

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS INC.,

Petitioner,

v.

PERSONALIS, INC.,

Patent Owner.

IPR2023-00545

U.S. Patent No. 11,299,783

**PRELIMINARY RESPONSE TO PETITION FOR *INTER PARTES*
REVIEW OF U.S. PATENT NO. 11,299,783**

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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	Exemplary Embodying Product Claim Chart for U.S. Patent No. 11,299,783

I. INTRODUCTION

Patent Owner Personalis Inc. (“Personalis” or “Patent Owner”) submits this Preliminary Response to Petitioner Foresight Diagnostic Inc.’s (“Foresight” or “Petitioner”) Petition for *Inter Partes* Review of U.S. Patent No. 11,299,783 (“Petition”). For the reasons stated below, the Board should not institute review.

U.S. Patent No. 11,299,783 (“the ’783 Patent”) represents a novel approach for personalized genetic testing of a subject. 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. This method was far ahead of its time when the invention was made, and continues to receive acclaim to this day.

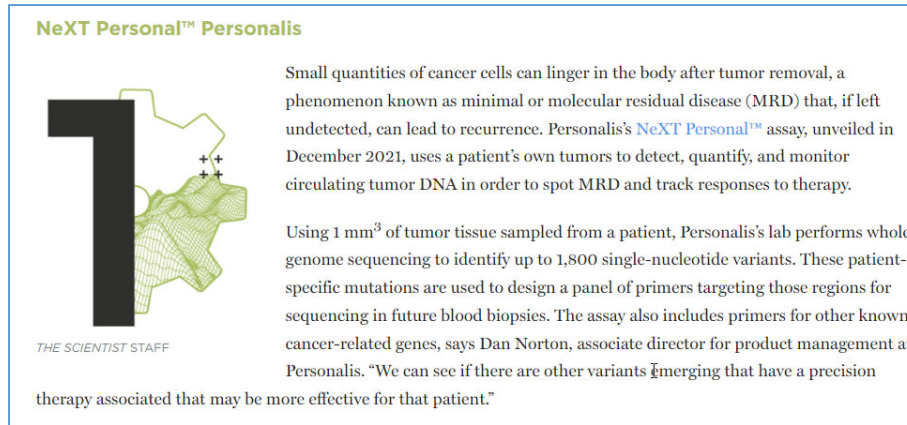
Briefly, the claims of the ’783 Patent recite a specific personalized method that uses sequence data from a subject’s biological sample to identify and obtain personalized probe sets to genetic variants, including a variable portion from said sequence data and a fixed portion independent of said sequence data, then using the personalized probe sets on an additional biological sample to enrich or amplify and sequence only the genetic variants, followed by generating a report identifying the presence or absence of a health condition or disease and genetic variants which inform further therapy. As the ’783 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 4:43-45),¹ but high costs prohibited “leverag[ing] array synthesis of DNA *in a personalized manner*” (*id.* at 4:37-45).

The inventors of the '783 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. Ex. 1001 at 63:20-24. 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 64:40-52.

By using this approach, Patent Owner was able to pioneer new frontiers in techniques for detecting and monitoring disease with utmost sensitivity. The Personalis probe set that practices the '783 Patent, for instance, can detect biologically or clinically important variants in tumor DNA from blood plasma at levels of about one part per thousand (or 0.001%); a related probe set in the Personalis assay can detect minimal or molecular residual disease (MRD) with one part per million (or 0.0001%) sensitivity. Recently, *The Scientist* magazine hailed the Personalis assay as the #1 scientific innovation of 2022:

¹ Quoted text in bold is “emphasis added” unless otherwise noted.



See Ex. 2001.

Now, years after the Personalis inventors conceived of their approach, Petitioner contends that the '783 Patent was unpatentable in view of Ley or the combination of Forshew and Dawson. Yet, as proven herein, none of these references is anywhere close to the personalized approach of the '783 Patent, which also utilizes a fixed portion of probes to track the presence or absence of additional genetic variants:

- Rather than disclosing a method for personalized genetic testing, as claimed in the limiting preamble, or the obtaining of a personalized probe set, as recited in the body of the claim, Ley discloses methods for discovering or identifying variants recurrent in particular types of cancers *across a whole set of human patients and/or research subjects*. Nowhere does the Ley reference mention using the series of protocols disclosed to uniquely characterize a single individual's personalized genetic profile.

Indeed, Ley teaches away from using personalized panels to detect, discover, or identify cancer variants.

- Likewise, the Ley reference does not disclose applying the probe sets to an additional biological sample for the claimed purpose of identifying the presence or absence of the genetic variants. Rather, Ley 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—*i.e.*, the results of discovering or identifying mutations recurrent to particular cancers.
- Ley does not “generat[e] a report identifying (i) a presence or absence of a health condition or disease of the subject in said additional biological sample based on said identified at least a subset of (c) and (ii) genetic variants which inform a therapy choice or a change in therapy choice or a change in therapy for the subject.” The examples of “reports” provided by Petitioner are nothing more than the data obtained from the experiments described therein.
- Finally, Ley does not disclose the claimed method as arranged in the claim. Specifically, Ley discloses a series of protocols designed for different purposes and does not disclose using any of the steps or protocols as a going-forward method for personalized genetic testing.

- Forshew and Dawson do not contemplate probe molecules comprising at least one variable portion from a result of sequencing data and at least one fixed portion independent of sequencing data. Specifically, although Dawson discloses that the *TP53* gene is commonly mutated in breast cancer, nowhere does Forshew or Dawson disclose that a probe for a mutation of *TP53* (or for any other mutation) should be included in a personalized probe set identified from whole genome sequencing. In fact, Forshew teaches away from using fixed probes to mutants from the *TP53* gene.
- Likewise, neither Forshew nor Dawson, alone or in combination, discloses or renders it obvious for a POSA to “generat[e] a report identifying (i) a presence or absence of a health condition or disease of the subject in said additional biological sample based on said identified at least a subset of (c) and (ii) genetic variants which inform a therapy choice or a change in therapy for the subject.” The example provided by Petitioner of a “report” disclosed in Forshew is nothing more than the data obtained from the experiments described therein, and Petitioner does not argue that such a report would have been obvious in view of Forshew or Dawson.
- Finally, Forshew and Dawson do not disclose or render obvious the claimed method as arranged in the claim. Specifically, Forshew discloses

a series of protocols designed for different purposes and does not disclose using any specific protocol of elements as arranged in the claim as a going-forward method for personalized genetic testing, nor does Forsheew or the combination with Dawson render such a method obvious.

Therefore, the Board should not institute.

II. BACKGROUND

A. Overview of the '783 Patent

The '783 Patent relates to “systems and methods for sample processing and data analysis,”—including “method[s] for personalized genetic testing”—for use in the diagnosis, monitoring, treatment, and prevention of diseases. Ex. 1001 at Abstract, 72:19. Representative claim 1 recites:

1. A method for personalized genetic testing, comprising:

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

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

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

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

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 4:30-32; 4:33-36. And “[w]hile array-based DNA synthesis is now widely used to capture...application-specific subsets of exomes (e.g., the genes involved with a specific Mendelian disease), a limitation of the field, as recognized herein, is the potential to *leverage array synthesis of DNA in a personalized manner.*” *Id.* at 4:37-42. Instead, “[t]he field has largely used array-based synthesis to develop standard products which are broadly applicable across a *whole set of human patients and/or research subjects.*” *Id.* at 4:42-45; *see also id.* at 4:45-47 (“Even where

custom array synthesis is proposed, it is to sequence regions of the genome defined independent of a specific sample.”). Sequencing costs remained high, and personal assay synthesis generally remained “unattractive” due to uncertainty caused by variations based on “conditions of the nucleic acid sequence (e.g., % GC, alignment degeneracy, primer-dimer formation.).” *Id.* at 39:43-45.

The claimed method, however, is directed to a method for “*personalized* genetic testing.” The claimed method first requires obtaining a personalized probe set, which can “include probes to a genomic region or a panel comprising multiple genomic regions” and “can be amplification based or capture hybridization-based.” Ex. 1001 at 29:17-19. A probe “generally refer[s] to a nucleic acid molecule comprising a single-stranded portion capable of hybridizing to a complementary nucleic acid sequence,” and “can be used for detection or enrichment of [said] nucleic acid molecules.” *Id.* at 29:5-9. “A probe may be included in a set, or plurality, of probes.” *Id.* at 29:14-15. The claimed probe set includes probes that are complementary to and thereby configured to enrich or amplify the identified genetic variants. *Id.* at 29:4-9; *see also generally* Ex. 1001 at Example 7 (describing exemplary methods to synthesize probes). Further, the probe molecules include oligonucleotide-directed genomic content comprising (i) at least one variable portion from the sequencing assay and (ii) at least one fixed portion independent from the sequencing assay. *Id.* at 7:47-52. The variable portion may correspond to genes

which are “more highly expressed” than genes at the fixed portion and have more sample-to-sample variety in gene expression. *Id.* at 7:57-59. The fixed portion may correspond to genes with “on average lower levels of gene expression” and correspond to various cancer genes of interest. *Id.* at 19:6-8; 8:5-13.

Second, the personalized probe set is then applied to an “additional biological sample” to selectively enrich or amplify sequences comprising the genetic variants. *Id.* at 11:3-7. 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.*, Ex. 1001 at Example 1; *id.* at 5:4-10. The enriched or amplified sequences of the genetic variants generate a sequencing library. *Id.* at 42:52-62.

Third, the sequencing library is sequenced to identify a presence or absence of the genetic variants in the additional biological sample. The sequencing footprint of this step is less than the sequencing footprint of the sequencing data used to generate the capture probe set in the first step. For example, to test for 500 variants this lower footprint sequencing step may require synthesis of about “175,000 bases...[c]ompared to [sequencing] an exome, where the footprint assay is typically at least 35 million bases, [] may result in 200x less sequencing.” *Id.* at 63:17-20. This allows for a “dramatic reduction” in required sequencing and allows sequencing to be more affordable for family members. *Id.* at 63:20-24. 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 64:41-52 (“To increase the confidence of detecting a potentially mosaic variant in the parents, they will need to be sequenced at greater depth than the child. If the assay for additional members of a family pedigree is exome sequencing, it may be cost prohibitive to sequence at that depth. Using method provided herein, the footprint of the assay for incremental family members is much smaller (e.g., 175,000 bases vs 35 million bases, as discussed above). This smaller footprint makes it affordable to sequence the incremental samples at much greater depth, thus improving the sensitivity for detection of mosaic variants in the parents.”).

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

“in part on a possibility that one or more of the genetic variants are gonadal mosaic in a father of the subject”).

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. 1030, “Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA” (“Forshev”)
- Ex. 1070, “Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer” (“Dawson”)

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 had changed little in the past two decades, because, according to Ley, most of the genetic variants responsible for initiating the disease or contributing to its pathogenesis 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 in 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 to “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[.]” *Id.* at 69 (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.* 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. Forshew

Forshew is entitled “Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA” and describes the development of “TAm-Seq,” a tagged-amplicon deep sequencing method that can be used to identify cancer mutations present in circulating DNA. Ex. 1030 at Abstract. Forshew focuses on high-grade serious ovarian carcinomas (HGSOC), where, previously, mutations of the tumor suppressor gene *TP53* have been observed in 97% of the genome, but are located throughout the gene and are difficult to assay. *Id.* at 1. Forshew states that a “cost-effective method that could detect and measure allele frequency (AF) of *TP53* mutations in plasma may be highly applicable as a biomarker for HGSOC.” *Id.*

Forshew describes a series of experiments using the TAm-Seq method and other validation techniques to deep sequence fragmented circulating DNA. Forshew describes using overlapping short (150-200 bp) amplicons to “tile” regions of

interest in a gene, while attaching 5' adaptors. *Id.* at 2-3. Specifically, Forshew describes a “two-step amplification process,” wherein limited cycle multiplex pre-amplification is used to capture starting molecules, followed by “individual amplification to purify and select for intended targets.” Then, additional sequencing adaptors and a barcode are added via additional PCR steps. *Id.* at 3.

In the paper, Forshew describes the validation of primer pairs to cover coding regions of certain genes known to account for ovarian tumor mutants. To do so, Forshew sequences regions covering 38% of all point mutations in the COSMIC database, and sequences the DNA extracted from formalin-fixed paraffin-embedded (FFPE) tumor specimens of ovarian cancer. *Id.* The mutations identified in the resulting data set were then matched by Sanger sequencing of the same FFPE samples. *Id.*

Forshew next characterizes the quantitative accuracy of TAm-Seq as applied specifically to circulating DNA. *Id.* Forshew mixed plasma DNA from two healthy individuals and used the set of primers from the FFPE experiment to identify SNP loci that differed between the two individuals in order to simulate rare circulating tumor mutations. *Id.*

Then, Forshew applied TAm-Seq to directly identify mutants in the plasma of cancer patients. Digital PCR was used to analyze tumor-specific mutations in a cohort of individuals with HGSOC. *Id.* at 4. Forshew mentions that digital PCR,

while “highly accurate,” “requires design and validation of a different assay for every mutation screened and relies on previous identification of mutations in tumor samples from the same patients.” *Id.* Seven cases were chosen for further analysis that had high levels of circulating mutant *TP53* DNA, and the mutants identified in the plasma samples therefrom were validated using Sanger sequencing and digital PCR. *Id.* TAm-Seq was then validated on a larger panel of plasma samples and levels of tumor-specific mutations were measured in parallel using patient-specific digital PCR assays, with TAm-Seq able to identify 95% of digital-PCR-detected mutations occurring at a frequency higher than 2%. *Id.* at 4, 8.

Forsheew also describes the use of TAm-Seq as a “generic tool to measure changes in frequency of DNA over time” and its flexible adaption to sequence different genomic regions by “designing primers to amplify regions of interest.” *Id.* at 8. Forsheew describes using this to “study [the] dynamics of multiple mutations in parallel.” *Id.* Specifically, Forsheew used whole-genome sequencing of tumor material to identify tumor mutations in a patient with metastatic breast cancer who was undergoing two phases of chemotherapy. *Id.* From the whole-genome sequencing, ten mutations were selected. *Id.* Short amplicons of less than 120 bp were “designed to cover the mutation loci” and serial plasma samples were collected and TAm-Seq used to follow the mutations, which were shown to decline in frequency on onset of therapy and increase in frequency upon disease progression

thereafter. *Id.* Forshew also performed a retrospective analysis on the FFPE samples from a patient with two primary cancers collected over a course of years, as well as plasma samples. *Id.* The plasma samples at relapse contained a mutant, identified via TAm-Seq. *Id.*

3. Dawson

Dawson is entitled “Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer” and, like Forshew, is concerned with the analysis of circulating DNA, comparing the use of circulating DNA as a biomarker with other forms of biomarkers in women with metastatic breast cancer. Ex. 1070 at Abstract. Dawson describes the use of tagged amplicon deep-sequencing for the *PIK3CA* and *TP53* genes in combination with paired-end whole genome sequencing. *Id.* at 1200. The targeted deep sequencing for those two genes was used to “screen for point mutations.” *Id.* at 1201. Allele frequency of mutations in circulating DNA was compared using deep sequencing and digital PCR, which results were found to agree. *Id.* at 1202. The dynamic patterns of mutations in tissue-samples were compared to the dynamic patterns in plasma. *Id.* at 1204. Other biomarker approaches were compared to circulating tumor DNA, such as CA 15-3, and circulating tumor cells, with circulating tumor DNA being shown to have greater sensitivity and dynamic range. *Id.* at 1204-05.

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. 2021). 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. This essence is further supported by the use of the term “personalized probe set,” and the generation of a report, emphasizing the personalized use to which this method is directed. Divorced from the process of personalized genetic testing using a personalized probe set, 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.* When read as a whole with the preamble language, the claim indicates that the method is directed to a process for personalized genetic testing using a personalized probe set and generating a report, 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 4:37-47. 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 4:37-47. 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 31:27-28.

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, 5-7, 9, 14-15, 17-19, 21, 23-25, and 27 of the ’783 Patent should be cancelled as anticipated by Ley. Pet. at 14. The Board should deny institution because Ley: (1) does not disclose “[a] method for

personalized genetic testing” or a “personalized probe set,” (2) does not disclose claim element 1(c); (3) does not disclose claim element 1(d); and/or (4) 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, or a “personalized probe set,” 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 or personalized probe sets 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 references that even consider such targeted approaches only vaguely speculate about them as future possibilities, thus confirming how ahead of its time the Personalis approach was. Ex. 1008 at 212.

Petitioner argues that 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 (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 or a “personalized probe set.”

2. Claim 1(c) subjecting said sequencing library to sequencing to identify a presence or absence of at least a subset of said set of genetic variants in at least said additional biological sample from said subject, wherein a sequencing footprint of said sequencing of (c) is less than a sequencing footprint of said sequence data of (a)

Ley does not disclose claim element 1(c), which claims “subjecting said sequencing library to sequencing to identify a presence or absence of at least a subset of said set of genetic variants in at least said additional biological sample from said subject, wherein a sequencing footprint of said sequencing of (c) is less than a sequencing footprint of said sequence data of (a),”

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 at least 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 18-19; Ex. 1020 ¶ 122.

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 or contributing to its pathogenesis in the general patient population—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. Claim 1(d): generating a report identifying (i) a presence or absence of a health condition or disease of the subject in said additional biological sample based on said identified at least a subset of (c) and (ii) genetic variants which inform a therapy choice or a change in therapy for the subject

Ley does not disclose claim element 1(d), which claims “generating a report identifying (i) a presence or absence of a health condition or disease of the subject in said additional biological sample based on said identified at least a subset of (c) and (ii) genetic variants which inform a therapy choice or a change in therapy for the subject.”

First, Ley does not expressly disclose “generating a report identifying (i) a presence or absence of a health condition or disease of the subject.” Petitioner argues that “Ley discloses generating a report . . . through tabular summary of results,” such as in Table 1 of Ley. Pet. at 33. Petitioner further argues that “Figure 3 also provides a report depicting . . . sequence information regarding the relative abundance of particular somatic mutations that were observed in samples taken at (i) primary onset, and (ii) relapse,” which are compared in frequency to the skin sample a control. *Id.* Because Ley 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 further in Section IV.A.4, below, the presence of tabular data in Ley does not mean that Ley discloses generating a report based on the claimed method. Furthermore, the data that Petitioner points to in Ley is nothing more than the results of the experiments performed therein, and is not being used to report on the health of the patient.

Second, Ley does not disclose “genetic variants which inform a therapy choice or a change in therapy for the subject.” Petitioners argue that Figure 3, which shows elevated levels of certain variants, “informs a therapy choice or a change,” that is “switching away from conventional therapy, or resuming therapy upon relapse.” *Id.* at 34. Petitioner likewise argues that Ley’s Supplementary Information “provides a detailed case report” and “presents the clinical and therapeutic implication of mutations in the SCL29A1 gene”—namely, that such mutations are associated with cytarabine resistance in a human leukemia cell line. *Id.* Petitioner argues that “one skilled in the art would know that the characteristics of the disease and the patient’s positive mutation[] in the FLT3 and NMP1 would contraindicate the use of allogenic stem cell transplant for this patient.” *Id.* at 35 (citing Ex. 1075). Once again, however, as explained further in Section IV.A.4, below, Ley does not disclose the claimed steps of the method as arranged in the claim as a going-forward method for personalized genetic testing. Thus, the few mentions of particular

therapies scattered throughout Ley do not indicate that Ley intends for the generation of a report which informs the therapy of a specific subject upon completion of the claimed method. Furthermore, nothing in Petitioner's definition of a POSA indicates that a POSA would have knowledge of treatments for a particular type of cancer.

Therefore, Ley does not disclose this limitation.

4. 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 or contributing to its pathogenesis 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 on the eight variants that Ley found. Even in those instances, there is no indication from Ley that the validation experiment should be repeated in each instance. A 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 '783 Patent Because It Does Not Teach Key Elements Of The Claimed Invention As Arranged

Petitioner alleges that claims 1-9, 13-19, and 21-29 of the '783 Patent should be cancelled because they would have been obvious in view of Ley. Pet. at 14. 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(c). 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 43-46.

Third, Ley does not render obvious claim element 1(d). Ley does not disclose “generating a report” detailing the “presence or absence of a health condition” or “genetic variants which inform a therapy choice,” for reasons described above. Section IV.A.3. And Petitioner does not argue that it would have been obvious to generate such a report based on the validation experiment of Ley. Pet. at 46-48.

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.4. 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: Forshew and Dawson Do Not Render Obvious The '783 Patent Because They Do Not Disclose Key Elements of The Claimed Invention

Petitioner alleges that claims 1-9, 13-19, and 21-29 of the '783 Patent should be cancelled as obvious based on the combination of Forshew and Dawson. Pet. at 14. The entirety of Petitioner's argument with regard to Forshew relates to a single experiment performed on a patient with metastatic breast cancer. Ex. 1030 at 9. The Board should deny institution because Forshew, in view of Dawson: (1) does not

disclose a “personalized probe set [that] comprises nucleic acid probe molecules having oligonucleotide-directed genomic content comprising: (i) at least one variable portion from a result of said sequence data and (ii) at least one fixed portion independent of said result of said sequencing data” (2) does not disclose claim element 1(d); (3) discloses a series of experiments, which are not arranged as a going-forward method for personalized genetic testing as claimed.

1. **Forsheew and/or Dawson do not disclose or render obvious “personalized probe set [that] comprises nucleic acid probe molecules having oligonucleotide-directed genomic content comprising: (i) at least one variable portion from a result of said sequence data and (ii) at least one fixed portion independent of said result of said sequencing data”**

Forsheew does not disclose a “personalized probe set [that] comprises nucleic acid probe molecules having oligonucleotide-directed genomic content comprising: (i) at least one variable portion from a result of said sequence data and (ii) at least one fixed portion independent of said result of said sequencing data.” Petitioner admits that “Forsheew does not expressly disclose including PCR primers (probes) for sequences or markers that constitute a fixed portion in the breast cancer patient.” Pet. at 64. Instead, Petitioner states that “it would have been obvious to include such probes in Forsheew’s panel for such a patient” because “Forsheew discloses including such probes, for example, in the context of ovarian cancers where ‘mutations in the tumor suppressor gene *TP53* have been observed in 97% of cases.’” *Id.* (citing Ex.

1030 at 1). Petitioner argues that Forshew “discloses including in its set of probes or primers ‘primer pairs to amplify 5995 bases of genomic sequence covering coding regions (exons and exon junctions) of *TP53*’” and that “[i]ncluding such additional probes in addition to sequence-based probes in a single panel would require nothing more than the predictable use of techniques used in other examples of the very same reference.” Pet. at 64-65.

However, the inclusion of such additional probes is far from predictable according to the methods taught in Forshew. The ten variable probes identified by Petitioner as being used in the breast cancer example of Forshew were determined based on the identification of tumor mutants from whole genome sequencing, and amplicons of less than 120 bp were designed to cover the mutation loci for each mutant. Ex. 1030 at 8-9. Thus, the probe set from this experiment, as shown in table S7 of Forshew, consists of ten amplicons of less than 120 bp each, which are used on serial plasma samples to track the mutations. *Id.* at 8-9, Ex. 1042. In contrast, the 97% of cases with TP53 mutations are, according to Forshew “located throughout the gene and are *difficult to assay*.” Ex. 1030 at 1. The example that Petition argues, of “primer pairs to amplify 5995 bases,” was done via the 16 primer pairs disclosed in Table S1 to create “overlapping short amplicons” as shown in Fig. 1A. *Id.* at 3. Moreover, these primer pairs were created as part of a larger set covering multiple genes, that resulted in 3.5 gigabases of data covering 18,000 possible single-base

substitutions. *Id.* Nothing about the primer pairs covering *TP53*, nor the mutations of *TP53* described in Forshew, suggest that *TP53* probes should be used as a fixed portion of the personalized probe set according to the claim. In fact, the large number of “difficult to assay” mutations in *TP53* would **disincentivize** a POSA from including probes to *TP53* as part of the fixed portion.

In the alternative, Petitioner argues that Dawson “explains that *TP53* is also ‘known to be recurrently mutated in breast cancer.’” Pet. at 65, Ex. 1070 at 1207. Petitioner argues that, because Dawson likewise uses the TAM-Seq technique, “a POSA would have found it obvious to include one or more ‘fixed’ probes in Forshew’s breast cancer panel independent of any sequencing data in order to detect and amplify variants of *TP53* in the patient.” Pet. at 65. However, neither Dawson nor Forshew provides any disclosure or motivation to include **any** fixed probe, nor does Dawson provide any disclosure or motivation that would overcome the teachings of Forshew disincentivizing a POSA from specifically including probes to the *TP53* gene.

Therefore, Petitioner has failed to satisfy its burden of demonstrating that Forshew and/or Dawson disclose or render obvious this claim element.

2. **Claim 1(d): generating a report identifying (i) a presence or absence of a health condition or disease of the subject in said additional biological sample based on said identified at least a subset of (c) and (ii) genetic variants which inform a therapy choice or a change in therapy for the subject**

Neither Forshew nor Dawson discloses claim element 1(d), which claims “generating a report identifying (i) a presence or absence of a health condition or disease of the subject in said additional biological sample based on said identified at least a subset of (c) and (ii) genetic variants which inform a therapy choice or a change in therapy for the subject.”

Neither Forshew nor Dawson expressly discloses “generating a report identifying (i) a presence or absence of a health condition or disease of the subject” or “genetic variants which inform a therapy choice or a change in therapy for the subject.” Petitioner argues that “Figure 4D shows a report depicting the fraction of the various mutant alleles over time, including in response to therapy.” Pet. at 69. Petitioner further argues that because Figure 4D tracked the dynamics of the ten mutations in time, including over the course of chemotherapy treatment, that this constitutes a “report,” which informs therapy choice. *Id.* at 70. Because neither Forshew nor Dawson discloses the claimed steps of the method as arranged in the claim as a going-forward method for personalized genetic testing, as explained further in Section IV.C.3, below, the presence of Figure 4D in Forshew does not equate to Forshew disclosing the generation of a report based on the claimed method, nor does it mean that Forshew discloses use of such a report to inform a therapy choice. Furthermore, the data that Petitioner points to in Forshew is nothing more than the results of the retrospective experiments performed therein, and is not being

used to report on the health of the patient or inform a therapy choice. Rather, Figure 4D is showing the correlation of the results in the experiment with the already known health conditions and therapy choices for that patient. Furthermore, Petitioner does not argue that such a report would have been obvious in view of Forshew and/or Dawson.

Therefore, neither Forshew nor Dawson, alone or in combination, discloses or renders obvious this limitation.

3. Forshew and/or Dawson, alone or in combination, does not disclose or render obvious the claimed steps of the method as arranged in the claim

Neither Forshew nor Dawson, alone or in combination, discloses key elements of the claimed invention as arranged in the claim. *First*, Forshew and/or Dawson do not disclose or render obvious a “personalized probe set [that] comprises nucleic acid probe molecules having oligonucleotide-directed genomic content comprising: (i) at least one variable portion from a result of said sequence data and (ii) at least one fixed portion independent of said result of said sequencing data” for the reasons described above. Section IV.C.1.

Second, neither Forshew nor Dawson, alone or in combination, renders obvious claim element 1(d). Neither Forshew nor Dawson discloses “generating a report” detailing the “presence or absence of a health condition” or “genetic variants which inform a therapy choice,” for reasons described above. Section IV.C.2. And

Petition does not argue that it would have been obvious to generate such a report. Pet. at 69-71.

Finally, Petitioner has failed to demonstrate that Forshew and/or Dawson discloses the claim elements as arranged as a going-forward method for personalized genetic testing. Nor does Petitioner argue that it would have been obvious to do so. All Petition states is that “Forshew in view of Dawson renders obvious each step of claim 1 by teaching to analyze multiple nucleic acid samples isolated from an individual by using its personalized genetic testing methods ‘to monitor tumor dynamics, and tracked 10 concomitant mutations in plasma of a metastatic breast cancer patient over 16 months.’” Pet. at 59. Although Petitioner addresses each element in turn (some of which are not disclosed in Forshew and Dawson, as stated above), Petitioner does not state what this “personalized genetic testing method[]” is, nor does Petitioner describe how the method could be used going forward according to claim 1.

Therefore, neither Forshew nor Dawson discloses the claimed method as arranged or combined in the claim.

**D. 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’ assay embodies claim 1 of the ’783 Patent. Ex. 2003.

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’ 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 Personalis assay that practices the approach disclosed in the ’783 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 ’783 Patent yield radically different

results. Personalis' probe set that practices the '783 Patent can detect biologically or clinically important variants in tumor DNA from blood plasma at levels of about one part per thousand (or 0.001%), and can detect MRD with one part per million (or 0.0001%) sensitivity. By comparison, the best sensitivity from plasma DNA in Leary was about 0.3%, which is one hundred times or more 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:

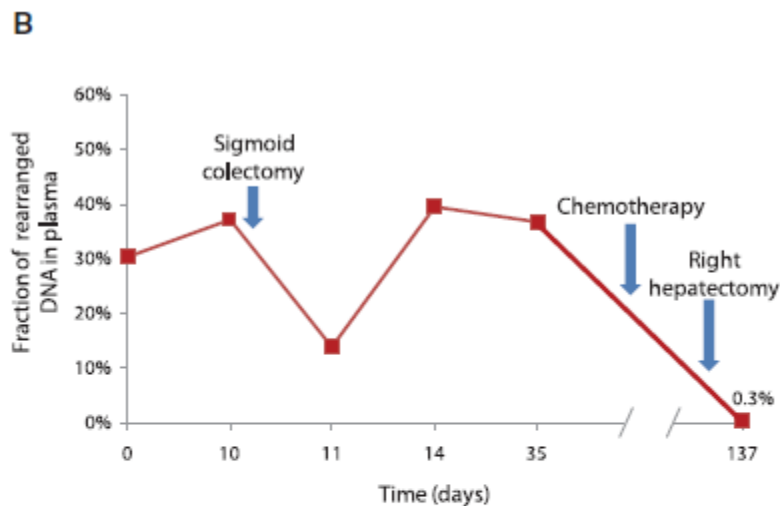


Fig. 4. Detection of tumor-specific rearrangements in plasma of cancer patients. (A) The identified chromosome 4:8 and 16 rearrangements were used to design PCR primers spanning breakpoints and to amplify rearranged DNA from tumor tissue and plasma from patients Hx402 and Hx403, respectively. A plasma 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 ’783 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. 1008 at 212; Ex. 1043 at 554.

Moreover, Forshew, used by Petitioner in the Grounds, acknowledges that using probes for cancer monitoring was “expensive” and that achieving sensitive monitoring for mutations across entire genes has been “more challenging.” Ex. 1030 at 10; *id.* at 1; *see also* Ex. 1031 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. 1030 at 10.

Other references outline clear industry-wide problems with NGS at the time, which were unexpectedly solved by the methods in the ’783 Patent. For example, a review paper by Anderson et al. emphasizes that “difficult engineering challenges must be overcome before these technologies could become commercially viable.” Ex. 1004 at 48. Further, Lo identifies difficulties facing experts regarding “how to handle the massive amount of sequencing data” when utilizing NGS for profiling cancer genomes.” Ex. 1017 at 3.

These objective real-world evidence supports a finding that the claims of the '783 Patent are nonobvious and, consequently, Petitioner's attempt to demonstrate that a claim of the '783 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 11, 2023

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 et seq., the undersigned certifies that this document complies with the word count limitation of 37 C.F.R. § 42.24(a)(1) (i) because the Preliminary Response contains 9,998 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 11, 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. 11,299,783** is being served on May 11, 2023, via email pursuant to 37 C.F.R. § 42.107 to counsel for Foresight Diagnostics, Inc., at the addresses below:

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