman does not teach the “additional biological sample” required by limitation 1(e). *Supra* Section V.A.3. To allegedly meet limitation 1(e), Foresight relies on the *same* GBM Relapse and GBM PBL samples from Newman that it also relies upon to supposedly meet the “at least one biological sample of a subject” required by limitation 1(a). *Supra* Section V.A.3; Petition 57, 61-62. By relying on the same tumor samples from Newman for both limitations 1(a) and 1(e), Foresight failed to identify the “additional biological sample” required by limitation 1(e).

Foresight provides no explanation why a POSA would have been motivated to obtain an additional biological sample from the GBM patient to use in Newman's method. A POSA would have been dissuaded from obtaining an additional biological sample from Newman's glioblastoma patient because it would have involved an invasive procedure. EX2169 ¶280. The procedure for the GBM patient would include a particularly invasive brain surgery because glioblastoma is a type of brain cancer. Forsheew teaches that “[b]iopsies are invasive and costly.” EX2005

1. Even Foresight's founders admit that tumors "cannot be repeatedly sampled without invasive procedures." EX1044 2.

**3. Limitation 1(a)**

As discussed above, Newman does not teach "sequencing nucleic acid molecules from at least one biological sample of a subject to generate sequencing data, *wherein said sequencing comprises sequencing 12 gigabases (GB) or more*" as required by limitation 1(a). *Supra* Section V.A.1. Foresight relies on Newman's disclosure of whole genome sequencing of the GBM Relapse and GBM PBL samples to allegedly meet this limitation. Petition 71. Newman discloses that sequencing all of the at least 287 samples throughout Newman was performed using either "2 x 100 or 2 x 150 paired-end reads." EX1043 Online Methods page 1. Newman does not disclose whether "2 x 100" or "2 x 150" was used for the two GBM samples. EX2169 ¶¶282-283. If 2 x 100 was used, then sequencing the 82,247,848 reads for the GBM Relapse sample would only constitute 8.2 GB (100 bp read length \* 82,247,848) and sequencing the 86,781,192 reads for the GBM PBL sample would only constitute 8.7 GB (100 bp read length \* 86,781,192). Such sequencing does not meet the 12 GB limitation.

A POSA would have been motivated to use the "2 x 100" paired-end read length instead of the "2 x 150" read length because it would provide 50% less data, which would reduce the time and expense of Newman's CAPP-Seq assay for the

GBM samples as well as simplify the assay and the computational analysis for the data generated by the assay. The lower 2 x 100 read length is what Dr. Quackenbush's colleagues from the Dana-Farber Instituted selected. EX2177 21. Selecting the lower read length conforms with Dr. Quackenbush's testimony that a POSA would have found it desirable to reduce the cost of an assay, EX2163 27:15-30:22, to simplify an assay, *id.* 36:7-21, and to simplify computational analysis for data generated by an assay, *id.* 41:18-44:17.

**4. Limitation 1(e)**

As discussed above, Foresight relies on the incorrect premise that the claimed “sequencing at a coverage of 175 kilobases (kb) or less” as required by limitation 1(e) is inherently anticipated by the use of Newman's 157 kb selector capture panel. *Supra* Section V.A.4. For inherency to supply a missing claim limitation in an obviousness analysis, “the limitation at issue necessarily must be present.” *Southwire*, 870 F.3d at 1311. As explained by Dr. Furneaux, Newman's 157 kb selector likely captures much more than 175 kilobases. EX2169 ¶260. Foresight provides no explanation why it believes a POSA would have been motivated to modify Newman's CAPP-Seq assay on the GBM samples to arrive at the claimed “sequencing at a coverage of 175 kilobases (kb) or less.” Petition 70-72.

**5. No motivation to modify Newman**

As discussed above, a POSA would not have been motivated to modify Ley's assay to (1) combine Newman's GBM tissue samples with the "non-invasive (biopsy-free)" CAPP-Seq application described in Newman Figure 1b to arrive at the "additional biological sample" required by limitation 1(d), (2) perform an invasive brain surgery procedure to obtain an additional biological sample from Newman's glioblastoma patient to arrive at the "additional biological sample" required by limitation 1(e), (3) generate 50% more data by using a "2 x 150" read length that would increase the time, expense, and complexity of Newman's assay to arrive at the "sequencing 12 gigabases (GB) or more" required by limitation 1(a), and (4) change Newman's assay to be performed "at a coverage to 175 kilobases (kb) or less" as required by limitation 1(e). EX2169 ¶285. Foresight fails to provide a persuasive motivation for any one of these modifications, much less the overhaul of Newman's assay that would be required to do all of them—especially in view of Newman's express teaching away from limitation 1(d). Accordingly, Foresight failed to prove obviousness of independent claim 1 and all dependent claims.

**B. Claim 5**

Foresight asserts that Newman's lung cancer "NSCLC selector" meets the claimed "fixed portion" and that "a person of ordinary skill in the art knew that a panel of 175 kb or less *could* be designed and produced with fixed and variable

sequences.” Petition 73. “[O]bviousness concerns whether a skilled artisan not *only could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.” *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (emphasis in original). What a POSA “could” have designed or produced says nothing about what a POSA “would” have been motivated to do. Foresight’s anticipation and obviousness positions for claim 1 rely on Newman’s GBM (glioblastoma) samples—not Newman’s lung cancer patient. Newman uses a 157-kb personalized selector panel on the GBM samples for the purpose of determining the “ctDNA detection limits for iDES” enhanced CAPP-Seq. EX1043 Online Methods (last page). Foresight provides no explanation why it believes Newman’s detection limit determination using **GBM samples** and a personalized selector panel designed for the GBM samples *would* benefit from being combined with the separate and distinct 175-kb panel designed for *lung cancer samples*.

Foresight incorrectly refers to Newman’s NSCLC selector as comprising “PCR probes.” Petition 73. Newman’s NSCLC selector contained capture probes; not PCR probes. EX1043 Online Methods.

Foresight argues that a POSA would have “found it obvious to include probes targeted to genetic variants involved in the pharmacogenomics of cancer drugs, *i.e.*, genetic variants that were known to have companion diagnostics, as well as to tumor-

driver mutations that were known in the art.” Petition 73-74. First, Foresight’s anticipation and obviousness positions for claim 1 rely on Newman’s GBM samples that were used the purpose of determining the “ctDNA detection limits for iDES” enhanced CAPP-Seq. Foresight provides no explanation how Newman’s process for determining the ctDNA detection limits would benefit from adding more probes targeted to genetic variants involved in the pharmacogenomics of cancer drugs and tumor-drive mutations that were known in the art. More importantly, adding probes would increase the size of Newman’s 157kb selector, which would pulldown even more kilobases of target DNA (which was already significantly higher than the “175 kilobases or less” required by limitation 1(e)). EX2169 ¶¶287-288.

Foresight confusingly refers to “methods expressly disclosed by Ley” and “the types of assays described in Ley” to assert obviousness of claim 5 in its Newman-only ground 4. Petition 75. Ley’s assay was PCR-based, which has a different core reaction principle from the capture probes used by Newman’s selector panels. EX2169 ¶289. Foresight does not explain how a POSA would have been motivated to combine Ley’s PCR-based assay with Newman’s capture probes within Newman’s overall workflow to arrive at the invention recited by claim 5 with a reasonable expectation of success.

Rather than increasing the number of capture probes in Newman’s selector panel, a POSA would have instead sought to *decrease* the number of capture probes

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. Foresight's proposal to increase the number of capture probes used by Newman's selector panel is counterproductive to these motivations. EX2169 ¶290. For example, increasing the number of capture probes would increase the cost of the assay by requiring the design and synthesis of more capture probes. Adding more capture probes would complicate the assay as well as the computation analysis required for the assay, rather than simplify them.

**C. Claims 10, 11, and 28**

Foresight fails to explain why it believes the specific requirements of dependent claims 10, 11 and 28 are obvious over Newman. Petition 70-72. Newman fails to teach or suggest claims 10, 11, and 28 for reasons discussed above. *Supra* Section V.C-D.

## **VII. OBJECTIVE INDICIA OF NONOBVIOUSNESS**

Objective indicia “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 Personalis’ NeXT Personal<sup>®</sup> assay embodies claim 1. EX2169 ¶293; *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018).

Also, the evidence independently shows a nexus.

### **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). *The Scientist* magazine ranked the patented approach disclosed in the ‘611 patent as the top innovation of 2022. *See* EX2001; EX2035 ¶11.

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 '611 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, Ley's assay was only able to detect allele frequencies at approximately 3% for the "skin" sample. EX1012 69, Figure 3; EX2169 ¶295. Thus, Ley was 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 the claimed 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 personalized probes for cancer monitoring was "expensive" and that achieving sensitive monitoring for mutations across entire genes has been "more challenging." EX2005 10; *id.* 1; *see also* EX1031 686 (discussing "the key challenges in cancer genome sequencing"). Experts in the field were clearly skeptical of the probes Forshew described as "difficult to implement on a routine basis." EX2005 10.

Other references outline industry-wide problems with next-generation sequencing (NGS) at the time, which were unexpectedly solved by the methods in the '611 Patent. Anderson emphasizes that “difficult engineering challenges must be overcome before these technologies could become commercially viable.” EX2174 48. Lo identifies difficulties regarding “how to handle the massive amount of sequencing data” when utilizing NGS for profiling cancer genomes. EX2171 3; EX2169 ¶¶296-297.

This objective real-world evidence supports a finding that the claims of the '611 patent are nonobvious and, consequently, Foresight’s attempt to demonstrate that the claims of the '611 patent are unpatentable fails.

### **VIII. CONCLUSION**

For the foregoing reasons, the Board should confirm patentability of all challenged claims of the '611 patent.

Respectfully submitted,

WEIL, GOTSHAL & MANGES LLP

Dated: November 3, 2023

/\*/

---

Derek C. Walter  
Lead Counsel  
Reg. No. 74,656  
Weil, Gotshal & Manges LLP  
201 Redwood Shores Parkway  
Redwood Shores, CA 94065-1134  
Telephone: 650-802-3000

Foresight Diagnostics Inc. v. Personalis, Inc.  
IPR2023-00546

Nathanael R. Luman  
Reg. No. 63,160  
Knobbe, Martens, Olson & Bear LLP  
2040 Main St.  
Irvine, CA 92614  
Telephone: 949-760-0404

Counsel for Patent Owner Personalis, Inc.

**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 13,974 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

/Derek C. Walter/  
Derek C. Walter,  
Lead Counsel for Personalis, Inc  
Reg. No. 74,656

**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, and 2163-2177** are being served electronically on November 3, 2023, to the e-mail addresses shown below:

|                                                                                                                                                                                              |                                                                                                                                                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Andrew E. Krause<br>IRELL & MANELLA LLP<br>1800 Avenue of the Stars, Ste. 900<br>Los Angeles, CA 90067<br>T: 310-277-1010<br>F: 310-203-7199<br>akrause@irell.com<br>ForesightIPRs@irell.com | Amir Naini<br>NAINI P.C.<br>2632 Wilshire Blvd., Suite 268<br>Santa Monica, CA 90403<br>T: 310- 592-3030<br>F: 310-453-9008<br>amir@nainipc.com |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|

Dated: November 3, 2023

/Derek C. Walter/

Derek C. Walter,  
Lead Counsel for Personalis, Inc  
Reg. No. 74,656