

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS INC.,

Petitioner,

v.

PERSONALIS, INC.

Patent Owner.

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

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

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35 U.S.C. § 312	19
37 C.F.R. § 42.6	30
37 C.F.R. § 42.24	29
37 C.F.R. § 42.8	29

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
2004-2009	RESERVED
2010	<i>Curriculum Vitae</i> of Dr. Henry Morrice Furneaux
2011-2034	RESERVED
2035	Declaration of Dan Norton
2036-2150	RESERVED
2151	Foresight Diagnostics, About, https://foresight-dx.com/about
2152	RESERVED

Exhibit No.	Description
2153	“Personalis MRD Assays to Support UK’s TRACERx ctDNA Monitoring Study,” Precision Medicine Online, April 5, 2023
2154	“Personalis, AstraZeneca Extend Collaboration Around Residual Cancer Detection Test,” GenomeWeb, March 7, 2023
2155	RESERVED
2156	Labrousse, “MATRIX plasma-in-plasma contrived samples assessment and detection of MRD using the Personalis NeXT Personal assay,” American Society of Clinical Oncology, e15056, 2023.
2157-2162	RESERVED
2163	Transcript of the deposition of John Quackenbush, Ph.D., taken on October 20, 2023.
2164	Bratman and Alizadeh and Diehn, Expert Rev Mol Diagn 15:715-719 (2015)
2165	Chaudhuri and Alizadeh and Diehn et al., Semin Radiat Oncol 25:305-312 (2015)
2166	Dudley and Diehn, Annu. Rev. Pathol. Mech. Dis. 16:199-222 (2021)
2167	Forshew Supplemental Information, EX1032, from related <i>Foresight Diagnostics Inc. v. Personalis, Inc.</i> , IPR2023-00317
2168	Quackenbush Declaration, EX1061, from related <i>Foresight Diagnostics Inc. v. Personalis, Inc.</i> , IPR2023-00546

Exhibit No.	Description
2169	Declaration of Henry Morrice Furneaux
2170	American Heritage Dictionary definition of “identify”
2171	RESERVED
2172	Lewin, “Genes V,” Oxford University Press, 1994.
2173-2176	RESERVED
2177	Sholl, Institutional implementation of clinical tumor profiling on an unselected cancer population,” JD Insight. 1:e87062 (2016)

I. INTRODUCTION

Personalis identified numerous deficiencies in Grounds 1-3. The most egregious is Foresight's failure to prove that its references teach or suggest the "variable portion" and "fixed portion" required by limitation 1(a)(i)-(ii). Foresight's grounds require the references to inherently disclose PCR primers having genomic content that meet the claimed "variable" and "fixed" portions. But Foresight's references are bereft of any information about the genomic content of PCR primers. Foresight therefore fails to prove that any of its references teach or suggest the claimed "variable" and "fixed" portions.

Foresight also fails to prove that its references teach or suggest the additional biological sample required by limitation 1(b), subjecting the sequencing library to sequencing to identify a presence or absence of a subset of the set of genetic variants required by limitation 1(c), and generating a report identifying genetic variants which inform a therapy choice or change in therapy for the subject required by limitation 1(d). Based on the full trial record, it is clear that Foresight has not proven unpatentability by a preponderance of the evidence for any of Grounds 1-3.

Additionally, dependent claim 22 requires "hybrid capture probes." Foresight's references disclose PCR-based assays that do not use hybrid capture probes. A POSA would not abandon the core reaction principle of PCR amplification to instead use hybrid capture probes in view of specificity, uniformity,

reproducibility, and expense issues. Foresight has not proven unpatentability of dependent claim 22.

II. GROUND 1

Foresight failed to prove that Ley anticipates the “variable” and “fixed” portions required by limitation 1(a)(i)-(ii), the additional biological sample required by limitation 1(b), subjecting the sequencing library to sequencing to identify a presence or absence of a subset of the set of genetic variants required by limitation 1(c), and generating a report identifying genetic variants which inform a therapy choice or change in therapy for the subject required by limitation 1(d). It also fails to prove that Ley anticipates dependent claims 3, 8, 15, 16 and 22.

A. Limitation 1(a)(i)-(ii)

Foresight does not dispute that there is no anticipation under Personalis’s construction of the “variable” and “fixed” portions required by limitation 1(a)(i)-(ii). Also, it does not dispute that its anticipation theory requires Ley to *inherently* disclose the claimed “variable” and “fixed” portions. Personalis’s construction is required by the specification and Ley fails to inherently disclose the claimed “variable” and “fixed” portions. POR 13-17.

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 41:45-50.¹ 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 11-13.

Foresight incorrectly asserts that this sentence is not a definition because it starts with “[i]n some applications.” Reply 2. 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 41:45-50; EX2169 ¶51.

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 2. Such embodiments do not negate the express definition provided by the specification. *Braintree*, 749 F.3d at 1356 (“the

¹ All emphases supplied unless otherwise noted.

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 1-2 (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 ¶¶51-53; EX1001 41:40-50, 66:36-39, 72:32-35. 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. Reply 2-3. Personalis explained that 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 13-15.

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 4.

Ley does not *inherently* disclose PCR primers having the claimed variable and fixed portions because Ley provides no information about its primers. EX2169 ¶54; POR 14-15. Dr. Quackenbush admitted that Ley is devoid of any information about its primers. EX1020 ¶124; EX2163 250:4-14, 248:11-249:3, 232:17-22, 261:10-18. Foresight fails to prove that Ley's undisclosed primers inherently meet the claimed variable and fixed portions. POR 14-15.

Foresight does not dispute that Ley fails to teach the claimed variable and fixed portions under Personalis's construction. Reply 4. Instead, Foresight incorrectly asserts that Personalis's construction is inconsistent with the preliminary district court infringement exhibit. Reply 4-5. Foresight omits that the exhibit necessarily accounts for the preliminary stage of that litigation by explaining "[t]o the extent the accused product is argued by Foresight or found by the Court not to literally infringe certain limitations of the '783 patent, infringement of such limitations can be found under the doctrine of equivalents," including the personalized probe set of limitation 1(a). EX1072 3. The exhibit cautions "[t]his case is in its early stages" and "discovery is ongoing." *Id.* 1. That litigation has been stayed. 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 4. 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,” *id.* 119:24-120:9.

B. Limitation 1(b)

Limitation 1(b) requires an “*additional* biological sample from said subject.” Ground 1 fails because Foresight relies on the *same* biological samples from Ley to supposedly meet limitations 1(a) and 1(b). POR 18-19.

Foresight’s Reply seeks to rewrite the Petition by alleging it “explains that when the primary tumor is considered the first sample, Ley’s use of the personalized probe set in at least an additional biological sample, i.e., the relapse tumor and the skin biopsy satisfies step 1(b).” Reply 7. In reality, the Petition relies on all three samples—“the primary tumor, skin sample, and relapse tumor sample”—to meet the first sample of limitation 1(a). Petition 27. The Petition improperly double-counts Ley’s samples and therefore fails to anticipate claim 1.

C. Limitation 1(c)

Limitation 1(c) requires “subjecting said sequencing library to sequencing *to identify* a presence or absence of at least a subset of said set of genetic variants.”

Ley does not teach limitation 1(c) under the appropriate construction of “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 19-20; EX2170 871; EX2169 ¶¶65-69.

Foresight’s Reply provides unsupported attorney argument, Reply 8-9, 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(a) instead of 1(c). Reply 8. In limitation 1(a), a “set of genetic variants are identified in sequence data for said at least one biological sample.” EX1001 72:28-30. Limitation 1(c) has its own, additional, requirement “to identify a presence or absence of at least a subset of said genetic variants in at least said additional biological sample.” *Id.* 72:41-44. There is no contradiction.

Foresight footnotes an assertion that the plain meaning of “to identify” is contradicted by limitation 1(d) and U.S. 11,384,394. Reply 8 n.3. Limitation 1(c) requires “sequencing *to identify*,” whereas limitation 1(d) requires “generating a report *identifying*.” The ’394 patent requires “**identifying**” by observation. EX1081 80:11-12. The different claim language in limitation 1(d) and the ’394 patent that

recite “identifying” do not contradict the plain meaning of “to identify” in limitation 1(c).

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 8-9. Limitation 1(c) 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. EX1020 ¶55.

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

2. Ley does not teach limitation 1(c)

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’s genetic content.” Reply 9. The tallying of readcounts merely quantifies the amount of variants that are present in Ley’s subject. EX1012, Fig. 3; EX2169 ¶72. This tallying does not involve establishing the identity of variants because it was established in a previous step. POR 20-23; EX1012 69; EX2169 ¶¶71-72.

D. Limitation 1(d)

Limitation 1(d) requires “generating a report identifying... (ii) genetic variants *which inform a therapy choice or a change in therapy for the subject.*”

1. Construction

Foresight incorrectly asserts that limitation 1(d) is not entitled to patentable weight because it is more analogous to *Praxair* claims 1-8 and 10 than *Praxair* claims 9 and 11. Reply 11-12; *Praxair Distrib. v. Mallinckrodt Hosp. Prods. IP*, 890 F.3d 1024, 1033-35 (Fed. Cir. 2018).

Praxair claims 1-8 and 10 were not entitled to patentable weight because they “merely require[d] a medical provider to think about the information claimed.” *Id.* at 1033. Here, limitation 1(d) requires more than merely thinking about genetic variants—it requires the specific action of making a therapy choice or change in therapy. EX2169 ¶76. This required specific action is analogous to claim 9 from *Praxair*, which “require[d] a medical provider to take a specific action, discontinuing treatment,” as a result of the report. 890 F.3d at 1035. The concrete step of making a therapy choice or change in therapy informed by the genetic variants identified in the report is entitled to patentable weight. *Id.*; POR 23-24.

2. Ley does not teach limitation 1(d)

Foresight incorrectly asserts that Ley discloses treating patients with “targeted therapies,” or at least “would at once envisage” doing so. Reply 13-14. Ley explains that its assay merely uncovered “new candidate genes that may be relevant for AML

pathogenesis.” EX1012 71. Ley cautions that “until hundreds (or perhaps thousands) of normal genomes and other AML tumors are sequenced, the contextual relevance of the mutations found in this genome will be unknown.” *Id.* Ley’s caution confirms that a POSA would not at once envisage using Ley’s mutations of unknown relevance to treat patients. EX2169 ¶106. Ley fails to anticipate limitation 1(d).

E. Claims 3, 8, 15, 16 and 22

Foresight fails to prove anticipation of claims 3, 8, 15, 16, and 22. POR 25-26.

III. GROUND 2

Foresight fails to prove that Ley renders obvious limitations 1(a)(i)-(ii), 1(b), 1(c), and 1(d). It also fails to prove obviousness of claims 3, 8, 15, 16 and 22.

A. Limitation 1(a)(i)-(ii)

Ground 2 rests on the faulty premise that Ley’s PCR protocol inherently discloses the “variable portion” of limitation 1(a)(i). Reply 5-6. Dr. Quackenbush admitted that “Ley doesn’t disclose the PCR protocol that was used” and he “can’t speculate on what Ley did or did not do.” EX2163 250:4-14, 261:2-18. Also, Ley’s patient had “a typical acute myeloid leukaemia genome,” EX1012 66, whose mutations may not change from one subject to another. POR 16-17; EX2169 ¶58. 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.

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... is inherently limited, and will miss key mutations.” EX1012 70; POR 28-31.

Foresight wrongly asserts that Personalis did not address “clinically relevant reasons” why a POSA would have gone against Ley’s counseling. Reply 5. The Petition raised two supposedly clinically relevant reasons: (i) targeting genetic variants that were known to have companion diagnostics, and (ii) targeting tumor-driver mutations that were known in the art. Petition 43-46. 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 28-34.

Foresight asserts that these issues “are inconsistent with the knowledge and creativity of a POSA.” Reply 6. 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 29 (citing EX2163 17:19-20:1, 21:12-23:10), and Founder’s statements, *id.* 33 (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 6-7. *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.

Finally, Foresight footnotes an allegation that Dr. Furneaux did not render his opinions from the perspective of a POSA. Reply 6 n.2. He applied the Board’s definition of a POSA. EX2169 ¶32; EX1078 155:19-156:5.

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 28-34.

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 7. 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 28-35.

B. Limitation 1(b)

Foresight failed to establish that Ley teaches limitation 1(b). *Supra* Section II.B. Foresight’s Reply raises a new theory that a POSA would have added more tumor biopsy samples to Ley’s assay. Reply 7-8. Foresight fails to address the strong lack of motivation because “[b]iopsies are invasive and costly,” EX1030 1,

and tumors “cannot be repeatedly sampled without invasive procedures,” EX1044 2; POR 35-36.

C. Limitation 1(c)

Foresight does not dispute that the Petition fails to include an obviousness position on limitation 1(c). 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(c). POR 37.

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

Foresight relies on *In re Aller* to assert that it would take “routine optimization” to redesign Ley’s readcount tallying to arrive at the claim. Reply 10-11. That case addressed non-inventiveness in discovering “optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). But optimizing ranges has nothing to do with redesigning Ley’s readcount tallying to instead establish the identity of a presence or absence of genetic variants. Foresight fails to prove obviousness because it does not articulate any “reasoning with some rational underpinning” why a POSA would redesign Ley’s assay to arrive at the claimed invention. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007); POR 36-37.

D. Limitation 1(d)

Foresight asserts that it was obvious to use Ley’s mutations to make a therapy choice or change in therapy based on “a POSA’s knowledge of mutation-therapy pairs.” Reply 14. This assertion ignores that Ley’s mutations had unknown clinical value. POR 38; 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 ¶106.

Foresight asserts—without explanation—that “numerous post-Ley and pre-priority studies” utilized Ley’s approach. Reply 15. Such empty assertions do not prove obviousness. *KSR*, 550 U.S. at 418.

E. No motivation

A POSA would not have modified Ley’s assay to (1) add PCR primer pairs having a “variable portion” and “fixed portion” to meet limitation 1(a)(i)-(ii), (2) add an additional biological sample from the subject to meet limitation 1(b), (3) add a protocol to re-establish the identity of mutations that Ley had already established to meet limitation 1(c), and (4) make a therapy choice or change in therapy based on mutations of unknown clinical value to meet limitation 1(d). EX2169 ¶108. Accordingly, Foresight failed to prove obviousness of claim 1.

F. Claims 3, 8, 15, and 16

Ley teaches that its assay requires “high sample purity” and that “contaminating normal cells would complicate our analysis.” EX1042 2; EX2169 ¶¶113-114. A POSA would not have used Ley’s assay on cell-free tumor DNA with a reasonable expectation of success in view of the admissions by Dr. Quackenbush that such DNA is extremely impure. EX1020 ¶86; EX2163 11:16-12:19, 12:20-14:9; POR 39-40.

Faced with Ley’s teachings and Dr. Quackenbush’s admissions, Foresight desperately points to statements made by Personalis’s counsel in *Neogenomics*

regarding Forshew and Leary to confuse issues between cases. Reply 15-16. These statements do not concern Ley, and are therefore irrelevant. Foresight provides no reason why a POSA would have discarded **Ley's** method to instead use Forshew's or Leary's assays to arrive at the claimed method. Regardless, the *Neogenomics* statements are inadmissible hearsay.

Foresight argues that using cell-free DNA would be acceptable for Ley's supposed "PCR-directed resequencing step." Reply 16. Foresight's Founders disagree. They described the "major technical challenge" of analyzing cell-free tumor DNA. EX2164 715. There was no motivation to use Ley's assay that required a highly pure DNA sample on extremely impure cell-free tumor DNA with a reasonable expectation of success.

G. Claim 22

A POSA would not have replaced Ley's PCR primers with hybrid capture probes. POR 40-45.

In its Reply, Foresight asserts that the specification considers PCR primers to be interchangeable with hybrid capture probes. Reply 16-18. The specification, however, is written to the POSA, who would recognize that PCR primers were not interchangeable with hybrid capture probes in Ley's assay. EX2169 ¶¶116-121. Moreover, Foresight's assertion fails to prove obviousness because, at best, it merely concerns whether a POSA *could* substitute capture probes for PCR primers.

Foresight fails to explain why a POSA *would* have changed the core reaction principle of Ley's particular PCR-based assay to use hybrid capture probes. *Belden*, 805 F.3d at 1073.

While PCR primers and capture probes are both “enrichment” techniques, a POSA would not have viewed them as interchangeable in Ley's assay. Foresight has no reply to:

- PCR and hybrid capture probes having different “core reaction principles,” with different “operational characteristics” that “vary in their suitability for different fields,” and give “very divergent” results. EX1006 375, 383; POR 41-45.
- Seven parameters/metrics a POSA would evaluate to weigh pros/cons before selecting PCR primers or capture probes for an experiment. POR 42-45.
- Its Founder's admission that hybrid capture workflows “typically have longer turnaround times, since the target enrichment process often takes days (instead of hours with PCR), and are more expensive.” EX2166 203.

Foresight vaguely avers that it was obvious to replace Ley's PCR primers with hybrid capture probes in Ley's steps requiring “probes for the amplification and/or enrichment of target DNA over normal DNA.” Reply 18. Foresight fails to articulate which of Ley's steps would benefit from enrichment by hybrid capture probes. Foresight attempts to justify its vagueness by asserting it need not show “a

physical combination of two systems.” Reply 18-19. However, “[a] petitioner may not rely on a vague, generic, and/or meandering petition.... it is the petitioner’s burden to present a clear argument.” *Netflix, Inc. v. DivX, LLC*, 84 F.4th 1371, 1377 (Fed. Cir. 2023); 35 U.S.C. §312(a)(3). Foresight’s obviousness ground fails because it does not present a clear argument as to what aspect of Ley’s workflow it believes a POSA would have sought to improve, and how the addition of hybrid capture probes would have supposedly provided the unnamed improvement.

IV. GROUND 3

Forsheew and Dawson do not render obvious limitation 1(a)(i)-(ii), limitation 1(d), and claim 22.

A. Limitation 1(a)(i)-(ii)

Forsheew does not teach or suggest the claimed “variable portion,” and Forsheew in view of Dawson does not suggest combining a variable portion with a fixed portion to arrive at the claimed invention.

1. No “variable portion”

Foresight asserts—without explanation—that Forsheew *expressly* discloses the claimed “variable portion.” Reply 20. There is no such express disclosure because Forsheew does not disclose the sequences of its PCR primers. POR 47; EX2163 147:22-148:2; EX2169 ¶¶128-129. Forsheew’s silence left Dr. Quackenbush speculating that “Forsheew may have been using a commercially available set of

probes,” EX2163 152:16-155:3, such as “a standard probe set that he purchased off the shelf,” *id.* 155:5-157:16.

Such a standard probe set would not meet the claimed variable portion because: (1) it would not change from one subject to another, and (2) it would not “result from said sequence data” from “at least one biological sample,” as required by limitation 1(a)(i). POR 47-48; EX2169 ¶129. Foresight has no reply to the first issue, which remains unrebutted.

On the second issue, Foresight incorrectly asserts that Forshew’s undisclosed PCR primers must result from sequence data for ten mutational loci. Reply 20. Forshew’s primers were “standard amplification primers,” EX1030 10, which were likely “purchased off the shelf.” EX2163 155:5-157:16. Dr. Furneaux’s unrebutted declaration explains that standard amplification primers purchased off the shelf would be the result of extraneous criteria applied by the manufacturer of the primers. EX2169 ¶129. Thus, standard amplification primers would not “result from said sequence data” as required by limitation 1(a)(i). POR 47-48.

The POR explained that Forshew does not suggest the claimed “variable portion” because it teaches that TAm-Seq should be used “without requiring any specially designed probes,” which are “expensive” and “difficult to implement on a routine basis.” EX1030 10; POR 48-49. Foresight has no reply other than to double-down on its disproven theory that “Forshew expressly discloses the claimed variable

portion.” Reply 20. Foresight’s Ground 3 requires Forshew to expressly disclose the claimed variable portion, which it does not. POR 47-49. Ground 3 therefore fails.

2. No motivation

Foresight’s obviousness theory relies on combining Forshew’s alleged variable portions with Dawson’s alleged fixed portions. This theory fails because Forshew does not teach or suggest the claimed variable portion. *Supra* Section IV.A.1; POR 47-50.

If the Board were to accept Foresight’s theory that Forshew’s undisclosed PCR primers constitute a “variable portion”—which it should not—a POSA still would not have added Dawson’s PCR primers in a manner that would arrive at the claimed “fixed portion.” Adding such additional primers is undesirable because it would decrease the accuracy of the TAm-Seq assay, complicate the assay with amplification issues, reduce the sensitivity and specificity of the assay, and increase its cost. POR 49-55.

Foresight’s Reply mischaracterizes the POR as asserting that a POSA would never add “*any* additional primers” to Forshew’s assay under any circumstances. Reply 21 (emphasis in original). The POR explained that a POSA would not have modified Forshew’s assay to specifically add PCR primers *constituting the claimed variable and fixed portions*. POR 49-55.

Foresight clings to statements from *Neogenomics* to confuse issues between cases with inadmissible hearsay regarding whether a POSA could add up to 9,216 primers to Forshew's TAm-Seq. Reply 22. In *Neogenomics*, it would have been obvious to multiplex TAm-Seq with 20 to 50 primers. EX1080 38-39. Here, it would take over 1,000 PCR primers to cover the TP53 gene in accordance with Foresight's obviousness theory. POR 50; EX2169 ¶135. Although multiplexing with that many primers was possible, Foresight still fails to provide a compelling rationale why a POSA would have taken on the decreased accuracy, sensitivity, and specificity, as well as the increased amplification issues and costs that come with such a high degree of multiplexing. POR 50-55.

Finally, Foresight retreats to an ambiguous position that a POSA would have added just “*one* or more ‘fixed’ probes” to Forshew's TAm-Seq assay “to detect and amplify variants of TP53 in the patient.” Reply 22 (emphasis in original). A single PCR primer, however, does not allow amplification. Forshew already included PCR primers for exons 5 and 6 of TP53. EX1030 Fig. 1; EX2169 ¶135. These exons, along with the other genes sequenced by Forshew, already “cover mutations that account for 38% of all point mutations in the COSMIC database.” EX1030 3. To meaningfully expand Forshew's investigation of the TP53 gene, a POSA would need to cover the rest of the TP53 gene, which would require over 1,000 PCR primers. EX2169 ¶135. Complicating Forshew's assay to be so highly multiplexed was

undesirable for reasons discussed above. *See also* POR 50-55. Foresight's ambiguous position does not address the underlying issue that Forshew fails to teach or suggest the claimed "variable portion." Thus, even if a POSA would have modified Forshew's assay with some undisclosed number of Dawson's supposedly "fixed probes," the POSA still would not arrive at the "variable portion" required by limitation 1(a)(i).

3. Relevance

Foresight argues that the complexity, cost, accuracy, sensitivity, and specificity issues associated with its proposed combination of Forshew and Dawson are "tangential" to the claimed invention. Reply 23-24. These issues are highly relevant to Foresight's proposed combination. Forshew's Editor Summary criticizes the TAm-Seq assay as "need[ing] to achieve a more sensitive detection limit (<2% allele frequency) to identify mutations in the plasma of patients with less advanced cancers." EX1030 (Editor's Summary). Foresight's Ross exhibit teaches that "[c]linical applications, particularly in oncology, demand high levels of accuracy, sensitivity, and specificity." EX1014 535. Foresight's proposed combination would reduce the accuracy, sensitivity, and specificity of Forshew and Dawson's TAm-Seq. Thus, "[a]n inference of nonobviousness is especially strong [because] the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements" of Forshew and Dawson.

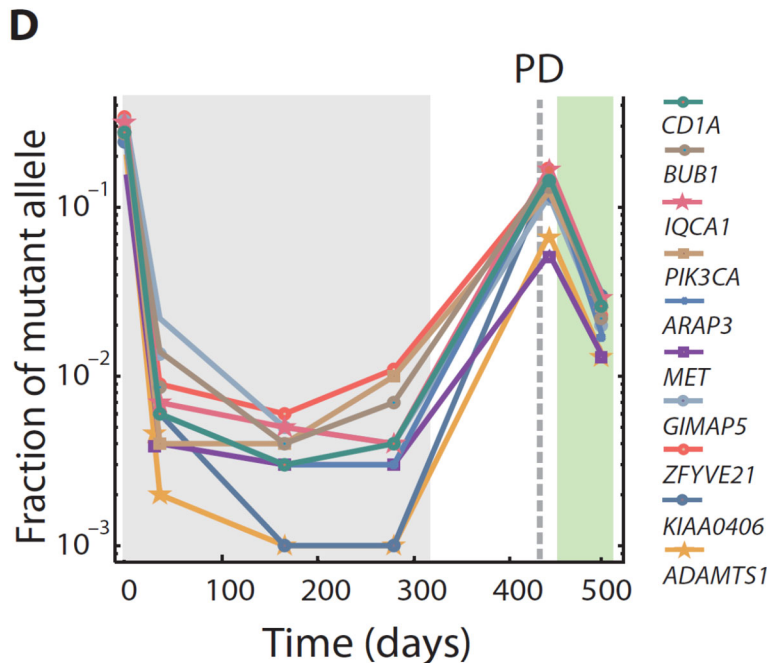
DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314, 1326 (Fed. Cir. 2009).

Foresight reverts to distractions by confusing issues between cases with inadmissible hearsay to incorrectly allege contradictions between arguments presented here and *Neogenomics*. Reply 24. The cited statements from *Neogenomics* concern increasing ***sequencing depth***, EX1080 26-28, 32, 43, which has nothing to do with Foresight's proposal to arrive at the presently claimed ***variable and fixed portions*** by adding PCR primers to Forshew's assay.

B. Limitation 1(d)

Neither Forshew nor Dawson teach or suggest limitation 1(a)(i)-(ii). *Supra* Section IV.A; POR 46-55. Thus, Forshew does not teach or suggest generating a report based on the claimed method.

Foresight asserts that Forshew's Figure 4(D) discloses limitation 1(d):



EX1030, Fig. 4(D). Forshew’s patient was treated with epirubicin during the gray-shaded time-period based on preexisting knowledge that the patient had breast cancer. *Id.* 9. The patient was treated with paclitaxel during the green-shaded time-period based on a CT scan that revealed progressive disease (PD). *Id.* No therapy choice was made based on the results of the TAm-Seq assay. EX2169 ¶¶145-146; POR 56-58.

Foresight asserts that Figure 4(D) “informs a therapy choice at least by confirming efficacy.” Reply 25-26. This assertion is contradicted by the Forshew’s Editor Summary, which cautions that the TAm-Seq assay must be further “optimized” before it can “inform clinical decision-making on an individual basis.” EX1030 (Editor’s Summary). Forshew further cautions that TAm-Seq will require “faster, more accurate sequencing” before “this approach could potentially be used

for personalized medicine at point of care.” *Id.* 2. Thus, Forshew teaches that TAm-Seq was not ready to inform a therapy choice or change in therapy for a patient. EX2169 ¶¶147-148; POR 58.

C. Claim 22

Foresight’s Reply on claim 22 contains a single sentence. Reply 27. This sentence fails to rebut the many reasons articulated in the POR why a POSA would not have replaced Forshew’s PCR primers with hybrid capture probes. POR 59-62.

A POSA would not have made the drastic change of replacing Forshew’s PCR-based assay with hybrid capture probes. For example, Foresight’s Mertes exhibit teaches that capture probes and PCR are two different enrichment techniques that are “categorized according to the nature of their *core reaction principle*.” EX1006 375; EX2169 ¶151. Foresight’s Mamanova exhibit teaches that “[t]here are several enrichment approaches, each with unique advantages and disadvantages” such that a user must “find the best compromise between sensitivity, specificity and uniformity for their particular project.” EX1007 111. Mamanova teaches that a POSA would need to evaluate seven parameters associated with the disadvantages of capture probes before discarding the core reaction principle of the PCR-based TAm-Seq assay and replacing it with capture probes.

The vast majority of these parameters would have counseled a POSA to avoid redesigning TAm-Seq. Mamanova teaches that “[t]he *specificity* of PCR will almost

certainly always exceed that of hybrid capture, and its ***uniformity*** may never be matched by either hybrid capture or MIPs.” *Id.* 117. Mamanova further teaches that PCR has higher ***reproducibility*** of “up to 100%” than capture probes. *Id.* Table 1. Forshew already had a working assay, so switching the core reaction principle to hybrid capture probes would entail more ***costs*** for redesigning the experiment, and risk making the assay ***harder to use***. EX2169 ¶¶152. The ***sensitivity*** and ***amount of DNA required*** are parameters that would, at best, be considered neutral; but the risks associated with modifying Forshew’s already-working assay could very well cause the assay to lose sensitivity or even worse, not work at all.

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

V. OBJECTIVE INDICIA OF NONOBVIOUSNESS

The Scientist's ranking of NeXT Personal[®] as the #1 innovation of 2022 constitutes industry praise. EX2001; POR 62-63. Foresight asserts this praise lacks nexus, Reply 27, but fails to substantively rebut Dr. Furneaux's explanation that NeXT Personal[®] embodies claim 1. POR 62; EX2169 ¶156. This objective evidence supports nonobvious.

Respectfully submitted,

WEIL, GOTSHAL & MANGES LLP

Dated: April 2, 2024

/Derek C. Walter/

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

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

Counsel for Patent Owner Personalis, Inc.

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), Counsel for Patent Owner Personalis, Inc. hereby certifies that this document complies with the type-volume limitation of 37 C.F.R. § 42.24(b). This document contains approximately 5,596 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

/Derek C. Walter/

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

CERTIFICATE OF SERVICE

I hereby certify that, pursuant to 37 C.F.R. § 42.6(e) and with the agreement of counsel for Petitioner, a true and correct copy of **PATENT OWNER’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:

Andrew E. Krause, Lead Counsel akrause@irell.com ForesightIPRs@irell.com IRELL & MANELLA LLP 1800 Avenue of the Stars, Suite 900 Los Angeles, California 90067 Telephone: (310) 277-1010 Facsimile: (310) 203-7199	Amir Naini, Backup Counsel NAINI P.C. 2632 Wilshire Blvd., Suite 268 Santa Monica, CA 90403 T: 310- 592-3030 F: 310-453-9008 amir@nainipc.com Abigail Sellers, Backup Counsel asellers@irell.com ForesightIPRs@irell.com IRELL & MANELLA LLP 1800 Avenue of the Stars, Suite 900 Los Angeles, California 90067 Telephone: (310) 277-1010 Facsimile: (310) 203-7199
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Dated: April 2, 2024

/Derek C. Walter/

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