

IPR2023-00545
Patent No. 11,299,783

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Foresight Diagnostics Inc.,
Petitioner,

v.

Personalis, Inc.,
Patent Owner.

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

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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I. Grounds 1 and 2

A. Claim 1

1. Step 1(a): Ley discloses a probe set with a “variable portion” and “fixed portion.”

Step 1(a)¹ requires obtaining a “personalized probe set” 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.” EX1001, cl.1. Ley’s probe set satisfies the “fixed portion” and “variable portion” under the claim’s plain meaning. *See* EX1020, ¶¶93, 119-20.

(a) Claim Construction

The claim language alone sufficiently defines the “variable” and “fixed” portions: “at least one variable portion *from a result of said sequence data*” and “at least one fixed portion *independent of said result of said sequencing data*.” EX1001, cl. 1(a).

(i) Personalis’s constructions are incorrect.

Personalis’s opposition urges incorrect claim constructions requiring the creation of at least two probe sets for two different subjects to determine if the “variable” set “changes from one subject to another,” and if the “fixed” set “does not

¹ The disputed claims have been reproduced in Appendix A.

change from one subject to another.” POR13. This contradicts the claims, which describe the “personalized genetic testing” of “a subject.” EX1001, cl. 1(pre), 1(a).

Contrary to Personalis’s assertion, these terms are not expressly defined in the specification, POR11-12, and the language Personalis cites to suggest otherwise is explicitly limited to “*some applications*.” EX1001, 41:45-50; *see also id.*, 66:36-39 (exemplary embodiment cited in POR). It is a basic canon of claim construction that “it is improper to read limitations from a preferred embodiment described in the specification...into the claims.” *Liebel–Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 913 (Fed.Cir.2004). Moreover, the specification provides multiple embodiments which do not require comparing probes from more than one subject to classify content as “variable” and “fixed.” EX1001, 7:47-53 (mirroring claim language); 18:48-51 (“(i) at least one variable portion, defined based on results of the first assay and (ii) at least one fixed portion, independent of the results of the first assay.”); 42:12-20 (“fixed portion may be selected from,” e.g., “cancer driver genes”).

(ii) Personalis improperly conflates “genomic content” with “genetic variants.”

Personalis also argues the claimed probe set must hybridize directly to sequences containing the identified “genetic variants” of step 1(a) because the claim requires the probes include “oligonucleotide directed genomic content.” POR15-17.

First, this argument cannot be correct because the claimed “genetic variants” include “deletions.” EX1001, cl. 21.

Second, the specification repeatedly identifies “genomic content” as a location in the genome, not a specific sequence. EX1001, 7:66-67 (“the genomic content includes coding regions of genes.”); 19:4-5 (“the variable portion of the oligo-directed genomic content corresponds to genes....”). Dr. Furneaux similarly testified that “the probe that is being used in these endeavors does not necessarily have to cover that particular base” consisting of “the mutation itself.” EX1078, 117:19-118:1.

Third, Example 2 of the ’783 patent confirms that the claimed “genomic content” refers to the genomic location at which a mutation may occur, and that such locations can be defined based on the change in a protein sequence that would result from such a modification. EX1001, 66:33-36 (“[*L*locations such as EGFR T790M can be considered fixed content.”). Similarly, Ley identified locations such as *CDH24* Y590X and *PTPRT* P1235L as variable content (based on WGS) and *BRCA2* N372H and *TP53* P72R as fixed content (based on the literature, independent of sequencing). EX1012.70-71; EX1020, ¶119 (describing variable content); *id.* ¶120 (describing fixed content).

(b) Anticipation

Ley's probe set satisfies the "fixed portion" and "variable portion" under the claim's plain meaning. EX1020, ¶¶93, 119-20. Specifically, it included a "variable portion" that targeted newly "discovered somatic mutations" based on the WGS results, *id.*, ¶119, and a fixed portion that targeted "[c]ontrol amplicons containing [] **known**" mutation-bearing loci in the *tp53* or *BRCA2* genes, which a POSA understood were selected independent of the WGS results. *Id.*, ¶120; EX1078, 21:15-17; 118:7-14 (Dr. Furneaux testifying that "in my definition the fixed portion, the most typical example of that would be...standard PCR primers that have been used in the past to ascertain perhaps mutations in cancer driver genes....").

Personalis interpreted "fixed portion" and "variable portion" the same way in accusing Foresight of infringing the '783 Patent. Personalis considered the "variable portions" satisfied by probes for "variants that have been identified in the sequence data," and the "fixed portion" satisfied by "probe molecules that are designed to detect oncogenic and clinically relevant SNVs that are independent of the result of the sequencing data." EX1072.2. It did not consider any of the extraneous requirements it attempts to import here.

'783 Patent Claim Language	Infringement Support
	Court not to literally infringe certain limitations of the '783 Patent, infringement of such limitations can be found under the doctrine of equivalents.
(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	The Foresight Diagnostics Solid Tumor Recurrence test generates a personalized probe set that are designed to specifically enrich or amplify sequences comprising a set of genetic variants that have been identified in the sequence data generated from the whole genome sequencing data obtained from the tumor biopsy sample. Further, the Foresight Diagnostics Solid Tumor Recurrence test also provides probe molecules that are designed to detect oncogenic and clinically relevant SNVs that are independent of the result of the sequencing data obtained from the tumor.

(c) Obviousness

- (i) Ley encourages the combination of tumor-informed and hypothesis-driven approaches.

Personalis misconstrues Ley’s discussion regarding limitations of hypothesis-driven target selection in 2008 as a suggestion to never make use of such methods. POR28-31. However, a POSA reading Ley in 2016 would have been motivated to include probes for hypothesis-driven content in a follow-up cancer assay for several clinically relevant reasons addressed in the Petition, none of which Personalis rebuts. EX1020, ¶¶182-87.

For example, the Petition established that it would have been obvious to add

to Ley's existing "fixed portion" additional primers targeting known variant-drug combinations. PET43-46. Given this motivation, Personalis's arguments regarding potential future investigation of mutations in the "variable portion" are immaterial. *Cf.* POR32-33.

Personalis's remaining arguments regarding the balancing of factors like "accuracy, sensitivity, and specificity," POR32-34, are inconsistent with the knowledge and creativity of a POSA.² They are also inconsistent with the arguments Personalis's lead counsel made in IPR2024-00346 (*Neogenomics*), where it asserted that a POSA in 2015 "would have been motivated to increase sensitivity by modifying Forsheew [EX1030] so as to sequence more molecules and reach a depth of at least 50,000, and would have expected success." EX1080.26. Counsel further asserted that "this would have been an obvious approach in view of rapidly improving capabilities of sequencing instrumentation during the three-year timeframe between publication of Forsheew and [] April 2015." *Id.*, 27; *accord*

² While the POR purports to apply the agreed level of ordinary skill, it implicitly maintains Personalis's prior contention that this definition "credited a POSA with too much knowledge and too many skills." EX1079.12. Dr. Furneaux made this explicit at deposition. EX1078, 156:8-10 ("I've never met such a person apart from myself..."); *id.*, 194:10-11 ("This is the person of super duper ordinary skill."). Since Dr. Furneaux rendered his opinions from the perspective of a person with less than ordinary skill, they should not be given weight. *See Avail Medsystems v. Teladoc Health*, IPR2022-00444, Paper 10 at 24 (PTAB July 21, 2022) (affording testimony not "from the perspective of a skilled artisan" no weight).

EX1020, ¶60.

(ii) Adding PCR primers was within the level of ordinary skill.

Personalis also asserts that a POSA would not have added additional PCR primers to Ley's assay "because it would complicate the assay." POR36, 38, 41-42. Yet Personalis's cited references disclose multiplex PCR with 4,000 primer pairs, orders-of-magnitude greater than required by the proposed combination. POR31-32; *see* EX1007.113, EX1080.7, 37-40. Moreover, amplification reactions to generate the 13+ amplicons suggested by the proposed combination would be readily amenable to parallel PCR. EX1078, 186:24-187:2 (Dr. Furneaux confirming that for "20 PCR primers," "[y]ou could run 20 singleplex PCR wells.").

2. Step 1(b): Ley uses its probe set on "an additional biological sample."

Personalis's argument that the Petition "relies on all three samples" (*i.e.*, Ley's primary tumor, relapse tumor, and skin sample) to meet limitations 1(a) and 1(b), POR18-19, 35, is a distortion. The Petition 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 tumour and the skin biopsy" satisfies step 1(b). PET31; *see also* PET26-27.

Additionally, while no samples beyond those raised in the Petition are required to meet this step, adding additional samples to Ley's methods would have

been obvious. *See* Section I.B.

3. Step 1(c): Ley’s second assay “sequenc[es]... to identify...genetic variants.”

(a) Anticipation

(i) Personalis’s construction of “to identify” is baseless and incorrect.

Personalis contends that “to identify” means “to establish the identity of.” POR20. This requires “a genetic variant [to be] identified de novo in an unknown sample” in step 1(c), which the Board correctly rejected. Institution Decision (“DI”) at 29; EX2169, ¶67 (Dr. Furneaux disagreeing with the Board’s determination).

Personalis’s construction also contradicts the context in which “to identify” is used in the claims.³ By the time the method reaches step 1(c), knowledge of the variants is already established. In step 1(a), the variants are identified and probe sets are created to generate the sequencing library in step 1(b). Then, in step 1(c), the sequencing library of known, amplified, variants is sequenced.

Inserting Personalis’s construction in the claim confirms it to be nonsensical: “subjecting said sequencing library to sequencing **[to establish the identity of]** a

³ Relatedly, Claim 11 of Personalis’s ’394 patent recites, “wherein said *identifying comprises observing* an allele frequency.” EX1081, cl.11. Identifying by observing an allele frequency presupposes knowledge of the allele’s identity, consistent with the Petition’s analysis of Ley. Similarly, Personalis does not interpret step 1(d) of the ’783 Patent to require “generating a report [establishing the identity of] (i) a presence or absence of a health condition.”

presence or absence of at least a subset of said set of genetic variants....” A POSA would not have understood how to “establish[] the identity of a presence or absence of variants,” POR23, which is either nonsense or a metaphysical question.⁴ This forecloses that Personalis’s cherry-picked dictionary definition, which makes no sense in the context of the claim, could be a correct construction *Dayco Prod., Inc. v. Total Containment, Inc.*, 258 F.3d 1317, 1324 (Fed. Cir. 2001) (“convoluted and artificial” arguments in support of a construction are “simply unhelpful”).

(ii) Ley’s second assay “establishes the identity” of the genetic variants it resequenced.

Based on its incorrect claim construction, Personalis argues that Ley does not meet step 1(c) because “Ley initially identifies variants of interest, and then separately validates the variants of interest by sequencing.” POR20-21. However, Personalis admits that Ley quantified “mutation frequencies...during the validation protocol by tallying readcounts.” POR22. Ley’s tallying of readcounts involved determining whether a given read contained the variant or reference sequence, thus “establish[ing] the identity” of each amplicon’s genetic content. EX1012, Table 3.

⁴ The direct object of the verb “to identify” in step 1(c) is “a presence or absence.” Specifically, the claim requires identifying a “presence or absence of at least a subset of said set of genetic variants.” “Said set of genetic variants” finds antecedent basis in step 1(a), which specifies “said set of genetic variants are identified in sequence data for said at least one biological sample.”

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

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

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

(b) Obviousness

Personalis argues, based on its erroneous construction, that “[a] POSA would not be motivated to *re*-establish the identity of mutations that had already been established.” POR37. This is incorrect, as discussed in the preceding section.

Personalis’s additional arguments that this was “an innovative part of the claimed invention” based on “(1) short read lengths, (2) tumor heterogeneity, and (3) cost,” bear no relation to the claims. *Id.* Moreover, Personalis failed to present any competent evidence on cost, on which Dr. Furneaux confirmed he was not qualified to opine: “I think the best people to ask for that would be the folks who do insurance, the attending physician, and the patient.” EX1078, 44:5-10. Personalis’s argument that Ley “sidestepped the heterogeneity issue by using an atypical tumor sample,” POR37, is similarly unmoored from the claims.

Moreover, to the extent Ley’s assay required modifications to satisfy the claims, such modifications would involve the routine optimization of its resequencing assay, see *In re Aller*, 220 F.2d 454, 456 (CCPA 1955), not what

Personalis calls a “redesign.” POR39.

4. Step 1(d): Ley discloses “a report...which inform[s] a therapy choice.”

Personalis does not dispute that Ley discloses generating a report. POR23. It disputes only that Ley discloses the printed matter containing information “which inform[s] a therapy choice,” which is not entitled to patentable weight.

(a) Claim Construction

In the Institution Decision, the Board correctly determined that after “generating a report,” the remainder of step 1(d) merely claims printed matter that is not entitled to patentable weight. DI23-25; *see, e.g., Praxair Distrib. v. Mallinckrodt Hosp. Prods. IP*, 890 F.3d 1024, 1031 (Fed.Cir.2018).

Personalis contends that when printed on a report, “genetic variants which inform a therapy choice or change in therapy” bear a functional relationship to the substrate. POR23. But just like claims 1-8 and 10 in *Praxair* (found to claim printed matter not entitled to weight), this limitation “merely requires a medical provider to *think about* the information claimed,” which is “an ineligible mental process.” *Id.* at 1033-35 (claims requiring, e.g., weighing “the potential benefit” of a particular treatment versus “the potential risk” that the treatment would increase a side effect, “in order to arrive at a decision of whether or not to” use the treatment was patent ineligible printed matter).

Personalis analogizes to “[t]he *claim* at issue in *Praxair*,” POR24, though it acknowledges only the Court’s analysis of claims 9 and 11, which bear little resemblance to step 1(d). They involved (1) determining that the patient had a specific ailment; (2) treatment; (3) providing a recommendation that treatment be discontinued; and (4) the actual discontinuation of treatment “based on” the recommendation. *Id.* at 1035. Step (4), “the concrete step of discontinuing treatment because of the information” was critical to the Court’s finding that “the printed matter in claim 9 has a functional relationship to the rest of the claim.” *Id.*

At most, step 1(d)’s information that “inform[s] a therapy choice” is analogous to step (3) in *Praxair*’s claim 9 (i.e., providing a recommendation), which merely provides the content of information, and would not have been afforded patentable weight absent step (4). *See id.* at 1032-36. And here, the claim does not even use “inform” in the active sense, explaining Personalis’s misguided attempt to recast it as “the concrete step of ‘inform[ing].’” POR24.

Since step 1(d) lacks any affirmative steps such as actually changing therapy based on the alleged “inform[ing],” the claimed printed matter is not entitled to patentable weight.

(b) Anticipation

Even if the limitation “identifying...genetic variants which inform a therapy choice” were entitled to patentable weight, Ley anticipates it. Personalis attempts to

discount Ley’s teachings because the analysis was performed post-mortem, in effect seeking to apply a heightened “actual creation or reduction to practice” standard for anticipation, even though all the law requires is that Ley “discloses all of the claim limitations and enables the subject matter that falls within the scope of the claims at issue.” *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009). Accordingly, “anticipation does not require actual performance of suggestions in a disclosure,” instead, “anticipation only requires that those suggestions be enabling to one skilled in the art.” *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001).

A POSA would have understood Ley’s disclosure as enabling its genetic testing on patients “to develop methods to discover, monitor, and track mutations in cancer patients,” including to discover mutations “that may respond to targeted therapies.” EX1020, ¶¶80, 98 (quoting Ley). *See In Depth Geophysical, Inc. v. Conocophillips Co.*, No. IPR2019-00850, 2020 WL 5261306, at *7–8 (P.T.A.B. Sept. 3, 2020) (disclosure of a seismic survey that “was modeled on a computer, rather than performed in the real world,” anticipated because a POSA would have understood that such a model “both expressly and inherently disclos[ed] survey parameters and reconstruction techniques that apply to real-world seismic surveys”). Moreover, it is undisputed that Ley collected samples in coordination with the patient’s treatment. EX1078, 82:7-14 (Dr. Furneaux agreeing “the patient was alive

and receiving treatment for cancer when they took these samples”). Accordingly, a POSA would at once envisage using the results of the assay to inform treatment given its stated goal of predicting patients “that may respond to targeted therapy.” EX1012.66; EX1020, ¶¶91-92. *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015).

Personalis does not dispute Ley’s treatment and therapy-related disclosures, PET34-35, which themselves are much more detailed than the specification’s “disclos[ure] at a very high level of generality.” DI21. Indeed, in asserting infringement by Petitioner’s assay, Personalis interpreted step 1(d) to be satisfied based on “Foresight’s website stat[ing] that the technology can identify patients in need of therapy.” EX1072.5-6.

(c) Obviousness

Personalis argues that “the mutations identified by Ley’s assay have unknown clinical value,” and thus that it is unclear “how a POSA would use Ley’s mutations of unknown clinical relevance to inform a therapy choice or a change in therapy for a subject.” POR38. Even accepting this as true, Personalis ignores that the combination is based on Ley in view of a POSA’s knowledge as of 2016, which includes a POSA’s knowledge of mutation-therapy pairs. EX1020, ¶¶188-192; EX1080.9 (explaining that “by at least 2013,” similar assays were used “to provide patient-specific care and allow[] detection of recurrent tumors without the need for

invasive surgeries, and can also be used to monitor treatment progress”).

Moreover, a POSA would have found it obvious to implement Ley’s sequencing protocols during treatment, as evidenced by the numerous post-Ley and pre-priority studies that utilized Ley’s approach. EX1020, ¶180.

B. Claims 3, 8, 15, and 16: Ley discloses and renders obvious the use of its methods on the claimed additional samples.

The Petition explained that a POSA would have been motivated to utilize plasma samples containing cfDNA as additional samples, including to ease sample collection. PET49-53 (claims 3, 8, 15, 16). In connection with these claims, Dr. Quackenbush explained that a POSA would have been familiar with the use of cfDNA from tumors as a biomarker for cancer, including others’ successful use of PCR to amplify and/or enrich target cfDNA for sequencing as a tumor biomarker. EX1020, ¶¶83-84; 85-88.

As the expert declaration Personalis’s lead counsel presented to the Board in *Neogenomics* confirms, techniques that performed “1) WGS or WES of the cancer/tumor...and 2) follow-up cfDNA sequencing,” were “routinely conducted as of 2013.” EX1082, ¶¶87-88. Using these techniques, “plasma samples can be taken over time, and the cfDNA contained within may be analyzed to continue monitoring tumor burden or recurrence.” *Id.* ¶92. Counsel confirmed these techniques were “routinely conducted by at least 2013 through a range of different approaches,”

EX1080.9 (adopting EX1082, ¶¶87-93), which included “techniques [that] have been used to monitor cfDNA, including” Forshe’s TAm-Seq and Leary’s PCR-directed rearrangement screen. EX1082, ¶93.

Additionally, Personalis’s arguments regarding sample purity are unmoored to the claim, and as noted above, contradicted elsewhere by Personalis’s counsel. *Cf.* POR39-40. Moreover, the reference to “[h]igh sample purity,” in Ley’s supplemental materials refers to the selection criteria for the initial WGS step (“Rationale for selection an AML genome for sequencing”), and in any event refers only to the convenience of a pure sample for that step, rather than it being a necessary predicate. EX1042.1. This section says nothing about the effect of sample purity on the PCR-directed resequencing step, which Ley itself confirmed worked on contaminated samples, EX1020, ¶122; EX1012, Fig. 3, and which the subsequent prior art confirmed worked on cell-free tumor DNA from plasma samples, as discussed above.

Finally, Personalis’s reliance on the status of Ley’s patient is misplaced for the reasons discussed in Section I.A.4.

C. Claim 22: Modifying Ley by using hybrid capture probes would have been obvious.

The Petition established that a POSA would have found it obvious to substitute Ley’s PCR probes with a panel of hybrid capture probes “directed to the

genetic variations one would monitor in Ley's methods." PET54-55. This rationale is supported by a POSA's knowledge that each technique was suitable for "amplification and/or enrichment of target DNA over normal DNA in [a] sample to prepare [a] sequencing library." *Id.*

Personalis advances several factually and legally dubious arguments to suggest that a POSA would have lacked the motivation to make this routine design choice. POR41-45.

First, Personalis suggests that a POSA would not have been motivated to "make [the] drastic modification" of replacing Ley's PCR primers with hybrid capture baits. POR41. That argument contradicts the specification, which considers the techniques interchangeable. EX1001, 29:3-22 ("Non-limiting examples of probes include molecular inversion probes, ***amplification probes***, ***biotinylated affinity probes***, or any probe comprising a detectable label."). Dr. Quackenbush explained that this passage "confirms that those skilled in the art considered these techniques to be interchangeable." EX1020, ¶225. Personalis did not address the specification or rebut this testimony. Perhaps unsurprisingly, the specification provides no guidance regarding how to choose between these techniques for a given assay,⁵ consistent with the maxim that "a patent need not teach, and preferably omits,

⁵ *E.g.*, Personalis's specification does not analyze the "seven parameters and seven metrics" it trumpets in this proceeding. POR42-44.

what is well known in the art.” *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

Second, the legal premise of Personalis’s argument appears to be that there can be no motivation to modify a functioning prior art method. *See* POR45 (questioning why one would “modify[] Ley’s already-working assay”); *see also* EX1078,185:1-4 (“[Q.] [W]ould you argue there’s a not a motivation to improve upon [a working assay]? A. I think an American phrase is if it ain’t broke, don’t fix it.”). This is not the law. *See In re Ethicon, Inc.*, 844 F.3d 1344, 1349-1352 (Fed. Cir. 2017) (affirming Board’s obviousness finding based on rationale that “substitution of one element for another known in the field...must do more than yield a predictable result” to negate obviousness).

Third, Personalis claims that it is left “guessing...which steps in Ley’s workflow would need to be kept, jettisoned, or rearranged.” POR45. This ignores the Petition’s statement that it would have been obvious to replace Ley’s PCR probe set with hybrid capture probes in the steps requiring “probes for the amplification and/or enrichment of target DNA over normal DNA.” PET54-55; *accord* Claim 22 (claim language at issue further limits only “said personalized probe set” recited in step 1(b)). Moreover, the detail that Personalis alleges to be missing is inconsistent with the high level of generality of the claims, in particular given that “[t]he inquiry is not whether a relevant artisan would combine a first reference’s features with a

second reference's feature to meet requirements of the first reference that are not requirements of the claims at issue." *Axonics, Inc. v. Medtronic, Inc.*, 73 F.4th 950, 957-58 (Fed. Cir. 2023); *see also MCM Portfolio LLC v. Hewlett-Packard Co.*, 812 F.3d 1284, 1294 (Fed. Cir. 2015). "Thus, Petitioner is not required to show a physical combination of two systems." *Samsung Elecs. Co. v. Netlist, Inc.*, No. IPR2022-00711, Paper 42 at 17 (PTAB, October 17, 2023).

Finally, and as discussed below in Section II.A.1(a), the use of commercially available probes tailored to mutation loci identified via sequencing (e.g., WGS) satisfies the claimed "variable portion." *Cf.* POR41, 45.

II. Ground 3

A. Claim 1

Personalis disputes only (1) that Forshew and Dawson render obvious the combination of the claimed "variable portion" with the claimed "fixed portion" in step 1(a); and (2) the treatment limitations of step 1(d).

1. Step 1(a): Forshew in view of Dawson discloses a probe set with a "variable portion" and "fixed portion."

(a) Forshew discloses the claimed "variable portion."

Forshew discloses "the use of a variable portion from the result of the [WGS] data." PET63-64. Specifically, Forshew's assay uses probes based on "[w]hole-genome sequencing of tumor material...to identify tumor mutations in a patient," of which "[t]en mutations were selected." PET63-64; EX2163, 125:22-6.

Personalis contends that since Forshew may have used commercially-available primers, it does not disclose the “variable portion.” POR47-48. However, using commercially available probes is entirely consistent with the “variable portion,” which merely needs to be “from a result of said sequence data.” *See* Section I.A.1(a). As Dr. Quackenbush explained, “what Forshew told us is that he selected ten mutational loci *and specifically targeted those.*” EX2163, 154:10-13. Because “the probes...were specifically selected to target mutations that were found based on said sequence data” and “[t]hey were custom selected based on the mutations,” they satisfy the “variable portion” requirement of the claim. *Id.*, 157:4-16; *accord id.* 149:12-150:8; EX1080.22-23 (Forshew “identified [SNVs] based on WGS data”). Personalis’s insistence that one must have knowledge of the sequences of the primers to determine whether they constitute a “variable portion” based on sequencing data, is once again contrary to the plain language of the claim. *Cf.* POR47.

Lastly, since Forshew expressly discloses the claimed “variable portion,” the POR’s section headed “No suggestion for the claimed ‘variable portion’” is irrelevant. POR48-49. Additionally, in this section, Personalis appears to concede that Dawson discloses the claimed “fixed portion.” POR49.

(b) The Petition established motivation to combine.

Personalis argues that “Forsheew still fails to teach or suggest combining a ‘variable portion’ with a ‘fixed portion.’” POR49-54. In essence, Personalis’s complaint is that the Petition’s *obviousness* ground did not establish *anticipation* based on Forsheew.

But the proposed combination involves the addition of Dawson’s fixed probes for detecting *TP53* mutations for breast cancer in its own TAm-Seq assay to Forsheew’s breast cancer TAm-Seq assay. A POSA would have been motivated to do so at least based on (i) Forsheew’s success in using similar *TP53* probe sets in a TAm-Seq assay for ovarian cancer; and (ii) Dawson’s success in using fixed *TP53* probe sets in a Tam-Seq assay for breast cancer. PET64-65; *cf.* POR50-51.

- (i) A POSA would have been motivated to add Dawson’s “fixed portion” to Forsheew’s “variable portion.”

Personalis’s argument appears to be that a POSA would not have been motivated to include *any* additional primers beyond what Forsheew disclosed for its breast cancer patient. POR50-53 (contending that adding primers would “convolute,” “complicate,” or “sully” the assay, and involve a “redesign”). Since the proposed combination involves the addition of Dawson’s TAm-Seq probes to Forsheew’s TAm-Seq assay, contending that it requires a “redesign” is not a serious argument.

Personalis also asserts that the proposed combination would involve the addition of 1,000 PCR primers for *TP53* to the 10 present in Forshew's breast cancer panel. POR50-51. Even accepting this assertion (which as described next misrepresents the proposed combination), modifying Forshew's assay to address 1,010 (or more) targets would have been obvious. As counsel admitted in *Neogenomics*: "At a minimum, Forshew renders obvious the ability to use even greater multiplex amplification as part of the TAm-Seq protocol because a POSA would have known that ***significantly greater multiplex amplification was already well-established.***" EX1080.38. The *Neogenomics* Petition further argued that there is a "natural" motivation to include more (up to 9,216) targets since "including more targets in the process allows one to track a broader spectrum of cancer-related mutations and hence better track and detect the cancer over time." *Id.*, 39.

Additionally, Personalis's suggestion that the proposed combination requires 1,000 additional probes is premised on a POSA "cover[ing] the [entire] *TP53* gene." POR50. Not so. Dr. Quackenbush proposed, based on the combination of Forshew and Dawson, the inclusion of "***one*** or more 'fixed' probes" "to detect and amplify variants of *TP53* in the patient." EX1020, ¶258.

Moreover, Forshew already disclosed the use of far less than 1,000 primers to target mutations in *TP53*, confirming that a POSA would not have required the use of 1,000 primer pairs to implement the combination. *See* EX1030.3 (describing

successful usage of “48 primer pairs to amplify 5995 bases of genomic sequences covering coding regions (exons and exon junctions) of TP53,” among other loci).

(ii) Personalis’s criticisms are untethered to the claims and do not negate motivation to combine.

First, there is no evidence that the proposed combination would decrease the accuracy of the assay. *Cf.* POR51-52, 54. In the POR, Personalis vaguely references “amplification issues,” *id.* 52, substantially rehashing the arguments regarding multiplexing addressed above. *See* Section II.A.1(b)(i). Tellingly, Personalis does not attempt to put these alleged “difficulties” of multiplex PCR it contends are an issue in context of the claims, which do not require multiplexing.

Second, Personalis’s unexplained discussion of the supposed limitations of particular sequencing platforms’ “multiplex capability” appears to be tangential to the issues at best, and Personalis provides no explanation of how they relate to the claims or proposed combinations. POR53.

Third, Personalis ignores key conclusions of Forshe’s “Editor’s Summary.” POR53. For example, the Summary notes that “TAm-Seq is a viable method for sequencing large regions of ctDNA.” EX1030.1. Moreover, nothing in the claim requires sensitivity at <2% allele frequency in ctDNA (which Personalis’s uncorroborated marketing documents report to be 1% at best in its 2023 assay). *See* Section III. Indeed, even if Personalis were correct, nothing in the claims “demand[s]

high levels of accuracy, sensitivity, and specificity,” nor does its POR even attempt to place in context what would constitute sufficiently “high levels” of each parameter. POR53-54.

Moreover, in *Neogenomics*, Personalis’s lead counsel took the following positions, which directly contradict the POR:

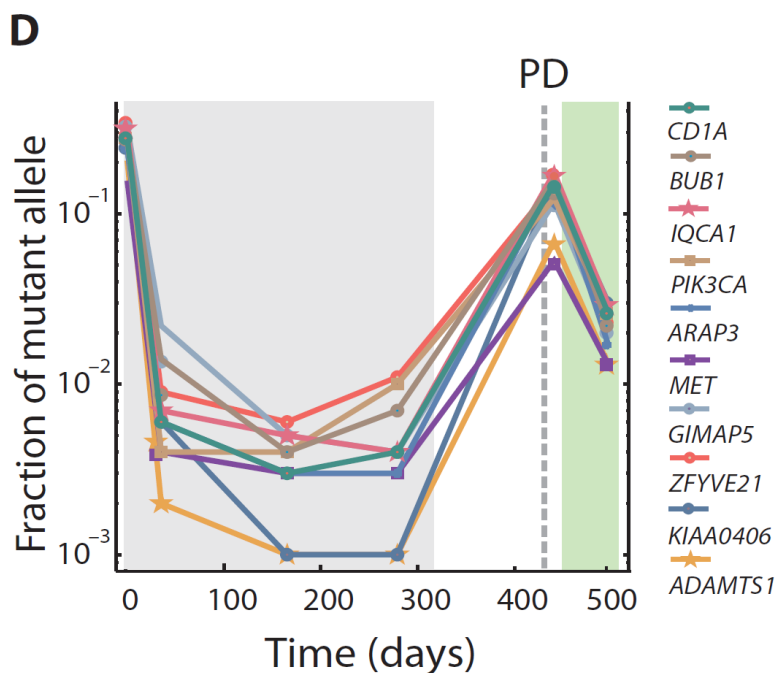
- Forshew’s sensitivity “for detecting an SNV that is present” “includ[es] frequencies of 0.015% and below.” EX1080.43.
- “Forshew, in fact, teaches [increasing sequencing depth to increase sensitivity], stating inter alia, that ‘higher read depth’ and using ‘additional replicates’ (increasing read depth) allows ‘enhanced mutation detection without change to protocols.’” *Id.*, 26-28.
- “[T]here is no basis for any suggestion that sequencing technology in 2015 was so problematic that a POSA would avoid increasing sequencing depth to improve accuracy.” *Id.* 32.

Similarly, when the POR finally mentions Dawson, Personalis merely rehashes its baseless sensitivity, cost, and multiplexing arguments. POR54-55.

2. Step 1(d): Forshew discloses “a report...which inform[s] a therapy choice.”

First, it is undisputed that Forshew discloses generating a report (see Figure 4D below), the only part of step 1(d) entitled to patentable weight under the correct claim construction. *See* Section I.A.4(a).

However, even if the remainder of the claim were entitled to patentable weight, Forshew’s report discloses “inform[ing] a therapy choice or a change in therapy for the subject.” PET69-70. For example, Figure 4D shows a “response to [epirubicin] therapy (grey box)” based on the decrease in “the fraction of the various mutant alleles over time.” EX1020, ¶¶264-265. For a time, the patient showed a positive response to treatment based on the “tracked dynamics of all mutations,” and thus the report informs a therapy choice at least by confirming efficacy. *Id.* Personalis quibbles that “the patient was treated with epirubicin **based on** her having breast cancer,” POR57, but this does not negate the fact that Forshew’s results inform the choice to continue with therapy/not change the therapy while it is working. EX1020, ¶¶264-265 (describing “sharp decline in AF [allele fraction] upon onset of therapy and an increase in AF upon disease progression after termination in therapy.”).



Similarly, even if the second chemotherapy phase (green box) “was based on the CT scan,” as Personalis speculates, POR57, the “observed relationship between therapy and disease status” would have informed that choice at least by confirming that it was working. EX1020, ¶265 (showing decline in AF at day 500). If anything, Personalis’s attempts to read physicians’ minds regarding particular treatment decisions underscores the fact that step 1(d) claims a purely mental exercise that is not entitled to patentable weight.

Finally, Personalis’s argument regarding “the length of time it would take to perform the assay and process the resulting data,” POR58, is directly rebutted by Forshew, which states: “Preparing TAm-Seq libraries for sequencing from 48 samples takes less than 24 hours and involves only a few hours of hands-on time.

New platforms for massively parallel sequencing allow for fast turnaround times, which make this approach practical in a clinical setting.” EX1030.9.

B. Claim 22

The Petition established that a POSA would have been motivated to replace Forshew’s PCR primers with hybrid capture probes. PET75-76. *See* Section I.C.

III. No Secondary Considerations

The Board need not address secondary considerations because claim 1 is anticipated, and Personalis failed to address them for any dependent claim.

In any event, Personalis failed to show that its “NeXT Personal” assay embodies the claims, having merely incorporated by reference Dr. Furneaux’s reproduction of the conclusory chart submitted with the POPR. POR62; *compare* EX2169, ¶156 with EX2003 (same). *See Microsoft Corp. v. Synkloud Technologies, LLC*, No. 2020-00316, Paper 43 at 40-42 (P.T.A.B. Jun. 14, 2021) (finding no nexus when it is unclear “how the various screen shots meet the limitations.”).

As Personalis acknowledges, cognizable industry praise must be for “the claimed invention.” POR62-63. Yet Dr. Furneaux merely evaluated “whether *Personalis* has received industry praise.” EX1078, 63:19-64:1; *see also id.* 66:5-7 (“I have actually not...looked at the Personalis assay in detail.”). Nevertheless, Personalis argues that the praiseworthy feature of its 2023 assay is its overall sensitivity of 1 ppm, POR63, though Dr. Furneaux previously confirmed that its

sensitivity for a specific variant is 1,000 ppm (1,000 times less sensitive than the POR claims). EX1083, 56:20-62:21. Critically, no challenged claim recites a sensitivity limitation, rendering irrelevant Personalis's allegations of praise based on sensitivity-focused industry collaborations. POR63; *see Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1342 (Fed. Cir. 2020).

Finally, Personalis alleges that "experts held skepticism toward...conducting highly sensitive genome sequencing using capture probes." POR64. Claim 1 does not require "capture probes," and Personalis does not dispute that Ley and Forsheew disclose a "probe set." And in a 180° about-face, Personalis's counsel has since told the Board that "it would have been routine to optimize [depth of read] to provide the required sensitivity" in sequencing methods by 2015. EX1080.30. Likewise, counsel confirmed a complete lack of skepticism for NGS by 2015. *Compare* POR64 with EX1080.30-32 ("[B]etween 2012 and 2015, the relevant amplification and sequencing technology simply became more accurate, more efficient, and less costly....").

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CERTIFICATE OF WORD COUNT

I hereby certify, pursuant to 37 C.F.R. § 42.24, that the Reply contains 5,599 words, excluding the words in the table of contents, this certificate of word count, and the certificate of service. The word count is based on the word count of the Microsoft Word program used to prepare the Reply.

Dated: February 9, 2024

/Andrew E. Krause/
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APPENDIX A

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.

3. The method of claim 2, wherein said plurality of biological samples comprises a tissue sample and a plasma sample.

8. The method of claim 1, wherein said additional biological sample of (c) is a blood sample.

15. The method of claim 1, wherein said additional biological sample is a blood sample comprising: (i) cfDNA, (ii) cfRNA, (iii) DNA or RNA from circulating tumor cells, or (iv) RNA or DNA from a tumor metastasis.

16. The method of claim 1, wherein said additional biological sample and one or more subsequent biological samples are each blood samples comprising: (i) cfDNA, (ii) cfRNA, (iii) DNA or RNA from circulating tumor cells, or (iv) RNA or DNA from a tumor metastasis.

22. The method of claim 1, wherein said personalized probe set comprises hybrid capture probes.

CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. section 42.6, that on February 9, 2024, a complete copy of the foregoing document **PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE AND EXHIBITS 1078-1083** were served upon the following, by ELECTRONIC MAIL:

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