

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS INC.,

Petitioner,

v.

PERSONALIS, INC.

Patent Owner.

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

**PATENT OWNER'S SUR-REPLY TO PETITIONER'S REPLY TO
PATENT OWNER'S RESPONSE**

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EXHIBIT LIST

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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), EX1030, from related <i>Foresight Diagnostics Inc. v. Personalis, Inc.</i> , IPR2023-00545
2006	Matthew W. Anderson & Iris Schrijver, “Next Generation DNA Sequencing and the Future of Genomic Medicine,” <i>Genes</i> (2010)
2007	Dennis Lo, “Cancer Genome Scanning in Plasma, <i>Clinical Chemistry Journal</i> ,” Jan. 3, 2013 https://www.aacc.org/science-and-research/clinicalchemistry/clinical-chemistry-podcasts/2013/cancer-genomescanningin-plasma-detection-of-tumor-associated-copynumberaberrations
2008-2009	RESERVED

Exhibit No.	Description
2010	<i>Curriculum Vitae</i> of Dr. Henry Morrice Furneaux
2011-2034	RESERVED
2035	Declaration of Dan Norton
2036-2150	RESERVED
2151	Foresight Diagnostics, About, https://foresight-dx.com/about
2152	RESERVED
2153	“Personalis MRD Assays to Support UK’s TRACERx ctDNA Monitoring Study,” Precision Medicine Online, April 5, 2023
2154	“Personalis, AstraZeneca Extend Collaboration Around Residual Cancer Detection Test,” GenomeWeb, March 7, 2023
2155	RESERVED
2156	Labrousse, “MATRIX plasma-in-plasma contrived samples assessment and detection of MRD using the Personalis NeXT Personal assay,” American Society of Clinical Oncology, e15056, 2023.
2157-2162	RESERVED

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2163	Transcript of the deposition of John Quackenbush, Ph.D., taken on October 20, 2023.
2164	Bratman and Alizadeh and Diehn, Expert Rev Mol Diagn 15:715-719 (2015)
2165	Chaudhuri and Alizadeh and Diehn et al., Semin Radiat Oncol 25:305-312 (2015)
2166	Dudley and Diehn, Annu. Rev. Pathol. Mech. Dis. 16:199-222 (2021)
2167	RESERVED
2168	RESERVED
2169	Declaration of Henry Morrice Furneaux
2170	American Heritage Dictionary definition of “identify”
2171	https://www.aacc.org/science-and-research/clinicalchemistry/clinical-chemistry-podcasts/2013/cancer-genomescanning-in-plasma-detection-of-tumor-associated-copynumber-aberrations , EX1017, from related <i>Foresight Diagnostics Inc. v. Personalis, Inc.</i> , IPR2023-00545
2172	Lewin, “Genes V,” Oxford University Press, 1994.
2173	Quackenbush Declaration, EX1020, from related <i>Foresight Diagnostics Inc. v. Personalis, Inc.</i> , IPR2023-00545

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

I. INTRODUCTION

Personalis identified numerous deficiencies with each of Grounds 1-4. Foresight's Reply does not correct these deficiencies. As a result, Foresight has not proven unpatentability by a preponderance of the evidence.

Grounds 1-2 are based on Ley. These grounds do not teach or suggest three distinct requirements of limitation 1(e): the required sequencing depth, the required sequencing coverage, and subjecting the sequencing library to sequencing to identify a presence or absence of a subset of the set of genetic variants. Foresight also fails to prove that Ley teaches or suggests the "variable" and "fixed" portions required by dependent claim 5, the "therapeutic intervention" required by claim 10, and treating a subject for a disorder according to claim 28.

Grounds 3-4, which are based on Newman, are even worse. They fail to teach or suggest four requirements of claim 1: the sequencing coverage of limitation 1(e), the additional biological sample of limitations 1(d) and 1(e), and sequencing 12 gigabases or more as required by limitation 1(a). Foresight also fails to prove that Newman teaches or suggests the "variable" and "fixed" portions required by dependent claim 5, the "therapeutic intervention" required by claim 10, the recited "at least one biological sample" with nucleic acid molecules "from cells in said tumor sample" of claim 11, and treating a subject for a disorder according to claim 28.

Based on the full trial record, the Board should confirm patentability of the challenged claims.

II. GROUND 1

Foresight fails to prove that Ley anticipates three requirements of limitation 1(e): the recited sequencing depth, the required sequencing coverage, and subjecting the sequencing library to sequencing to identify a presence or absence of a subset of the set of genetic variants. It also fails to prove that Ley anticipates dependent claims 5, 10, and 28.

A. Sequencing depth

Foresight does not dispute that Ley fails to *expressly* teach “a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a)” as required by limitation 1(e). Reply 1-2.

Ley does not *inherently* disclose the required sequencing depth because it does not provide sufficient information to calculate the sequencing depth. POR 10-12. Personalis explained that the read counts in Ley’s Table 3 only provide the number of reads, which is N in the Lander-Waterman equation, $C=L*(N/G)$. POR 11. Ley does not provide the relevant read length (L) or the relevant length of genes being studied (G) required to calculate the sequencing depth (C). POR 11-12.

Foresight’s Reply asserts that “the Lander-Waterman equation is unnecessary” and falls back on its incorrect theory that summing Ley’s readcounts

provides the sequencing depth. Reply 2. However, the experts agree that the Lander-Waterman equation is how sequencing depth is calculated. EX1061 ¶¶66; EX2169 ¶¶175-180. Foresight’s citation to Dr. Furneaux’s testimony simply verifies that Ley only provides readcount numbers. Reply 2. Because Ley’s readcount numbers are insufficient to calculate sequencing depth, Foresight failed to prove that Ley inherently discloses limitation 1(e). POR 11-12.

B. Sequencing coverage of 175 kilobases or less

Foresight does not dispute that Ley fails to *expressly* teach sequencing “at a coverage of 175 kilobases (kb) or less” as required by limitation 1(e). Reply 5-6.

Foresight fails to prove that Ley *inherently* discloses the required sequencing coverage because Dr. Quackenbush’s alleged “upper bound” for Ley’s sequence coverage improperly excluded the length of introns from the length of Ley’s genes. POR 13-14; EX2169 ¶¶182-183.

Foresight tacitly concedes that Dr. Quackenbush’s calculation is incorrect by improperly raising a new theory about what Ley’s sequence coverage might have been if one assumes Ley “sought to cover *every exon in each gene*.” Reply 5-6 (emphasis in original). Foresight’s new theory, like the original theory in its Petition, are based on nothing more than “assumption[s] and its own contentions” about what Ley’s undisclosed sequence coverage might have been, which fails to prove inherent anticipation. *Crown Operations Intern., Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1378

(Fed. Cir. 2002). Regardless, a POSA would not have been able to accomplish Foresight’s new theory by designing a PCR primer pair for just the exons because the exons within a gene are interrupted by introns such that the resulting amplicon would be “far more than 175 kilobases.” EX2169 ¶¶182-183.

C. Sequencing “to identify”

Limitation 1(e) requires “subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less *to identify* a presence or absence of at least a subset of said set of genetic variants.” Ley does not teach limitation 1(e) under the appropriate construction of “to identify.”

1. Construction of “to identify”

The appropriate construction of “to identify” is its plain meaning, which is compellingly demonstrated by dictionary authority and expert testimony. POR 15-16; EX2170 871; EX2169 ¶¶185-189.

Foresight’s Reply provides unsupported attorney argument, Reply 7-9, which “is not evidence and cannot rebut other admitted evidence.” *Elbit Sys. Of Am., LLC v. Thales Visionix, Inc.*, 881 F.3d 1354, 1359 (Fed. Cir. 2018).

Foresight argues that the plain meaning of “to identify” contradicts the claims because “the variants are identified” by limitation 1(b) instead of 1(e). Reply 8. In limitation 1(b), a set of genetic variants “are identified with respect to a reference.” EX1001 69:22-25. Limitation 1(e) has its own, additional, requirement

“to identify a presence or absence of at least a subset of said genetic variants.” *Id.* 69:38-45. There is no contradiction.

Foresight footnotes an assertion that the plain meaning of “to identify” is contradicted by U.S. 11,384,394. Reply 8 n.4. Limitation 1(e) requires “sequencing *to identify*,”¹ whereas the ’394 patent requires “*identifying*” by observation. EX1081 80:11-12. The different claim language in the ’394 patent that recites “identifying” does not contradict the plain meaning of “to identify” in limitation 1(e).

Foresight asserts that using the plain meaning of “to identify” would be “nonsensical” because a POSA “would not have understood how to establish the identity of a presence or absence of variants.” Reply 8. Limitation 1(e) instructs a POSA how to establish the identity of the presence or absence of genetic variants, which is by “subjecting said sequencing library to sequencing” to determine the order of the bases in the additional biological sample on a base-by-base level. EX1061 ¶57.

Personalis’s construction is supported by evidence, which is not rebutted by Foresight’s attorney argument.

¹ All emphases supplied unless otherwise noted.

2. Ley does not teach limitation 1(e)

Foresight’s attorneys assert—without any explanation and without any support from its expert witness—that Ley’s “tallying of readcounts involved determining whether a given read contained the variant or reference sequence, thus establishing the identity of each amplicon.” Reply 9. The tallying of readcounts merely quantifies the amount of variants that are present in Ley’s subject. EX1012, Fig. 3; EX2169 ¶192. This tallying does not involve establishing the identity of variants because the identity of the variants was established in a previous step. POR 16-19; EX1012 69; EX2169 ¶¶191-192.

D. Claim 5

Foresight does not dispute that there is no anticipation under Personalis’s construction of the “variable” and “fixed” portions required by Claim 5. Also, it does not dispute that its anticipation theory requires Ley to *inherently* disclose the claimed “variable” and “fixed” portions.

1. Claim construction of “variable” and “fixed” portions

The specification expressly defines “variable portion” and “fixed portion” as follows:

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

EX1001 38:42-47. This definition must be included in the construction these terms. *Braintree Labs., Inc. v. Novel Labs., Inc.*, 749 F.3d 1349, 1356 (Fed. Cir. 2014); POR 19-21.

Foresight incorrectly asserts that this sentence is not a definition because it starts with in “some applications.” Reply 13-14. Although the sentence teaches that “some applications” may contain a variable and a fixed portion, it also teaches that, whenever an application contains a variable portion it is “defined based on the genetic characteristics originally determined for the individual subject,” and whenever an application contains a fixed portion it “does not change from one subject to another.” EX1001 38:42-47; EX2169 ¶197.

Foresight asserts that the specification discloses some embodiments that “do not require comparing probes from more than one subject to classify content as ‘variable’ and ‘fixed.’” Reply 14. Such embodiments do not negate the express definition provided by the specification. *Braintree*, 749 F.3d at 1356 (“the patentee’s lexicography must govern the claim construction analysis”).

Foresight incorrectly argues that Personalis’s construction “require[s] the creation of at least two probe sets for two different subjects,” which it alleges “contradicts the claims,” which describe testing “a subject.” Reply 13 (emphasis in original). The construction only requires a probe set for a single subject, which—as Dr. Furneaux explains—has a variable portion that changes from one subject to

another and results from said sequence data, and a fixed portion that does not change from one subject to another and is independent of said result of said sequencing data. EX2169 ¶¶197-199; EX1001 38:42-47, 63:33-36, 69:63-67. Contrary to Foresight’s assertion, the preamble merely recites “[a] method for personalized genetic testing,” which clearly does not limit the method to a single subject. The claim only requires that the probe set be personalized to each subject being tested, which is indicated by the recited “a subject” of limitation 1(a).

Foresight incorrectly asserts that “Personalis also argues the claimed probe set must hybridize directly” to the genetic variants because the probes include “oligonucleotide directed genomic content.” Reply 14-15. Personalis explained that the oligonucleotide-directed genomic content of the fixed portion simply must not change from one subject to another and be independent of the result of the sequencing data, and the genomic content of the variable portion must change from one subject to another and result from said sequence data. POR 19-21.

2. Ley does not teach a variable portion or a fixed portion

Foresight does not dispute that Ley fails to *expressly* teach the claimed variable and fixed portions. Reply 12.

Ley does not *inherently* disclose PCR primers having the claimed variable and fixed portions because Ley provides no information about its primers. EX2169 ¶200; POR 22-23. Dr. Quackenbush admitted that Ley is devoid of any information

about its primers. EX1061 ¶121; EX2163 250:4-14, 248:11-249:3, 232:17-22, 261:2-18. Foresight fails to prove that Ley’s undisclosed primers inherently meet the claimed variable and fixed portions. POR 21-25.

Foresight does not dispute that Ley fails to teach the claimed variable and fixed portions under Personalis’s construction. Reply 12. Instead, Foresight incorrectly asserts that Personalis’s construction is inconsistent with the preliminary district court infringement exhibit. Reply 13. Foresight omits that the complaint to which the exhibit is attached necessarily accounts for the preliminary stage of that litigation by explaining infringement may be found “either literally or under the doctrine of equivalents.” EX1010 ¶42. The district court litigation has been stayed pending the outcome of this proceeding. The parties have not submitted claim construction briefing in that litigation. The PTAB will be the first forum to construe these terms.

Foresight inappropriately truncates Dr. Furneaux’s testimony to allege that the fixed portion is met by “standard PCR primers.” Reply 12. Dr Furneaux’s full testimony supports Personalis’s construction by explaining “what’s missing from our conversation here is one of the key distinguishing tests,” EX1078 118:2-22, and the missing test is “whether the probe has been derived from sequenced information from the individual or not,” *id.* 119:24-120:9.

E. Claims 10 and 28

Ley does not disclose a therapeutic intervention or using the presence/absence of genetic variants to treat the subject because the subject of Ley's assay was deceased when Ley's assay was performed. POR 26-27. Further, Ley's mutations had unknown clinical value. EX1012 66, 71; POR 43-44. Foresight fails to address this issue. Reply 17-18. A POSA did not (and would not) use Ley's mutations of unknown clinical value to treat a subject for a disorder. EX2169 ¶247.

III. GROUND 2

Foresight fails to prove that Ley renders obvious three requirements of limitation 1(e): the recited sequencing depth, the required sequencing coverage, and subjecting the sequencing library to sequencing to identify a presence or absence of a subset of the set of genetic variants. It also fails to prove that Ley renders obvious dependent claims 5, 10, and 28.

A. Sequencing depth

Ley fails to disclose sufficient information to determine Ley's sequencing depth. Thus, a POSA would have no baseline from which to determine whether it was desirable to increase (or decrease) Ley's undisclosed sequencing depth. POR 28-30.

Foresight vaguely asserts a POSA would see "a benefit to upgrading" Ley's undisclosed sequencing depth "depending on the particular application." Reply 3-4. Foresight provides no explanation as to which of Ley's particular applications

would be benefited by a higher sequencing depth. Increasing sequencing depth would adversely complicate Ley's assay with more sequencing, increase the complexity of its computational analysis, and increase its cost.² POR 29-30; EX2169 ¶¶213-214. The claimed invention is nonobvious because "the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" in modifying Ley. *Bayer Schering Pharma AG v. Barr Laboratories, Inc.*, 575 F3d 1341, 1347 (Fed. Cir. 2009).

Foresight desperately points to statements made by Personalis's counsel in *Neogenomics* (IPR2024-00346) regarding Forsheo to confuse issues between cases involving different parties, a different patent, a different specification, and different claims. Reply 4. These statements do not concern Ley, and are therefore irrelevant. Foresight provides no reason why a POSA would have discarded **Ley's** method to arrive at the claimed method. Regardless, the *Neogenomics* statements are inadmissible hearsay.

Finally, Foresight footnotes an allegation that Dr. Furneaux did not render his opinions from the perspective of a POSA. Reply 4 n.3. Dr. Furneaux applied the

² Foresight incorrectly asserts that the POR "focuses only on cost considerations."

Reply 4. The POR included other complications. POR 29-30.

Board’s definition of a POSA. EX2169 ¶32; EX1078 155:19-156:5.

B. Sequencing coverage of 175 kilobases or less

Foresight does not dispute that Ley fails to expressly disclose the sequencing coverage for the genes in Table 3. Foresight’s obviousness theory asserts that a POSA would use “routine optimization” to adjust Ley’s *undisclosed* sequence coverage to arrive at the specifically claimed “175 kilobases (kb) or less.” “[T]hat which is unknown cannot be obvious.” *Southwire Co. v. Cerro Wire LLC*, 870 F.3d 1306, 1310 (Fed. Cir. 2017). Foresight’s obviousness theory “simply retraced the path of the inventor with hindsight” by “discount[ing] the number and complexity of alternatives” facing the POSA to conclude that the claimed invention was obvious, which is “always inappropriate.” *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

Foresight asserts that a POSA would target a subset of Ley’s exons to arrive at the claimed sequencing coverage. Reply 6-7. Ley instructs that such targeting via “hypothesis-driven” examination of tumor genes “is inherently limited, and will miss key mutations.” EX1012 70. Thus, Ley would dissuade a POSA from pursuing Foresight’s obviousness theory. POR 31; EX2169 ¶218.

Foresight asserts that the specification ascribes no significance to the claimed sequencing coverage. Reply 7. However, the specification explains that the 175 kilobase limitation dramatically reduces the amount of sequencing required and

makes the claimed methods much more affordable than prior art methods. EX1001 59:29-62:3 (Example 1), 34:42-35:56, 23:48-54, Figs. 3-4; EX2169 ¶217; POR 30.

C. Sequencing “to identify”

A POSA would not have increased the complexity and cost of Ley’s assay to re-establish the identity of mutations that had already been established to arrive at limitation 1(e). POR 31-33.

Foresight argues that complexity and cost issues should be ignored because they supposedly “bear no relation to the claims.” Reply 10. However, “it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests” to a POSA. *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986). Foresight cannot ignore these issues because “[t]he benefits, ***both lost and gained***, should be weighed against one another.” *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019) (emphasis in original).

Foresight asked Dr. Furneaux the incredibly broad question of “Would you consider an assay that’s designed to determine specific mutations in a suspected tumor to be prohibitively costly?” and inappropriately uses his answer to assert that he is unqualified to opine on the specific cost ***of sequencing***. EX1078 44:5-10;

Reply 11. Both experts agree that the cost of sequencing was a motivating factor in evaluating the claimed invention. EX2163 29:6-30:10; EX2169 ¶103.

D. Claim 5

Foresight’s obviousness theory requires Ley to inherently disclose the “variable portion” of claim 5. Dr. Quackenbush admitted that “Ley does not disclose the PCR protocol that was used” and he “can’t speculate on what Ley did or did not do.” EX2163 250:4-14, 261:2-18. Also, Ley’s patient had “a typical acute myeloid leukaemia genome,” EX1012 66, whose mutations may not change from one subject to another. POR 24-25; EX2169 ¶204. Foresight therefore fails to prove that Ley inherently discloses the claimed “variable portion.”

Even if the Board finds that Ley teaches a variable portion—which it should not—Ley still fails to teach or suggest **combining** a variable portion with a fixed portion. Foresight asserts that a POSA would modify Ley by adding PCR primers that meet the claimed “fixed portion” because: (1) Ley supposedly encourages combining tumor-informed and hypothesis-driven approaches, and (2) adding PCR primers was within the level of ordinary skill. These assertions are addressed below.

1. No encouragement

Ley counsels against combining tumor-informed and hypothesis-driven approaches by explaining “[o]ur results strongly support the notion that hypothesis-driven (for example, candidate gene-based) examination of tumour genomes by

PCR-directed” methods “is inherently limited, and will miss key mutations.”
EX1012 70; POR 36-38.

The Petition raised two supposedly clinically relevant reasons why a POSA would go against Ley’s counseling: (i) targeting genetic variants that were known to have companion diagnostics, and (ii) targeting tumor-driver mutations that were known in the art. Petition 49-53. A POSA would not have discarded Ley’s counseling against such hypothesis-driven targeting because it would undesirably decrease the accuracy, sensitivity, and specificity of Ley’s assay, as well as undesirably increase complication and costs. POR 35-42.

Foresight asserts that these issues “are inconsistent with a POSA’s level of skill.” Reply 16. Foresight’s Ross exhibit, however, teaches that “accuracy, sensitivity, and specificity” are important factors that must be “high” for “[c]linical applications, particularly in oncology.” EX1014 535. Foresight cannot cast aside the knowledge and thinking of a POSA reflected in its own exhibit, especially in view of Dr. Quackenbush’s similar admissions, POR 36 (citing EX2163 17:19-20:1, 21:12-23:10), and Founder’s statements, *id.* 41 (citing EX2165 306).

Faced with the admissions by Ross, Dr. Quackenbush, and its Founders, Foresight points with desperation to statements made by Personalis’s counsel in *Neogenomics*, IPR2024-00346, to confuse issues between cases. Reply 16. *Neogenomics* is irrelevant because it involves different parties, a different patent, a

different specification, and different claims. EX1080. The statements are also inadmissible hearsay. The quoted statements from *Neogenomics* concern increasing ***sequencing depth*** (which “is a measure of how many sequence reads map to a given genetic locus,” EX1080 26). Sequencing depth has nothing to do with Foresight’s proposal to arrive at the presently claimed ***variable and fixed portions*** by adding PCR primers to Ley’s assay.

2. No motivation

There was no motivation to redesign Ley’s assay to include PCR primers having variable and fixed portions because a POSA would have expected such primers to decrease the accuracy of Ley’s assay, and increase its complication and cost. POR 36-42.

Foresight’s Reply merely asserts that a POSA ***could*** add PCR primers to Ley’s assay because it was within the level of skill in the art. Reply 16-17. However, “obviousness concerns whether a skilled artisan not only ***could have made*** but ***would have been motivated to make*** the combinations” to arrive at the claimed invention. *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (emphasis in original). A POSA ***would*** not have done so due to accuracy, sensitivity, specificity, complications, and cost issues. POR 36-42.

E. Claims 10 and 28

First, the Petition did not articulate any reason why claim 10 might be obvious over Ley. Petition 46-47. Petitioner presents a new obviousness theory for claim 10 on Reply, which must be rejected. *Henny Penny*, 938 F.3d at 1330-31 (“an IPR petition may not raise in reply an entirely new rationale for why a claim would have been obvious”).

Second, Foresight asserts that it was obvious to use Ley’s mutations to treat a subject based on “a POSA’s knowledge of mutation-therapy pairs.” Reply 18. This assertion ignores that Ley’s mutations had unknown clinical value. POR 43-44; EX1012 66, 71. A POSA would not have used Ley’s mutations of unknown clinical value to make a therapy choice or a change in therapy. EX2169 ¶247.

Third, Foresight asserts—without explanation—that “numerous post-Ley and pre-priority studies” utilized Ley’s approach. Reply 19. Such empty assertions do not prove obviousness. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness”).

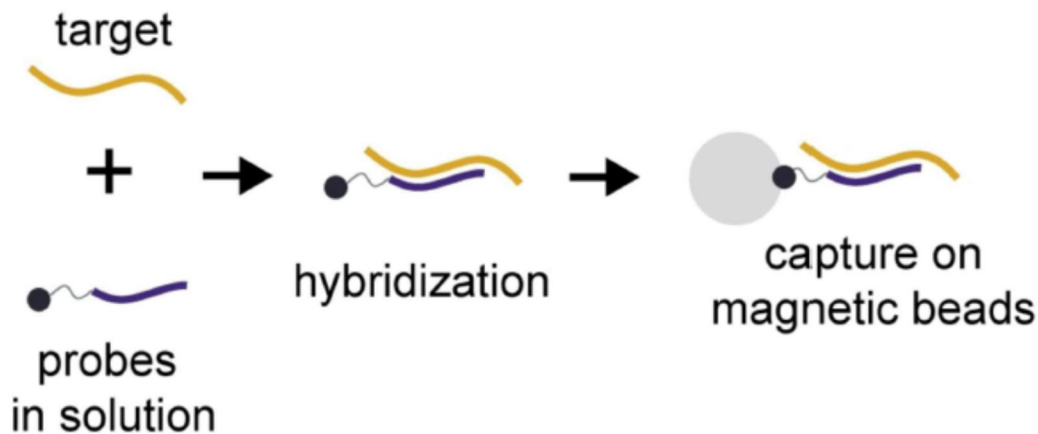
IV. GROUNDS 3 AND 4

Foresight fails to prove that Newman anticipates or renders obvious the sequencing coverage of limitation 1(e), the additional biological sample of limitations 1(d) and 1(e), and sequencing 12 gigabases or more of limitation 1(a). It

also fails to prove that Newman anticipates or renders obvious dependent claims 5, 10, 11, and 28.

A. Limitation 1(e): Sequencing coverage of 175 kilobases or less

Foresight’s entire unpatentability theory requires Newman’s 157-kb selector to capture target DNA *having the exact same length as the capture probes* so that it does not “pulldown overhanging sequence,” Reply 24, and captures only 157-kb “of the region targeted for sequencing,” *id.* 23. This theory is demonstrably incorrect. Petitioner’s figure shows that target DNA (yellow) is significantly longer than—and overhangs—the capture probe (black):



Petition 13. Also, Petitioner’s theory that Newman’s probe set must be the same length as the target DNA is contradicted by Grounds 1-2, which require Ley’s PCR primers to meet the claimed probe set that generates a sequencing library. Dr. Quackenbush admits that PCR primers are “short oligonucleotides that are complementary to a small portion of the DNA templates.” EX1061 ¶75. Ley’s PCR

primers are much shorter than the length of the template DNA.

Foresight incorrectly asserts that the specification of the '611 patent requires the capture probes to be the exact same length as the target DNA. Reply 23. But the specification teaches that “[t]he **genomic region** captured by such probe may be at least about 350 bases.” EX1001 60:3-11, 34:67-35:1. The capture probes can have a length much smaller than 350 bases and still capture target DNA having a genomic region of 350 bases. For example, the specification teaches that the capture probes can be 50 or 60 nucleotides long. *Id.* 68:43-46. The length of the **genomic region** captured by a capture probe, however, can be significantly longer than the length of the capture probe (which can be seen in Petitioner’s own figure reproduced above showing significant target DNA overhanging on both the 5’ and 3’ ends of the capture probe).

Dr. Furneaux explained that a POSA reviewing the details provided by Newman would understand that the 157-kb selector “comprised small capture probes that summed to 157kb.” EX2169 ¶260. Foresight asserts that the basis for this testimony is “unclear,” Reply 24, and suggests that Personalis should have deposed Dr. Newman to establish the length of Newman’s capture probes, *id.* n.7. Dr. Furneaux’s testimony is appropriately based on Newman’s disclosure and what a POSA would have understood from that disclosure. EX2169 ¶260. Foresight did not submit a rebuttal declaration by either Dr. Quackenbush or Dr. Newman.

Foresight merely presents unsupported attorney argument that Newman’s 157-kb selector “refers to the length of the genomic regions targeted by the selector, not the length of the capture probes.” Reply 24. Dr. Furneaux’s unrebutted testimony demonstrates that Newman’s 157-kb selector pulls down a sequencing library of, e.g., “544.3 kb,” which is “much greater” than 157-kb. EX2169 ¶260.

Foresight vaguely asserts that Newman’s selector “could easily be *reduced* in size depending on the application,” but fails to describe which application it believes would benefit from such a reduction. Reply 25. Elsewhere, Foresight speculates that a POSA would *increase* the size of Newman’s 157-kb selector by combining it with Newman’s 175-kb selector. Petition 73. Newman gives no direction as to whether the selector size should be reduced or increased to arrive at the claimed invention. A claim is not obvious “[w]hen a field is unreduced by direction of the prior art, and when prior art gives no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.” *Unigene Laboratories, Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1361 (Fed. Cir. 2011). Foresight has not proven that Newman teaches or suggests the claimed sequencing coverage.

B. Limitation 1(e): additional biological sample

Foresight does not deny that it relies on the *same* GBM Relapse and GBM PBL samples from Newman to supposedly meet the “at least one biological sample

of a subject” required by limitation 1(a) and the “***additional*** biological sample from said subject” required by limitation 1(e). Reply 20-22. Foresight therefore fails to establish that Newman discloses the additional biological sample required by limitation 1(e).

This failure is not a mere technicality. There is nothing in the record to establish that, if a POSA were to somehow have selected a different sample from Newman to arrive at the additional biological sample required by limitation 1(e), the different sample would also meet the other requirements of limitation 1(e) such as “sequencing at a coverage of 175 kilobases (kb)” and “wherein a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a).” Grounds 3-4 fail to prove unpatentability for this reason alone.

C. Limitation 1(d): additional biological sample

Foresight does not dispute that it relies on a GBM Relapse sample that was invasively obtained from a ***brain cancer*** patient to supposedly meet the “at least one biological sample of a subject” for limitation 1(a), and either a sample from a ***lung cancer*** patient or a ***biopsy-free*** assay to meet the “additional biological sample from said subject or at least one biological relative of said subject” for limitation 1(d). Reply 20-22. A sample taken from a lung cancer patient would not be from the ***same*** subject or a relative of the subject as the GBM Relapse sample. Thus, a sample taken from a lung cancer patient does not meet limitation 1(d). POR 47. As for the biopsy-

free assay, Newman teaches that biopsy-free samples should not be used with an invasive brain tissue biopsy. *Id.* Newman even includes the proverbial “prohibition sign” instructing a POSA not to use a tissue biopsy with the biopsy-free assay:



POR 46-47, 54-56.

Foresight asserts that a POSA would discard Newman’s express teachings and, instead, pick and choose different samples to arrive at the claimed method. Reply 20-22. However, the additional biological sample used for limitation 1(d) must be carried forward to limitation 1(e). As discussed above, if a POSA were to somehow have selected a different sample from Newman than the ones cited in the Petition, there is nothing in the record establishing that the different sample would meet the other requirements of limitation 1(e) such as “sequencing at a coverage of 175 kilobases (kb)” and “wherein a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a).”

Foresight asserts that a POSA would combine “both cancers” or apply

Newman “across cancer-types.” Reply 21. Such a combination of cancers would involve combining samples from *different* patients, which would not arrive at the requirement of limitation 1(d) to have the additional sample be from the *same* subject or relative of the subject. Foresight has not proven that Newman teaches or suggests the claimed additional biological sample from said subject or relative of said subject required by limitation 1(d).

D. Limitation 1(a): additional biological sample

Foresight resorts to invoking the Federal Circuit’s *Kennametal* decision to supposedly meet limitation 1(a). Reply 19. Foresight’s reliance on *Kennametal* highlights that it must pick and choose disclosures from Newman to allegedly “at once envisage” the claimed invention. *Id.* As discussed above, Foresight needs to pick and choose from numerous unrelated disclosures to patch together its unpatentability position. Specifically, a POSA would need to decrease the size of the sequencing library pulled down by Newman’s 157-kb selector to arrive at the sequencing coverage of 175 kilobases or less required by limitation 1(e). Also, a POSA would have to select some different sample from Newman than the GBM samples relied on by the Petition to supposedly arrive at the sample required by limitation 1(e). And a POSA would have to select some different sample from Newman than the samples relied on by the Petition to supposedly arrive at the additional biological sample from said subject or relative of said subject for

limitation 1(d). A POSA would not have followed such a tortured pathway through the prior art to arrive at the claimed invention. Foresight “simply retraced the path of the inventor with hindsight, discounted the number and complexity of the alternatives” in Newman and concluded that the invention was obvious, which “is always inappropriate for an obviousness test.” *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). Such hindsight bias cannot “be the thread that stitches together prior art patches into something that is the claimed invention.” *Metalcraft of Mayville, Inc. v. Toro Co.*, 848 F.3d 1358, 1367 (Fed. Cir. 2017).

E. Claim 5

Foresight asserts that a POSA would select Newman’s 157kb selector panel specific for a GBM (glioblastoma) patient and combine it with one of the two selector panels specific for a NSCLC (lung cancer) patient to arrive at the claimed “variable” and “fixed” portions of claim 5. POR 50-51. A POSA would not “immediately envision” this combination as Foresight avers. Reply 25-26. Foresight’s combination requires exactly the type of “picking, choosing, and combining various disclosures not directly related to each other” that is prohibited by *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370-71 (Fed. Cir. 2008). EX2169 ¶266. A POSA would not have combined the 157kb GBM panel with the 175kb NSCLC panel because they were designed for different patients having

different cancers. Such a combination would not have assisted with the purpose of the 157kb GBM panel for determining “ctDNA detection limits for iDES.” EX1043 (last page); POR 60-62.

More importantly, Foresight fails to rebut the simple fact that if a POSA were to combine the 157kb GBM selector panel with the NSCLC 175-kb selector panel, then the size of the combined panel would certainly have a coverage much higher than the “175 kilobases or less” required by limitation 1(e). POR 61; EX2169 ¶¶287-288. Foresight therefore fails to prove anticipation and obviousness of claim 5.

F. Claims 10 and 28

Newman does not expressly disclose a therapeutic intervention or using the presence/absence of genetic variants to treat the subject because its assay was merely “likely to play” a future role in personalized cancer therapy. EX1043 554. Foresight cannot establish anticipation by mere “probabilities or possibilities.” *Par Pharm., Inc. v. TWI Pharms. Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014). Foresight fails to present an obviousness position on these claims and therefore fails to establish unpatentability. POR 51, 62.

G. Claim 11

Foresight does not dispute that it relies on lung tumor samples from Newman to meet claim 11, and GBM (glioblastoma) samples to meet limitation 1(a). Reply 27. Contrary to Foresight’s assertions otherwise, a POSA would have readily

recognized that a biological sample from a lung cancer patient is a distinct embodiment from a biological sample taken from a brain cancer patient. EX2169 ¶¶272-273. Foresight fails to present an obviousness position on this claim and therefore fails to establish unpatentability. POR 52, 62.

V. OBJECTIVE INDICIA OF NONOBVIOUSNESS

The Scientist's ranking of NeXT Personal® as the #1 innovation of 2022 constitutes industry praise. EX2001; POR 63-64. Foresight asserts that this praise lacks nexus, Reply 27, but fails to provide a substantive rebuttal to Dr. Furneaux's explanation that NeXT Personal® embodies claim 1 of the '611 patent. POR 63; EX2169 ¶293. This objective evidence supports a finding that the claims are nonobvious.

Respectfully submitted,

WEIL, GOTSHAL & MANGES LLP

Dated: April 2, 2024

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), Counsel for Patent Owner Personalis, Inc. hereby certifies that this document complies with the type-volume limitation of 37 C.F.R. § 42.24(b). This document contains approximately 5,457 words, including any statement of material facts to be admitted or denied in support, and excluding the table of contents, table of authorities, mandatory notices under § 42.8, exhibit list, certificate of service or word count, or appendix of exhibits or claim listing.

Dated: April 2, 2024

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CERTIFICATE OF SERVICE

I hereby certify that, pursuant to 37 C.F.R. § 42.6(e) and with the agreement of counsel for Petitioner, a true and correct copy of **PATENT OWNER’S SUR-REPLY TO PETITIONER’S REPLY TO PATENT OWNER’S RESPONSE** is being served electronically on April 2, 2024, to the e-mail addresses shown below:

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