

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS INC.,

Petitioner,

v.

PERSONALIS, INC.,

Patent Owner.

IPR2023-00546

U.S. Patent No. 10,450,611

**PRELIMINARY RESPONSE TO PETITION FOR *INTER PARTES*
REVIEW OF U.S. PATENT NO. 10,450,611**

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PATENT OWNER'S EXHIBIT LIST

Exhibit No.	Description
2001	The Scientist Staff, "2022 Top 10 Innovations," Dec. 12, 2022, available at https://www.the-scientist.com/features/2022-top-10-innovations-70792
2002	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)
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 https://www.aacc.org/science-and-research/clinicalchemistry/clinical-chemistry-podcasts/2013/cancer-genomescanning-in-plasma-detection-of-tumor-associated-copynumber-aberrations

I. INTRODUCTION

Patent Owner Personalis Inc. (“Personalis” or “Patent Owner”) submits this Preliminary Response to Petitioner Foresight Diagnostic Inc.’s (“Foresight” or “Petitioner”) Petition for *Inter Partes* Review of U.S. Patent No. 10,450,611 (“Petition”). For the reasons stated below, the Board should not institute review.

U.S. Patent No. 10,450,611 (“the ’611 Patent”) represents a novel approach for personalized genetic testing of a subject. The personalized nature of this approach has number of useful applications, including for diagnosing Mendelian diseases and detecting and monitoring a subject’s cancer. This method was far ahead of its time when the invention was made, and continues to receive acclaim to this day.

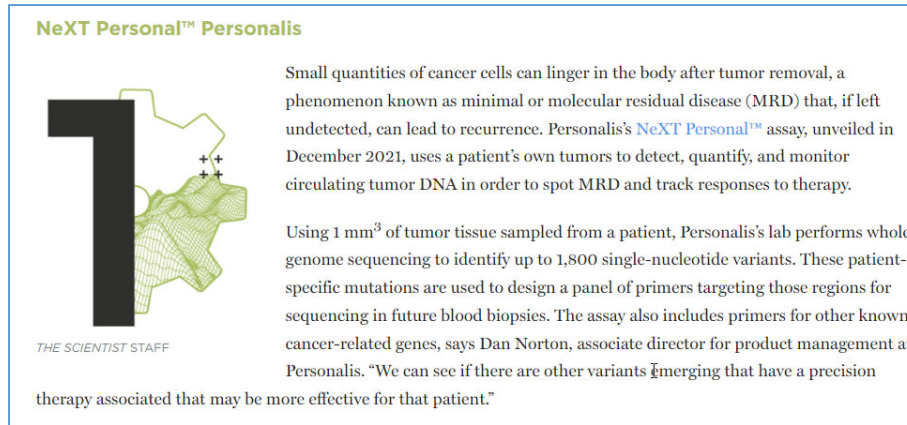
Briefly, the claims of the ’611 Patent recite a specific personalized method that sequences a subject’s biological sample, identifying and designing probe sets to genetic variants, then applying the probe sets to an additional biological sample to enrich or amplify and sequence only the genetic variants. As the ’611 Patent explains, prior art methods “used array-based synthesis to develop standard products which [we]re broadly applicable across a *whole set of human patients and/or*

research subjects” (Ex. 1001 at 4:35-38)¹, but high costs prohibited “leverag[ing] array synthesis of DNA *in a personalized manner*” (*id.* at 4:30-35).

The inventors of the '611 Patent recognized that this problem could be overcome by using targeted probes, which allow 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.* at 35:5-9. And because the use of targeted probes reduces the coverage, the sequencing depth can be greater without being cost prohibitive. *See, e.g., id.* at 61:37-49.

By using this approach, Patent Owner was able to pioneer new frontiers in techniques for detecting and monitoring disease with utmost sensitivity. The Personalis assay that practices the '611 Patent, for instance, can detect tumor DNA in blood plasma at levels of about one part per million (or 0.0001%). Recently, *The Scientist* magazine hailed the Personalis assay as the #1 scientific innovation of 2022:

¹ All emphasis added unless otherwise noted.



See Ex. 2001.

Now, years after the Personalis inventors conceived of their approach, Petitioner contends that the '611 Patent was unpatentable in view of Ley or Newman. Yet, as proven herein, neither reference is anywhere close to the personalized approach of the '611 Patent:

- Rather than disclose a method for personalized genetic testing, as claimed in the limiting preamble, Ley and Newman disclose methods for discovering or identifying variants recurrent in particular types of cancers. Nowhere does either reference mention using the series of protocols disclosed to characterize an individual's personalized genetic profile. Indeed, Ley and other references teach away from personalized panels to detect recurrence.
- Likewise, neither reference discloses applying the probe sets to an additional biological sample for the claimed purpose of identifying the presence or absence of the genetic variants. Rather, each reference

indicates that the probe sets are applied to the additional biological samples in order to validate the results obtained from the main protocols conducted in Ley and Newman—*i.e.* the results of identifying mutations recurrent to particular cancers. Moreover, Ley does not expressly or inherently disclose sequencing at a coverage of 175 kb.

- Finally, neither reference discloses the claimed method as arranged in the claim. Specifically, both references disclose a series of protocols designed for different purposes and neither discloses using any of the steps or protocols as a going-forward method for personalized genetic testing.

Therefore, the Board should not institute.

II. BACKGROUND

A. Overview Of The '611 Patent

The '611 Patent relates to “methods and systems for personalized genetic testing of a subject” for use in the diagnosis, monitoring, treatment, and prevention of diseases. Ex. 1001 at Abstract. Representative claim 1 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).

Ex. 1001 at 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×).” Ex. 1001 at 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.* at 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.* at 4:35-38; *see also id.* at 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.* at 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 (Ex. 1001 at 8:63-65, 10:7-8), to generate sequencing data of 12 gigabases (GB) or more of coverage. *See, e.g., Id.* at 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.* at 11:46-55. Genetic variant “generally refers to an alteration, variant or polymorphism in a nucleic acid sample or genome of a subject.” *Id.* at 25:4-6. The variants are identified with

respect to a reference, including genomes or sequences from the same subject or another individual. *Id.* at 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.* at 26:1-6. “A probe may be included in a set, or plurality, of probes.” *Id.* at 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.* at 26:1-19; *see also generally* Ex. 1001 at 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.,* Ex. 1001 at 26:1-19. The additional biological sample may be a samples 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.* at Example 1; *id.* at 5:4-9. The enriched and amplified sequences of the genetic variants generate a sequencing library. *See, e.g., id.* at 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* Ex. 1001 at 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.* at 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.* at 35:5-9. Because the coverage at this step is reduced, sequencing depth can be greater than the depth of the first sequencing step without being cost prohibitive. *See, e.g., id.* at 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.”).

B. The Level of Ordinary Skill in the Art

For the limited purpose of this Preliminary Response, Personalis does not challenge the definition of a POSA set forth in the Petition. Patent Owner reserves the right to challenge this definition should the Petition be instituted.

C. The Prior Art

The Petition asserts the following prior art:

- Ex. 1012, “DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome” (“Ley”)
- Ex. 1043, “Integrated digital error suppression for improved detection of circulating tumor DNA” (“Newman”)

Each of these references is summarized in turn below:

1. Ley

Ley is entitled “DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome,” and describes a sequencing approach to identify new candidate genes that may be responsible for acute myeloid leukaemia (“AML”). Specifically, Ley explains that AML is a highly malignant tumor that affects 13,000 adults a year in the United States. Ex. 1012 at 66. Despite this, the treatment of AML has changed little in the past two decades, because, according to Ley, most of the genetic variants responsible for initiating the disease remained undiscovered at the time of publication of Ley. *Id.* Ley therefore proposes using “whole-genome sequencing

as an unbiased method for discovering cancer-initiating mutations in previously unidentified genes that may respond to targeted therapies,” and describes a method for doing so in the context of AML. *Id.*

Ley describes sequencing “the genomic DNA of tumour and normal skin cells obtained from a patient with typical presentation of [AML] with normal cytogenetics.” *Id.* The sequence of the tumour genome is first aligned “to the human reference genome” through which a large number of “sequence variants were discovered in the tumour genome.” *Id.* at 67. These variants are further narrowed by filtering out any variants also present in the patient’s skin sample. *Id.* at 66 (“Of the 2,647,695 well-supported single nucleotide variants (SNVs) found in the tumour genome, 2,584,418 (97.6%) were also detected in the patient’s skin genome, limiting the number of variants that required further study.”); *see also* Ex. 1042 at 5 (“[W]e accepted any SNV as a potential tumor variant if it had no supporting reads in skin[.]”). Indeed, the authors explained that they could not “overemphasize the importance of parallel sequencing of the patient’s normal genome to determine which variants are inherited” because “the identification of the *true somatic mutations* in this tumour genome would not have been feasible without this approach.” Ex. 1012 at 71; *id.* at 67 (“We sequenced the genome of normal skin cells from the same patient to enable the identification of inherited sequence variants in the tumour genome.”); *id.* at 68 (“The patient had 3,813,205 sequence variants in

her tumour genome.... Of these, 2,647,695 were supported by the Decision Tree analysis in the tumour genome, of which 2,584,418 (97.6%) were also detected in the skin genome”); *id.* at Fig. 2 (filtering out 2,584,418 SNPs present in skin sample “to identify somatic point mutations the tumour genome”).

To determine which of the remaining variants were newly-discovered, the authors next compared the variants to a national database of single nucleotide polymorphisms and variants reported for two other human genomes; any variants that overlapped were filtered out. *Id.* at 67 (explaining that sequence variants discovered in the tumour, but not in the skin sample were compared “the dbSNP database, and to variants recently reported for two other human genomes; revealing new single nucleotide and small insertion/deletion (indel) variants genome-wide.”); *id.* (“To begin evaluating the quantity and quality of the detected sequence variants in the tumour and skin genomes, we compared the overlap and uniqueness of this genome’s variants with respect to the James D. Watson and J. Craig Venter genomes, and to dbSNP (v127; Fig. 1).”); *id.* at Fig. 2 (filtering out “31,645 in dbSNP/Watson/Venter” to identify the “new SNV”). The authors of Ley then filtered out any non-genic, non-coding, and synonymous variants. *Id.* at 68-69 (“Most of the 63,277 tumour-specific variants we detected were either present in dbSNP or were previously described in the Watson or Venter genomes (31,645), or

occurred in non-genic regions (20,440).... 216 of these variants were in untranslated regions, and 10,735 were in introns.... 60 were synonymous.”); *id.* at Fig. 2.

This resulted in 181 remaining variants. *Id.* at 68-69. Next, the authors sequenced PCR-generated amplicons from the tumor sample, skin sample, and a relapse tumor sample obtained 11 months after presentation 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.* at 69. This resulted in the identification of eight validated and newly-discovered somatic variants associated with AML. *Id.* at 69; *id.* at Fig. 2.

After identifying these new variants, Ley describes a separate protocol in which the authors “amplified each mutation-containing locus from non-amplified genomic DNA derived from the *de novo* and relapse tumour samples, and from the skin biopsy obtained at presentation[.]” (emphasis in original). According to the authors, this was done “[t]o better define ***the percentage of tumour cells*** that contained each of the discovered somatic mutations” and define the mutation frequencies in the tumour sample. *Id.* at 69. Specifically, the authors admitted that the “importance of the eight newly defined somatic mutations for AML pathogenesis [wa]s not yet known, and w[ould] require functional validation studies in tissue culture cells and mouse models to assess their relevance.” *Id.* at 70. The authors hypothesized, however, that the fact that “the same mutations were detected in

tumour cells in the relapse sample *at approximately the same frequencies* as in the primary sample” “suggest[s] that these mutations may not be random, ‘passenger’ mutations,” but rather actually recurrent in AML. *Id.*

2. Newman

Newman is titled “Integrated digital error suppression [(“iDES”)] for improved detection of circulating tumor DNA.” Newman attempts to improve the sensitivity of a method called cancer personalized profiling by deep sequencing or “CAPP-Seq” in order to facilitate the profiling of cancer using noninvasive circulating tumor DNA (ctDNA) samples rather than more invasive biopsy samples. Ex. 1043 at 547.

As the acronym suggests, CAPP-Seq is a method that profiles specific cancers across the general population through deep sequencing. Ex. 1044 at 2; *see also id.* (“For the initial implementation of CAPP-Seq we focus on NSCLC [(non-small cell lung cancer)], although our approach is generalizable to any cancer for which recurrent mutations have been identified.”). Specifically, it “combines optimized library preparation methods for low DNA input masses [(such as masses obtained from ctDNA)] with a multi-phase bioinformatics approach to design a ‘selector’ consisting of biotinylated DNA oligonucleotides that *target recurrently mutated regions* in the cancer of interest.” *Id.* The “selectors” in the CAPP-Seq method correspond to “recurrent mutations in potential driver genes,” the sequences of

which are pulled from online databases such as the Catalogue of Somatic Mutations in Cancer or “COSMIC” and any other sources or studies that sequence recurrent mutations present in certain cancers. *Id.* & nn. 14-16. These selectors derived from sequences of known recurrent mutations are then applied to ctDNA samples from actual patients to assess which mutations are actually present in the selected population. *Id.* at 4.

Newman also teaches, however, that there are “[t]wo important factors underlying the detection limit of all ctDNA profiling methods.” Ex. 1043 at 547. These “are the number of cfDNA molecules that are recovered and the number of mutations in a patient’s tumor that are interrogated.” *Id.* While the authors of Newman “developed strategies to optimize these variables from clinically relevant blood volumes, which are frequently limiting in cancer patients due to anemia, comorbidities, and poor patient performance status, among other factors,” “the degree to which analytical sensitivity can be further improved, whether through more efficient cfDNA recovery or increased coverage of tumor-specific aberrations, is ultimately limited by technical background.” *Id.*

Newman therefore proposes enhancing CAPP-Seq with what it terms “iDES” or integrated digital error suppression. *Id.* at 548-49. Specifically, iDES involves the “serial application of molecular barcoding and background polishing.” *Id.* at 549. The authors noted that, “[b]y integrating multiple tumor mutations in a single

assay, CAPP-Seq can detect ctDNA at lower fractional abundances than methods targeting single mutations in a given patient” and that, “[t]herefore, given the lower error rate observed for iDES (Fig. 2b), [they] sought to *experimentally validate its detection limit* for quantitating circulating tumor burden.” *Id.* at 551.

At the end of Newman and after describing this iDES enhanced CAPP-Seq technique, the authors briefly describe the below experiment to “establish the detection limit” (*id.*) of their technique:

Based on our modeling, and given considerations of cost and molecule recovery, we used a glioblastoma (GBM) tumor that was found to harbor ~1,500 coding mutations by whole exome sequencing (Supplementary Table 2). We designed a 157-kb “personalized” selector to cover these mutations, employing the same biotinylated oligonucleotide synthesis process as described for NSCLC selector design, above. We then applied this selector to perform deep resequencing of the GBM tumor (1/2 of a MiSeq lane), and confirmed 97% of expected SNVs, 99.7% of which had duplex support (n = 1,502).

Id. at “ctDNA detection limits for iDES, duplex sequencing, and other methods.” This protocol is ancillary to the iDES enhanced CAPP-Seq technique of Newman, is conducted for validation purposes alone, and is not described as an

experiment that should be conducted after every use of the iDES enhanced CAPP-Seq technique.

III. CLAIM CONSTRUCTION

For the reasons stated blow, the Board should find that the preamble is limiting.

A. Preamble: “A method for personalized genetic testing”

Whether a preamble is limiting is an issue of claim construction. *See Data Engine Techs. LLC v. Google, LLC*, 10 F.4th 1375, 1380 (Fed. Cir. 2022). For a preamble to limit the claims, one must establish that it is “not merely [a] statement[] of effect but rather [a] statement[] of the intentional purpose for which the method[] must be performed.” *Eli Lilly & Co. v. Teva Pharms. Int’l GmbH*, 8 F.4th 1331, 1342 (Fed. Cir. 2021). In other words, “preamble language will limit the claim if it recites not merely a context in which the invention may be used, ***but the essence of the invention without which performance of the recited steps is nothing but an academic exercise.***” *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003).

For example, in *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, the Federal Circuit found that the preamble reciting “growing and isolating...virus” was limiting because “‘growing’ and ‘isolating’ are not merely circumstances in which the method may be useful, but instead are the *raison d’être*

of the claimed method itself.” 320 F.3d at 1344-45 (emphasis in original). Similarly, in *E.I. Du Pont de Nemours & Co. v. Monsanto Technology LLC*, the Board concluded that “high-throughput method for analyzing *individual* seeds” in the claim’s preamble was limiting because the “body of claim 1 lack[ed] any clear language indicating that the utility of the invention is for the analysis of *individual* seeds.” IPR2014-00333, 2014 WL 3507803, at *4-5 (P.T.A.B. July 11, 2014).

The preamble term “[a] method for personalized genetic testing” should likewise be construed as limiting the claims based on the claim language and specification. The claim language establishes that “personalized genetic testing” is not merely a circumstance in which the method may be useful, but rather is the essence of the claimed method itself. Divorced from the process of personalized genetic testing, the claimed method reduces to nothing more than a process for identifying the presence or absence of genetic variants in a sample—“a process whose absence of fathomable utility rather suggests the academic exercise.” *Id.* Moreover, the body of the claim lacks any clear language indicating that the utility of the invention is for the genetic testing of an individual—*i.e.* “a method for *personalized* genetic testing.” When read as a whole with the preamble language, however, the claim indicates that the method is in fact directed to a process for personalized genetic testing, rather than merely sequencing samples to identify mutations in a general population.

The specification identifies the *personalized genetic* aspect of the method as an important and essential feature of the claimed invention. It explains that, while at the time of invention, “array-based DNA synthesis [was] widely used to capture whole exomes, transcriptomes, or application-specific subsets of exomes (e.g., the genes involved with a specific Mendelian disease), a limitation of the field...[was] the potential to leverage array synthesis of DNA in a *personalized* manner.” Ex. 1001 at 4:30-40. At the time, the specification explains that the field was largely used to develop products that were “broadly applicable across a whole set of human patients and/or research subjects.” *Id.* at 4:30-40. In other words, methods that existed at the time of invention were specific to a particular disease or cancer rather than personalized to a specific subject’s family genetics. The claimed method, however, is directed to personalized genetic testing and is “better focused on the personal characteristics of the subject.” *Id.* at 28:25-26.

Therefore, the Board should construe “a method for personalized genetic testing” as limiting.

IV. REASONS WHY THE PETITION SHOULD BE DENIED

A. Ground 1: Ley Does Not Anticipate The Challenged Claims Because It Does Not Teach Key Elements Of The Claimed Invention Nor Does It Disclose The Claim Elements As Arranged In The Claim

Petitioner alleges that claims 1, 2, 4, 5, 9-11, 13, 18, 19 and 28-30 of the ’611 Patent should be cancelled as anticipated by Ley. Pet. at 23. The Board should deny

institution because Ley: (1) does not disclose “[a] method for personalized genetic testing;” (2) does not disclose claim element 1(e); and/or (3) discloses a series of experiments, which are not arranged as a going-forward method for personalized genetic testing as claimed.

1. Preamble: A method for personalized genetic testing

Ley does not disclose a method for *personalized* genetic testing, but rather is a study about discovering “cancer-initiated mutations in previously unidentified genes” in the *general population* of patients with AML by using whole-genome sequencing as an unbiased method. Ex. 1012 at 66. For example, Ley notes that “[h]ere we present the results obtained from sequencing a *typical acute* myeloid leukaemia genome, and its matched normal counterpart obtained from the same patient’s skin.” *Id.* Ley further states that its results “demonstrate the power of whole-genome sequencing to *discover new cancer-associated mutations.*” *Id.*; see also *id.* at 66 (“[o]ur study establishes whole-genome sequencing as an unbiased *method for discovering cancer-initiating mutations* in previously unidentified genes that may respond to targeted therapies.”); *id.* at 71 (“In summary, we have successfully used a next-generation whole genome sequencing approach *to identify new candidate genes that may be relevant for AML pathogenesis....*the identification *of the true somatic mutations in this tumour genome* would not have been feasible without this approach.”). Accordingly, Ley does not describe a method

for personalized genetic testing of an individual as claimed, but rather for discovering mutations that are responsible for initiation and pathogenesis of AML and other types of cancer across entire patient populations.

Indeed, Ley teaches away from using personalized panels for achieving its goal of detecting recurrent mutations responsible for pathogenesis. *See, e.g.*, Ex. 1012 at 71 (“For AML and other types of cancers, whole-genome sequencing may therefore be the only effective means for discovering all of the mutations that are relevant for pathogenesis.”); *id.* at 70 (“Our results strongly support the notion that hypothesis-driven (for example, candidate gene-based) examination of tumour genomes by PCR-directed or capture-based methods is inherently limited, and will miss key mutations.”). This is consistent with other prior art that likewise teaches away from the use of personalized panels to detect recurrence and instead advocates for the continued use of shotgun sequencing so as to overcome the problem of tumor heterogeneity. *See* Ex. 2002 at 7. Prior art that even considers such targeted approaches, only vaguely speculate about them as future possibilities, thus confirming how ahead of its time the Personalis approach was. Ex. 2003 at 212.

Petitioner argues that, if the preamble is limiting, Ley discloses a method for personalized genetic testing because it describes that the patient’s tumor genome is compared to “its matched normal counterpart obtained from the same patient’s skin.” Pet. at 23-24 (citing Ex. 1012 at 66). But Ley admits that the tumor genome is

compared to the normal counterpart—not for personalized genetic testing as claimed—but rather to filter out inherited mutations and identify only the somatic mutations that are putatively recurrent in AML patients. Specifically, the authors explained that they could not “overemphasize the importance of parallel sequencing of the patient’s normal genome to determine which variants are inherited” because “the identification of the *true somatic mutations* in this tumour genome would not have been feasible without this approach.” Ex. 1012 at 71; *see also* Ex. 1012 at 70 (“A slightly lower coverage of the normal genome from this individual helped to identify nearly 98% of potential variants as being inherited, a critical filter that allowed us to more readily identify the true somatic mutations in this tumour.”); *id.* at 67 (“We sequenced the genome of normal skin cells from the same patient to enable the identification of inherited sequence variants in the tumour genome.”); *id.* at 68 (“The patient had 3,813,205 sequence variants in her tumour genome.... Of these, 2,647,695 were supported by the Decision Tree analysis in the tumour genome, of which 2,584,418 (97.6%) were also detected in the skin genome”); *id.* at Fig. 2 (filtering out 2,584,418 SNPs present in skin sample “to identify somatic point mutations the tumour genome”); *id.* at 68 (“Of the 2,647,695 well-supported single nucleotide variants (SNVs) found in the tumour genome, 2,584,418 (97.6%) were also detected in the patient’s skin genome, limiting the number of variants that

required further study.”); *see also* Ex. 1042 at 5 (“[W]e accepted any SNV as a potential tumor variant if it had no supporting reads in skin[.]”).

Therefore, Ley does not disclose the preamble.

2. Claim 1(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....

Ley does not disclose claim element 1(e), which claims “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).”

First, Ley does not expressly disclose “sequencing at a coverage of 175 kilobases (kb) or less.” Even Petitioner’s expert admits that Ley does not disclose the primer sequences or exact exons that were analyzed. Ex. 1061 ¶ 121. Therefore, Petitioner must “meet a high standard” to establish that Ley inherently discloses this limitation. *Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014). Inherent anticipation 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.” *Id.* at 1196. Inherency cannot be established “by probabilities or possibilities.” *Id.* (quoting *In re Oelrich*, 666 F.2d 578, 581

(C.C.P.A. 1981)). “The mere fact that a certain thing may result from a given set of circumstances is not sufficient.” *Id.* (citation omitted). Rather, a party must “show that *the natural result flowing* from the operation as taught would result in the performance of the questioned function.” *Id.* (emphasis in original).

As detailed below, Petitioner fails to meet this high standard because it cannot establish that the claimed “sequencing at a coverage of 175 kilobases (kb) or less to identify a presence or absence...of genetic variants in said additional biological sample” is necessarily present or is the natural result of the proposed method described in Ley.

Petitioner does not demonstrate that the protocols disclosed in Ley would necessarily result in a sequencing coverage of 175 kb or less. Instead, Dr. Quackenbush contends that looking up the mRNA corresponding to the coding region of the 10 specifically identified genes, one can easily obtain the total length of the entire coding sequence for each of the genes. Ex. 1061 ¶ 121. But this selective evaluation contradicts the method described in Ley. Ley specifically notes that the discovered somatic mutations were “neither predicted by the curation of previously defined cancer genes, nor by the study of this tumour using unbiased high-resolution array-based genomic approaches.” Ex. 1012 at 71. As such, a POSA would not have known to selectively identify only these 8 somatic mutations. Furthermore, given that a POSA would have been unaware of the specific mutations

to focus on, they would similarly have been unaware of the exact coding space to sequence for a coverage of 175 kb or less. Thus, Dr. Quackenbush's assertion that "even if all of the exons of every one of these genes were to be sequenced, the sequence would only cover 45.254 kb, far less than the 175 kb set out as a limitation of claim 1 of the '611 patent," is at best, misleading. Ex. 1061 ¶ 121.

Moreover, the fact that the variants identified in the relapse tumor sample happened to result in a sequencing coverage of 175 kb or less does not mean that every set of variants identified by using the experiments in Ley would result in a sequencing coverage of 175 kb or less. One could imagine a scenario in which a sample contained a greater number of variants and thereby resulted in a greater sequencing coverage. The specification states, for example, that "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"—or 175 kb. Ex. 1001 at 34:65-35:3. If, however, a sample contained 600 variants of at least about 600 sequences and each probe was likewise about 350 bases, then the footprint or sequencing coverage would be about 210 kb or greater than 175 kb. Therefore, the fact that the variants that happened to be identified in Ley might result in 175 kb coverage or less does not establish that following the experiments described in Ley necessarily results in a sequencing coverage of 175 kb.

Second, Ley does not disclose sequencing the sequencing library to “identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample,” as claimed. Petitioner contends that the additional biological sample in Ley is the relapse tumor sample, and points to Figure 3 of Ley to argue that Ley discloses identifying the presence or absence of genetic variants in the relapse tumor sample. Pet. at 31-32; Ex. 1061 ¶ 120.

But this does not establish that Ley discloses sequencing the relapse tumor sample for the purpose of *identifying* the absence or presence of the genetic variants. Rather, the variants in the relapse tumor sample were sequenced to validate the results obtained. Indeed, the goal of Ley—discovery of new somatic mutations that are putatively responsible for initiating AML—had already been satisfied before the relapse tumor was sequenced. Specifically, after narrowing the list to 181 variants (as depicted in Figure 2), the authors sequenced PCR-generated amplicons from the relevant samples 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).” Ex. 1012 at 69. This step resulted in the identification of eight validated and newly-discovered somatic variants associated with AML. *Id.* at 69; *id.* at Fig. 2.

After identifying these new variants, Ley describes a separate protocol in which variants in the relapse tumor sample were sequenced. *Id.* at 69. The authors

explain that this protocol was conducted “[t]o better *define the percentage of tumour cells* that contained each of the discovered somatic mutations” and define the mutation frequencies in the tumor sample. *Id.* Indeed, the results of this protocol—demonstrating that “the same mutations were detected in tumour cells in the relapse sample *at approximately the same frequencies* as in the primary sample”—supported the authors’ hypothesis that “these mutations may not be random, ‘passenger’ mutations,” but rather actually recurrent in this type of cancer. *Id.* at 70. Therefore, Ley describes this step not for the purpose of identifying the presence or absence of the variants as claimed, but rather for the purposes of validating its results.

Therefore, Ley does not disclose this limitation.

3. Ley Does Not Disclose The Claimed Steps Of The Method As Arranged In the Claim

Ley does not disclose the claimed steps of the method as arranged in the claim as a going-forward method for personalized genetic testing. Petitioner must show a reasonable likelihood of proving that “the four corners of a single, prior art document describe every element of the claimed invention.” *See NetMoneyIN, Inc., v. Verisign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). Moreover, “an anticipatory reference [must] show all of the limitations of the claims arranged or combined in

the same way as recited in the claims, not merely in a particular order.” *Id.* at 1370. Petitioner fails to meet this burden here.

Ley describes two sets of experiments. First, Ley describes a series of experiments used to discover new variants responsible for AML initiation and pathogenesis. Ex. 1012 at 66-69; *id.* at Fig. 2 (depicting “[f]ilters used to identify somatic point mutations in the tumour genome”). This resulted in the discovery of 8 genes with mutations that the authors hypothesized are responsible for initiating AML in the general patient population. *See id.* at 69. Second, Ley describes an experiment to validate these results. “To better define the percentage of tumour cells that contained each of the discovered somatic mutations,” the authors “amplified each mutation-containing locus from non-amplified genomic DNA derived from the *de novo* and relapse tumour samples, and from the skin biopsy obtained at presentation.” *Id.* (emphasis in original). “[A]ll eight somatic SNVs were detected at ~50% frequencies in the primary tumour sample,” which the authors concluded validated their discovery. *Id.* Another known mutation, however, was “only detected in 35.1% of the 454 reads at diagnosis and 31.3% at relapse,” which the authors concluded “suggest[ed] that the mutation was not present in all tumour cells at diagnosis or relapse.” *Id.*

There is no indication in Ley that these experiments should be or may be combined together as a going-forward method for personalized genetic testing. A

POSA, reading Ley, would be motivated to either replicate Ley to discover new driver genes or create a diagnostic test focused only on the eight variants that they found. Even in those instances, there is no indication from Ley that the validation experiment should be repeated in each instance. POSA would not be motivated, nor has Petitioner argued otherwise, to arrange the discovery protocols of Ley with the validation experiment of Ley and use them as a going-forward method for personalized testing, especially when validation experiments often use less efficient, but more accurate methodologies to confirm the accuracy of the new methods described.

Therefore, Ley does not disclose the claimed method as arranged or combined in the claim.

B. Ground 2: Ley Does Not Render Obvious The '611 Patent Because It Does Not Teach Key Elements Of The Claimed Invention As Arranged

Petitioner alleges that claims 1–5, 9-11, 13, 18, 19, and 28-30 of the '611 Patent should be cancelled because they would have been obvious in view of Ley. Pet. at 46. Ley does not disclose key elements of the claimed invention as arranged in the claim. *First*, Ley does not disclose a “method for personalized testing” for the reasons explained above. Section IV.A.1. Nor does Petitioner argue that this limitation would have been obvious in view of Ley. Therefore, the Board should

find that the Petitioner failed to satisfy its burden of demonstrating that Ley discloses or renders obvious the limiting preamble.

Second, Ley does not render obvious claim element 1(e). Ley does not disclose sequencing the sequencing library to “identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample,” for the reasons described above. Section IV.A.2. And Petitioner does not argue that it would have been obvious to use the validation experiment of Ley to identify the presence or absence of genetic variants in the relapse tumor sample. Pet. at 46-47.

Ley also does not disclose “sequencing at a coverage of 175 kilobases (kb) or less to identify a presence or absence...of genetic variants in said additional biological sample” for the reasons described above. Section IV.A.2. Petitioner admits that the limitation is not expressly disclosed, but argues that “a POSA would have found it obvious to sequence at a coverage of 175 kilobases (kb) or less based on Ley’s disclosure.” Pet. at 46. The use of inherency in the obviousness context must “be ‘carefully circumscribed’ because ‘that which may be inherent is not necessarily known and that which is unknown cannot be obvious.’” *Vivint, Inc. v. Alarm.com Inc.*, 741 F. App’x 786, 792 (Fed. Cir. 2018) (quoting *Honeywell Int’l Inc. v. Mexichem Amanco Holding S.A.*, 865 F.3d 1348, 1354-55 (Fed. Cir. 2017)). Petitioner has not met this high burden here.

Petitioner argues that “the ’611 Patent does not attach any significance to the claimed coverage of 175kb.” Pet. at 46. But the specification explains that the 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. Ex. 1001 at 35:5-9. A footprint of 75kb is far less than the 12 GB sequenced during the first step, and which “may result in 200× less sequencing.” *Id.* at 35:1-5. Because the coverage at this step is reduced, sequencing depth can be greater than the depth of the first sequencing step without being cost prohibitive. *See, e.g., id.* at 61:37-46 (“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[.]” *Id.* at 61:46-48. Therefore, the specification attaches significance to this limitation.

Petitioner next argues that “a POSA would have known that achieving a higher sequence depth in step 1(e) was desirable for increasing accuracy of detecting

and quantifying mutations in tumors, and, for a given number of sequencing counts, the use of fewer oligonucleotide probes to target smaller genomic regions would lead to higher sequencing depth.” Pet. at 46-47. Petitioner’s only support for this is Dr. Quackenbush’s Declaration, which merely parrots Petitioner’s assertion and cites no underlying factual support. See Ex. 1061 ¶¶ 167-68. The Board has held that declarations, such as these that “merely offer[] conclusory assertions without underlying factual support and repeat[], verbatim Petitioner’s conclusory arguments” are “giv[en] little weight.” *Xerox Corp. v. ByteMark, Inc.*, IPR2022-00624, Paper 12 at 5 (P.T.A.B. Feb. 10, 2023); see also *Xerox Corp. v. ByteMark, Inc.*, IPR2022-00624, Paper 9 at 16 (P.T.A.B. Aug. 24, 2022) (Petitioner’s expert “offers only a verbatim restatement of the assertion being supported, without any supporting evidence or technical reasoning....This is particularly problematic in cases where, like here, expert testimony is offered not simply to provide a motivation to combine prior-art teachings, ***but rather to supply a limitation missing from the prior art.***”); 37 C.F.R. § 42.65(a) (“Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.”). Therefore, Petitioner has failed to satisfy its burden of demonstrating that Ley inherently disclose and/or renders obvious claim element 1(e).

Finally, Petitioner has failed to demonstrate that Ley discloses the claim elements as arranged as a going-forward method for personalized genetic testing for

the reasons stated above. Section IV.A.3. Nor does Petitioner argue that it would have been obvious to do so.

Therefore, Petitioner has failed to satisfy its burden that Ley renders obvious the challenged claims.

C. Ground 3: Newman Does Not Anticipate The '611 Patent Because It Does Not Teach Key Elements of The Claimed Invention

Petitioner alleges that claims 1-5, 9-11, 13, 18, 19, and 28-30 of the '611 Patent should be cancelled as anticipated by Newman. Pet. at 54. The entirety of Petitioner's argument with regard to Newman is that a single paragraph describing a validation experiment conducted at the end of the reference discloses the claimed method. Ex. 1043 at "ctDNA detection limits for iDES, duplex sequencing, and other methods." The Board should deny institution because this paragraph: (1) does not disclose "[a] method for personalized genetic testing;" (2) does not disclose claim element 1(e); and/or (3) discloses a series of experiments, which are not arranged as a going-forward method for personalized genetic testing as claimed.

1. Preamble: A method for personalized genetic testing

Newman does not disclose a method for personalized genetic testing, but rather describes the authors' attempts to improve the sensitivity of CAPP-Seq in order to facilitate the profiling of cancers using noninvasive circulating tumor DNA (ctDNA) samples rather than more invasive biopsy samples. Ex. 1043 at 547.

Specifically, CAPP-Seq is a method that profiles specific cancers across the general population through deep sequencing. Ex. 1044 at 2; *see also id.* (“For the initial implementation of CAPP-Seq we focused on NSCLC [(non-small cell lung cancer)], although our approach is generalizable to any cancer for which recurrent mutations have been identified.”). The “selectors” used in the CAPP-Seq method correspond to “recurrent mutations in potential driver genes,” the sequences of which are pulled from online databases such as the Catalogue of Somatic Mutations in Cancer or “COSMIC” and any other sources or studies that sequence recurrent mutations *present in certain cancers*. Ex. 1043 & nn. 14-16. These selectors derived from sequences of known recurrent mutations are then applied to ctDNA samples from actual patients to assess which mutations are actually present in the selected population. Ex. 1044 at 4. Newman proposes enhancing the CAPP-Seq method iDES, which involves the “serial application of molecular barcoding and background polishing.” Ex. 1043 at 548-49. Newman therefore describes altering an existing method to enhance its ability to genetically test a *particular type of cancer* and is not directed to a method for personalized genetic testing of a particular individual’s genetics.

Petitioner contends that “[t]o the extent the preamble is limiting, Newman discloses it by stating, for example, that ‘[h]igh-throughput sequencing of circulating tumor DNA (ctDNA) promises to facilitate personalized cancer therapy.’” Pet. at

56 (quoting Ex. 1043 at Abstract). But this simply establishes that Newman is personalized to a specific cancer—not to a subject’s DNA. As explained above, personalized cancer therapy does not amount to “personalized genetic testing” of an individual. Indeed, in CAP-Seq, the selectors are designed not from the patient’s tumor samples, and instead correspond to “recurrent mutations in potential driver genes,” the sequences of which are pulled from online databases such as the Catalogue of Somatic Mutations in Cancer or “COSMIC” and any other sources or studies that sequence mutations *recurrent in certain types of cancers*. Ex. 1043 & nn. 14-16.

Petitioner also contends “Newman’s disclosure of the claimed method steps, as discussed further below, confirms that Newman meets the preamble.” Pet. at 56. But the only disclosure that Petitioner relies upon is the single validation experiment described at the end of Newman. Ex. 1043 at “ctDNA detection limits for iDES, duplex sequencing, and other methods.” This experiment also does not describe a method for personalized genetic testing. *Id.*; *see also id.* at 551. Rather, Newman states that this experiment was conducted in order to “[t]o establish the detection limit of iDES-enhanced CAPP-Seq[.]” *Id.* at 551. The authors explained that the previously described protocols had established that “CAPP-Seq can detect ctDNA at lower fractional abundances than methods targeting single mutations in a given patient (Fig. 1a).” “[G]iven the lower error rate observed for iDES (Fig. 2b),” the

authors therefore “sought to experimentally validate its detection limit for quantitating circulating tumor burden.” *Id.* Therefore, this experiment was also not a method for personalized genetic testing and instead was a validation experiment.

Therefore, Petitioner has failed to satisfy its burden of demonstrating that Newman discloses the limiting preamble.

2. Claim 1(e): subjecting said sequencing library to sequencing...to identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample....

Newman does not disclose claim element 1(e), which claims “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).”

Petitioner contends that “Newman discloses a 157 kb selector (capture panel) for the glioblastoma tumor, which they used to generate a library for targeted sequencing to identify the presence or absence of genetic variants.” Pet. at 61-62 (citing Ex. 1043 at “ctDNA detection limits for iDES, duplex sequencing, and other methods”). But this disclosure does not establish that the 157 kb selector was used “to identify the presence or absence of genetic variants.” Rather, and as explained above, Newman expressly states that this specific experiment was conducted in order

to “[t]o establish the detection limit of iDES-enhanced CAPP-Seq[.]” Ex. 1043 at 551; *see also* Section IV.C.1.

Therefore, Petitioner has failed to satisfy its burden of demonstrating that Newman discloses claim element 1(e).

3. Newman Does Not Disclose The Claimed Steps Of The Method As Arranged In the Claim

Newman does not disclose the claimed steps of the method as arranged in the claim as a going-forward method for personalized genetic testing. As explained, “an anticipatory reference [must] show all of the limitations of the claims arranged or combined in the same way as recited in the claims, not merely in a particular order.” *NetMoneyIN*, 545 F.3d at 1369. Petitioner fails to meet this burden here.

The majority of the protocols disclosed in Newman pertain to developing an iDES-enhanced method of CAPP-Seq. That is the entire purpose of the reference. Yet Petitioner does not rely on any of these protocols to demonstrate unpatentability of the challenged claims. Nor could it when the selectors used in CAPP-Seq are derived from sequences obtained from databases rather than from sequences obtained from a subject as claimed in the ’611 Patent.

Instead, Petitioner relies on a brief description of a validation experiment conducted at the end of Newman. But there is no indication in Newman that this ancillary, validation experiment should be used as a going-forward method for personalized genetic testing. A POSA, reading Newman, would only be motivated

to use the CAPP-Seq protocol as a going-forward method to profile specific cancers across the general population through deep sequencing. There would be no reason, and Petitioner has not provided one, why a POSA reading Newman would repeat the validation experiment, let alone use it for personalized genetic testing. Indeed, the validation experiment already “establish[ed] the detection limit” of iDES-enhanced CAPP-Seq method proposed by Newman, so there would be no reason to repeat it. Ex. 1043 at 551.

Therefore, Newman does not disclose the claimed method as arranged or combined in the claim.

D. Ground 4: Newman Does Not Render Obvious The '611 Patent Because It Does Not Teach Key Elements of The Claimed Invention As Arranged

Petitioner alleges that claims 1–5, 9-11, 13, 18, 19, and 28-30 of the '611 Patent should be cancelled because they would have been obvious in view of Newman. Pet. at 70. Newman does not disclose or render obvious key elements of the claimed invention as arranged in the claim. *First*, Newman does not disclose a “method for personalized testing” for the reasons explained above. Section IV.C.1. Nor does Petitioner argue that this limitation would have been obvious in view of Newman. Therefore, the Board should find that the Petitioner failed to satisfy its burden of demonstrating that Newman discloses or renders obvious the limiting preamble.

Second, Newman does not render obvious claim element 1(e). Newman does not disclose sequencing the sequencing library to identify “identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample,” for the reasons described above. Section IV.C.2. And Petitioner does not argue that it would have been obvious to use the validation experiment of Newman to identify the presence or absence of genetic variants in the relapse tumor sample. Pet. at 70-72. Therefore, the Board should find that the Petitioner failed to satisfy its burden of demonstrating that Newman discloses or renders obvious claim element 1(e).

Finally, Petitioner has failed to demonstrate that Newman discloses the claim elements as arranged as a going-forward method for personalized genetic testing for the reasons stated above. Section IV.C.3. Nor does Petitioner argue that it would have been obvious to do so.

Therefore, Petitioner has failed to satisfy its burden that Ley renders obvious the challenged claims.

**E. The Petition Fails To Address Secondary Considerations
Supporting The Non-obviousness Of The Claimed Inventions**

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

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

1. Nexus

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

“extraneous factors other than the patented invention.” *Id.* Here, Patent Owner is entitled to a presumption of nexus because, as detailed in the attached claim chart, Personalis’s assay embodies claim 1 of the ’611 Patent. Ex. 2004.

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

2. Industry Praise

Personalis’s assay has received widespread industry attention and praise due in part to its sensitivity relative to other methods. *Arctic Cat Inc. v. Bombardier Recreational Prod. Inc.*, 876 F.3d 1350, 1364 (Fed. Cir. 2017) (“Evidence that the industry praised a claimed invention or a product that embodies the patent claims weighs against an assertion that the same claimed invention would have been obvious.”) (citation omitted). For example, last December, *The Scientist* magazine published its list of the Top 10 Innovations of 2022. The patented approach disclosed in the ’611 Patent earned the #1 ranking. *See* Ex. 2001. Indeed, the differences between the method used in Leary—a reference cited in the Petition—and the method claimed in the ’611 Patent yield radically different results. Personalis’s assay can detect tumor in DNA in blood plasma at levels of about one part per million (or 0.0001%). By comparison, the best sensitivity from plasma DNA in

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

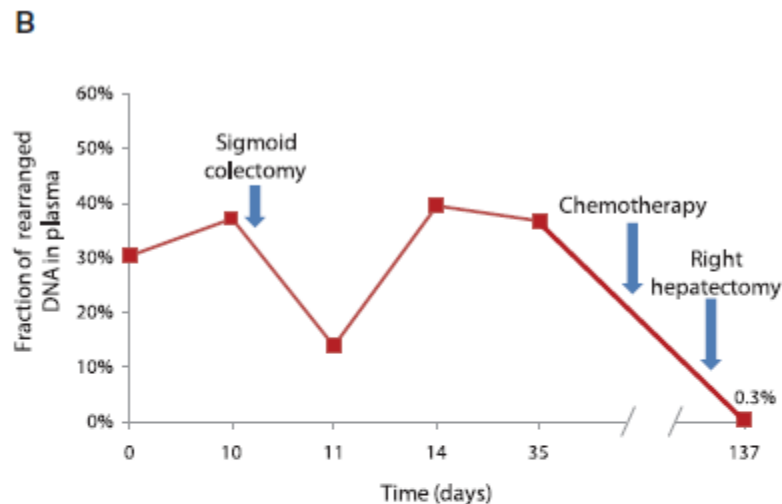


Fig. 4. Detection of tumor-specific rearrangements in plasma of cancer patients. (A) The identified chromosome 4:8 and 16 rearrangements were used to design PCR primers spanning breakpoints and to amplify rearranged DNA from tumor tissue and plasma from patients Hx402 and Hx403, respectively. A plasma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

Id. at Fig. 4. If it were really true that others had conceived of and disclosed the patented techniques “long before” the inventors of the ’611 Patent, as Petitioner alleges, then this patented technique would not be lauded by independent judges as the top scientific innovation of 2022.

3. Skepticism of Experts

Prior art as well as art cited by the Petitioner demonstrates that the industry's experts held skepticism toward solving the difficult challenges of conducting highly sensitive genome sequencing using targeted probes. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335 (Fed. Cir. 2016) (“Evidence of industry skepticism weighs in favor of non-obviousness.”).

As explained above, Ley discouraged using personalized panels for achieving its goal of detecting recurrent mutations responsible for pathogenesis. *See, e.g.*, Ex. 1012 at 71 (“For AML and other types of cancers, whole-genome sequencing may therefore be the only effective means for discovering all of the mutations that are relevant for pathogenesis.”); *id.* at 70 (“Our results strongly support the notion that hypothesis-driven (for example, candidate gene-based) examination of tumour genomes by PCR-directed or capture-based methods is inherently limited, and will miss key mutations.”). This is consistent with other prior art that likewise discouraged the use of personalized panels to detect recurrence and instead advocates for the continued use of shotgun sequencing so as to overcome the problem of tumor heterogeneity. *See* Ex. 2002 at 7. Prior art that even considers such targeted approaches, only vaguely speculate about them as future possibilities, thus confirming how ahead of its time the Personalis approach was. Ex. 2003 at 212.

Moreover, other art, such as Forshew, acknowledges that using probes for cancer monitoring was “expensive” and that achieving sensitive monitoring for

mutations across entire genes has been “more challenging.” Ex. 2005 at 10; *id.* at 1; *see also* Ex. 1031 at 686 (discussing “the key challenges in cancer genome sequencing” as of October 2010). Experts in the field were clearly skeptical of the probes Forshew described as “difficult to implement on a routine basis.” Ex. 2005 at 10.

Other references outline clear industry-wide problems with NGS at the time, which were unexpectedly solved by the methods in the ’611 Patent. For example, a review paper by Anderson et al. emphasizes that “difficult engineering challenges must be overcome before these technologies could become commercially viable.” Ex. 2006 at 48. Further, Lo identifies difficulties facing experts regarding “how to handle the massive amount of sequencing data” when utilizing NGS for profiling cancer genomes. Ex. 2007 at 3.

These objective real-world evidence supports a finding that the claims of the ’611 Patent are nonobvious and, consequently, Petitioner’s attempt to demonstrate that a claim of the ’611 Patent is unpatentable fails.

V. CONCLUSION

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

Respectfully submitted,

WEIL, GOTSHAL AND MANGES LLP

Dated: May 10, 2023

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

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 et seq., the undersigned certifies that this document complies with the word count limitation of 37 C.F.R. § 42.24(a)(1)(i) because the Petition contains 9,753 words, excluding the cover page, signature block, and the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

Respectfully submitted,

WEIL, GOTSHAL AND MANGES LLP

Dated: May 10, 2023

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

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PATENT OWNER'S PRELIMINARY RESPONSE TO PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 10,450,611** is being served on May 10, 2023, via email pursuant to 37 C.F.R. § 42.107 to counsel for Foresight Diagnostics, Inc., at the addresses below:

Andrew E. Krause
Reg. No. 76,276
IRELL & MANELLA LLP
1800 Avenue of the Stars, Ste. 900
Los Angeles, CA 90067
T: 310-277-1010
F: 310-203-7199
akrause@irell.com

Amir Naini
Reg. No. 45,770
NAINI P.C.
2632 Wilshire Blvd., Suite 268
Santa Monica, CA 90403
T: 310- 592-3030
F: 310-453-9008
amir@nainipc.com

Alan J. Heinrich (pro hac vice to be requested)
IRELL & MANELLA LLP
1800 Avenue of the Stars, Suite 900
Los Angeles, California 90067
T: 310-277-1010
F: 310- 203-7199
aheinrich@irell.com

Jordan Nafekh (pro hac vice to be requested)
IRELL & MANELLA LLP
1800 Avenue of the Stars, Suite 900
Los Angeles, California 90067
T: 310- 277-1010
F: 310- 203-7199
jnafekh@irell.com

Dated: May 10, 2023

By: /Derek C. Walter/
Derek C. Walter
Reg. No. 74,656