

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

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Foresight Diagnostics Inc.,
Petitioner,

v.

Personalis, Inc.,
Patent Owner.

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

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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Ex. 1001	U.S. Patent No. 10,450,611 issued to West <i>et al.</i>
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Ex. 1003	Quake <i>et al.</i> , WO 2011/057061 (Quake)
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Ex. 1006	Florian Mertes <i>et al.</i> , “Targeted enrichment of genomic DNA regions for next-generation sequencing, Briefings in Functional Genomics,” <i>Briefings in Functional Genomics</i> (2011) (Mertes)
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Ex. 1014	Jeffrey S. Ross and Maureen Cronin, “Whole Cancer Genome Sequencing by Next-Generation Methods,” <i>American Journal of Clinical Pathology</i> (2011) (Ross)

Ex. 1015	David J. McBride, et al., “Use of Cancer-Specific Genomic Rearrangements to Quantify Disease Burden in Plasma from Patients with Solid Tumors,” <i>Genes, Chromosomes & Cancer</i> (2010) (McBride)
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Ex. 1077	D. Bentley, et al., “Accurate whole human genome sequencing using reversible terminator chemistry,” Nature (2008) (Bentley)
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Ex. 1082	<i>Neogenomics Labs., Inc. v. Natera, Inc.</i> , IPR2024-00346, Expert Declaration of Niall Lennon, Ph.D in Support of Petition for <i>Inter Partes</i> Review of U.S. Patent No. 11,530,454
Ex. 1083	Deposition of Henry Morrice Furneaux, Ph.D., December 12, 2023, IPR2023-00224/IPR2023-00317

I. Grounds 1 and 2

Personalis only disputes that Ley anticipates and/or renders obvious limitations 1(e)[1]-[3] of independent claim 1 and dependent claims 5, 10, and 28.¹ POR at Table of Contents.

A. Claim 1

1. Step 1(e)(3): Ley's sequencing depth during PCR-directed targeted resequencing is greater than the depth of its WGS.²

(a) Anticipation

It is undisputed that Ley's WGS during step 1(a) had a sequencing depth of 13 to 33-fold. EX1061, ¶123. Ley further reports deep re-sequencing of amplicons from 12 mutation-harboring loci (10 somatic, 2 germline). EX1012.69. Ley's Table 3 shows that the 12 amplicons were sequenced at depths "rang[ing] from 588-fold to 12,365-fold" for the relapse tumor sample, satisfying step 1(e). PET32; EX1061, ¶166 ("sequencing depth,'...refer[s] to the *number of times* [a] genomic sequence has been sequenced.").

Personalis disputes that Table 3's readcounts reflect the sequencing depth of 1(e). It asserts the readcounts are synonymous with "N" (the number of sequence reads) in the Lander-Waterman equation, and claims Ley lacks sufficient

¹ The disputed claims are reproduced in Appendix A.

² Arguments are addressed in the order presented by the POR.

information to apply that equation to calculate depth. POR10-11. But since Ley reported “what actually happened,” use of the Lander-Waterman equation is unnecessary. *See* EX1083, 91:10-16 (Dr. Furneaux distinguishing between “the Lander theoretical depth equation, which is simply a way that an individual says ‘how much stuff do I need,’” and “what will actually happen.”).

At deposition, Dr. Furneaux confirmed that Table 3’s “readcounts” correspond to sequencing depth, agreeing that “the raw read count numbers [annotated in red] in the variant and reference numbers mean that *they read the variant 5,672 times and the reference 4,890 times*,” indicating that “the sequencer read that position *about 10,000 times*.” EX1083, 137:10-140:14 (discussing EX1012.69, Table 3 (annotated below)).

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
KND1	L799F	4640	4848	48.90	770	8972	7.90	3883	6342	37.98
PTPR	P1235L	998	1058	48.54	126	1489	7.80	350	493	41.52
GRIN1B	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.

This aligns with Dr. Quackenbush’s analysis, which identified sequencing depths of ≥ 588 -fold for the relapse tumor sample (compared to step 1(a)’s ≤ 33 -fold depth) by summing the “Variant” and “Ref” columns in Table 3 (green box). EX1061, ¶¶123-125.

(b) Obviousness

Personalis further contends that for a POSA to have been motivated to increase the depth of 1(e), Ley needed to show that “the assay that generated the data in Table 3 needed improvement.” POR28 But it is sufficient motivation that “a skilled artisan would have seen a benefit to upgrading” Ley by increasing its targeted resequencing depth. *Intel Corp. v. Qualcomm Inc.*, 21 F.4th 784, 797-798 (Fed. Cir. 2021).

Dr. Quackenbush explained that when designing an assay, a POSA would consider cost, complication, and accuracy, among other common-sense factors. Personalis argues that if a given modification would improve one parameter but may detract from another, a POSA would not move forward. POR29-30. This oversimplistic approach shows that when analyzing issues from the perspective of a POSA, Personalis failed to credit them with the requisite creativity, ingenuity, and skill. EX1078, 185:1-4 (“Q. “[W]ould you argue there’s...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.”).³

Dr. Furneaux agreed that experimental design involves “measur[ing] what one gains from a procedure versus what it costs,” *id.*, 44:21-22, consistent with Dr. Quackenbush’s testimony that a POSA would have balanced these considerations “depend[ing] on the particular application.” EX2163, 45:9-47:19. Furthermore, Personalis does not dispute that increasing sequencing depth was within the level of skill in the art, EX1061, ¶67, and instead focuses only on cost considerations, which were substantially mitigated by 2016. EX1061, ¶62.

Contradicting Personalis’s position, the Petitioner in IPR2024-00346 (Neogenomics), represented by Personalis’s lead counsel, asserted that a POSA in 2015 “would have been motivated to increase sensitivity by modifying Forsheew [EX2005] so as to sequence more molecules and reach a depth of at least 50,000, and would have expected success.” EX1080.26. Neogenomics further asserted that “this would have been an obvious approach in view of rapidly improving capabilities

³ 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.”); *id.* 199:13-201:9 (considering POSA to be in “this imaginary world” like “Alice in Wonderland.”). 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).

of sequencing instrumentation during the three-year timeframe between publication of Forshew and [] April 2015.” *Id.*, 27; *accord* EX1061, ¶¶65, 167-168.

2. Step 1(e)[1]: Ley sequences the library created in steps 1(b)-1(d) “at a coverage of 175 kilobases or less.”

(a) Anticipation

Ley’s disclosure of Steps 1(a)-1(d) creates the claimed sequencing library. PET29. Step 1(e)[1] requires sequencing that library “at a coverage of 175 kilobases (kb) or less.”

Ley’s sequencing library comprised amplicons for the 12 mutation-containing exons amplified by its probe set, substantially reducing the footprint of the assay as compared to its WGS in step 1(a). EX1012.69; PET28. Sequencing of the amplicons was necessarily “at a coverage of 175 kilobases or less,” given that for each locus, Ley targeted “*an exon* containing a genetic variant,” and even sequencing *all* exons (rather than the subset that were sequenced) would have had a coverage less than 175kb. PET30; EX1012, Table 3; EX1061, ¶120; EX1078, 130:3-5 (Dr. Furneaux agreeing that “Ley used these primers to create amplicons of the exons with the mutant alleles”).

Personalis urges that Ley used “PCR primer pair[s] that would generate an amplicon for the *entire* length of each of the genes.” POR12-13. This contradicts Ley, which targeted the specific mutation-harboring exons. Thus, Dr. Quackenbush’s analysis of the maximum sequence coverage that Ley would have

achieved had it sought to cover *every exon in each gene* substantially overestimates Ley's maximum sequencing footprint. EX1061, ¶121 (Ley would only cover 42.254 kb "*if all of the exons* of every one of these genes were to be sequenced").

For similar reasons, Personalis's inclusion of the introns in the calculation of Ley's sequence coverage is misplaced. POR12-13. Since Ley had already ruled out intronic and nongenic sequences (boxed in red below), Dr. Quackenbush's exclusion of introns/non-genic regions in determining the upper bound was entirely appropriate. EX1061, ¶120; EX1078, 97:22-98:9; EX1012, Figure 2.

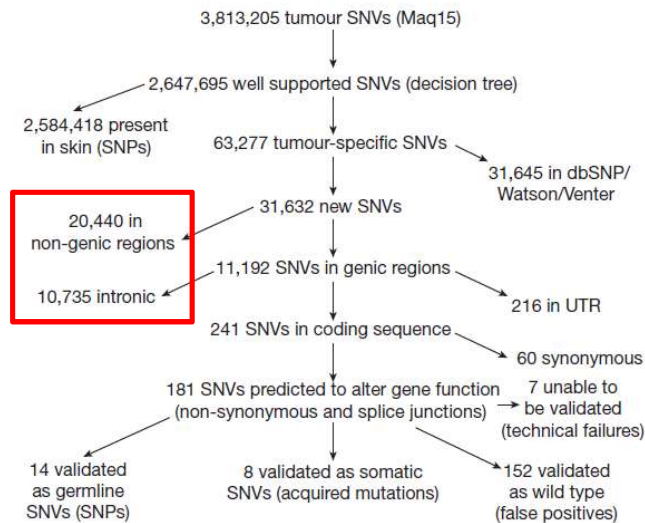


Figure 2 | Filters used to identify somatic point mutations in the tumour genome. See text for details. UTR, untranslated regions.

(b) Obviousness

Even if Ley had not expressly disclosed step 1(e)[1], the Petition established that a targeted assay covering 175kb or less would have been obvious. EX1061, ¶¶166-168 (explaining benefits in sensitivity, cost, simplicity, and accuracy). Doing

so would have involved nothing more than the routine optimization of result-effective variables to select the appropriate number of genes for follow-up with a reasonable expectation of success. *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). Indeed, Ley's analysis of amplicons from single exons of twelve genes would at a minimum suggest to a POSA that assaying a subset of those exons was equally likely to be successful. *See* EX1061, ¶168.

Personalis cannot establish the criticality of the claimed 175kb or less (as opposed to 250kb, 125kb, or any other subgenomic footprint) to show that it is the result of anything other than routine optimization. In fact, Example 1, which Personalis contends establishes the significance of 175kb, POR30, confirms that the "or less" part of the claimed "175 kilobases or less" is not even disclosed, but rather 175kb is the patent's lowest bound. EX1001, 60:2-15 (describing sequencing of "*at least* 500 sequences," each with a length of "*at least* about 350 bases," for a "footprint of...about 175,000 bases").

3. Step 1(e)[2] 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." POR16. This requires "a genetic variant [to be] identified de novo in an unknown

sample,” in step 1(e), which the Board correctly rejected. DI38; 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.⁴ By the time the method reaches step 1(e), knowledge of the variants is already established. In step 1(b), the variants are identified. In step 1(c), probe sets are created to generate the sequencing library in step 1(d). Then, in step 1(e), the sequencing library of known, amplified, variants is subjected to sequencing. Thus, the Board was correct to conclude that by “showing that variant alleles were present in both primary and relapse tumor samples, Ley’s Figure 3 satisfies claim step 1(e).” DI27; PET31-32.

Inserting Personalis’s construction in the claim further confirms it is nonsensical: “subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less [to establish the identity of] a 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,” POR32, which is either

⁴ Relatedly, Claim 11 of Personalis’s ’394 patent, the subject of IPR2023-00224, 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.

nonsense or a metaphysical question.⁵ This forecloses any possibility 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) (“If an argument offered in support of a particular claim construction is so convoluted and artificial that it would not be apparent to a skilled artisan reading the patent...the argument is simply unhelpful to the performance of our task.”).

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

Based on its incorrect claim construction, Personalis argues that Ley does not meet step 1(e)[2] because “Ley initially identifies variants of interest, and then separately validates the variants of interest by sequencing.” POR16-18. Personalis admits that Ley quantified “mutation frequencies...during the validation protocol by tallying readcounts.” POR18. This tallying of readcounts involved determining whether a given read contained the variant or reference sequence, thus “establish[ing] the identity” of each amplicon. EX1012, Table 3.

⁵ Step 1(e) requires identifying a “presence or absence of said genetic variants.” “Said genetic variants” finds antecedent basis in step 1(b) (not in dispute), which requires analyzing “sequencing data *to identify* a plurality of *nucleic acid sequences*.”

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
PTPR	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 does not dispute that step 1(e)[2] would have been obvious under the construction applied in the Petition and Institution Decision. It argues only that “[a] POSA would not be motivated to *re-establish* the identity of mutations that had already been established,” relying on its incorrect construction. POR32.

Personalis’s additional arguments that step 1(e)[2] 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. POR32-33. Personalis’s argument that Ley was required to address alleged “heterogeneity issues,” POR33, is similarly unmoored from the claims.

(i) Personalis’s obviousness positions are not credible.

As established above, to the extent Ley’s assay required modifications to satisfy the claims, such modifications would have involved the routine optimization of its resequencing assay, not what Personalis calls a “redesign.” POR33.

The POR’s discussion of the Dana-Faber Profile study in the section titled

“No motivation to modify Ley,” POR33-35, diminishes Personalis’s credibility. There, Personalis contends that only “a rare laboratory” in 2016 would have been motivated to sequence the 12GB or more required by step 1(a). POR34. Yet it is undisputed that by 2016, WES and WGS of 12GB or more was widely used and widely reported in the literature. EX1061, ¶68 (see Fig. 1); Ex1080.8 (*Neogenomics*) (citing EX1082, “a plethora of studies [by 2015] have conducted WES and WGS of cancers, usually from a tumor biopsy, in patients....” EX1082, ¶89).

Personalis invokes Profile’s reported annual cost,⁶ without grappling with the bounds for excessive cost, to strip the POSA of the ability to progress the field in any fashion. *Cf.* EX1080.8-9 (asserting exponential cost decreases by 2015). Personalis failed to present any competent evidence on the maximum acceptable cost of an experiment, as Dr. Furneaux confirmed such questions to be outside his expertise. EX1078, 44:5-10 (stating when asked about the cost of an assay “I think the best people to ask for that would be the folks who do insurance, the attending physician, and the patient.”).

Moreover, Personalis’s suggestion that labs would either pursue WES/WGS or targeted sequencing on a mutually exclusive basis is inconsistent with the many

⁶ The articles Personalis cites suggest that Profile cost \$6 million per year over 6 years, and sequenced 15,000 genomes, yielding an average cost of ~\$2,400/patient. EX2176.1. No record evidence suggests \$2,400/patient would have been excessive for personalized cancer testing.

references that performed targeted sequencing following an initial WES/WGS step. EX1061, ¶¶85-86; EX1080.9 (*Neogenomics*) (explaining that using “WGS or WES of the cancerous DNA to identify cancer-related (e.g., tumor-specific SNVs), and follow-up monitoring (involving multiplex PCR and sequencing) of these SNVs in cfDNA,” “was routinely conducted by at least 2013.”) (citing EX1082, ¶¶87-93).

B. Claim 5: Ley discloses the claimed “fixed portion” and “variable portion.”

1. Anticipation

Ley’s probe set satisfies the plain meaning of the claimed “fixed portion” and “variable portion.” *See* EX1061, ¶97.

Dr. Quackenbush explained that Ley’s probe set included a “variable portion” that targeted “discovered somatic mutations” based on WGS of the patient’s tumor. *Id.*, ¶135. Ley’s probe set also included 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.*, ¶136; EX1078, 21:15-17; 118:7-13 (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”); EX2169, ¶156 (Dr. Furneaux opining that Personalis’s assay includes “at least one variable portion” and “at least one fixed portion” because its “probe panel

design...surveys known cancer-related clinical variants, and quantifies and tracks investigational variants of interest”).

Moreover, the Petition is consistent with (and more detailed than) how Personalis asserted the claim against Foresight. Personalis considered the “variable portion” satisfied “based upon the prior whole genome sequencing,” and the “fixed portion” satisfied by “content that is related to genes with known oncogenic or clinically relevant variants.” EX1037.8-9.

5. The method of claim 1, wherein each of said plurality of nucleic acid probe molecules includes oligonucleotide-directed genomic content comprising (i) at least one variable portion from a result of said sequencing of (a) and (ii) at least one fixed portion independent of said result of said sequencing of (a).	The Foresight Diagnostics Solid Tumor Recurrence test includes both variable portions based upon the prior whole genome sequencing as well as fixed content that is related to genes with known oncogenic or clinically relevant variants.
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(a) Personalis’s proposed constructions are incorrect.

Personalis’s constructions would require 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 change from one subject to another.” POR21. This directly contradicts the claims, which describe the “personalized genetic testing” of “a subject.”

Personalis claims the specification expressly defines these terms, POR20, but the language it points to limits its relevance to “*some applications*.” EX1001, 38:42-47; *see also id.*, 63:33-36 (exemplary embodiment cited by POR). It is well-settled 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).

Here, the claim language alone provides sufficient context to define the terms without any further construction: “one variable portion *from a result of said sequencing of (a)*,” and “one fixed portion *independent of said result of said sequencing of (a)*.” EX1001, cl.5. 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, 7:39-44 (mirroring claim language); 16:60-64 (“(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.”); 39:7-17 (“fixed portion may be selected from,” e.g., “cancer driver genes”).

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

Personalis also argues that the claimed probe set must hybridize directly to sequences containing the identified “genetic variants” of step 1(b). POR22-24. Since the claimed “genetic variants” can include “deletions,” EX1001, cl.12, this cannot be correct. Moreover, the claims require only that the probes provide “oligonucleotide directed genomic content.” The specification repeatedly identifies “genomic content” as a location in the genome, not a specific sequence. EX1001, 7:58-61 (“the genomic content includes coding regions of genes.”); 17:16-26 (“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” that “would be, in fact, the mutation itself.” EX1078, 117:19-118:1.

Moreover, Example 2 of the ’611 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, 52:20-22 (“*[L]ocations* such as EGFR T790M can be considered fixed content.”). Cf. POR23-24. Similarly, for example, 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; EX1061, ¶¶134-135; Ex1012.70-71 (describing variable content); EX1061, ¶¶134, 136 (same).

2. Obviousness

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

Personalis misconstrues Ley’s acknowledgement of limitations of solely hypothesis-driven target selection in 2008 as a suggestion to never make use of such methods. POR36. However, a POSA reading Ley in 2016 would have been motivated to include probes for hypothesis-driven fixed content in a follow-up cancer assay for several clinically relevant reasons addressed in the Petition, none of

which Personalis rebuts. EX1061, ¶176.

The Petition observed that a POSA would have found it obvious to add to Ley fixed primers targeting known variant-drug combinations. PET49-52. Moreover, Ley already included primers for FLT3 and NPM1 based on their known relevance. EX1012.70. Whether mutations included in Ley’s “variable portion” required future investigation is thus immaterial. *Cf.* POR40-41. Personalis’s remaining arguments regarding the balancing of factors like “accuracy, sensitivity, and specificity,” POR41-42, are inconsistent with the POSA’s level of skill, as well as counsel’s statements in *Neogenomics*. *See* Section 1.A.1.(b). The inclusion of fixed primers also addresses issues with tumor heterogeneity and sample-to-sample variation. EX1061, ¶176. *Cf.* POR42.

(b) 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, 38-42. Yet Personalis’s cited references disclose multiplex PCR with 4,000 primer pairs, many more than required by the proposed combination. *See* EX1007.113; *see also* EX1080.7, 37-40. Moreover, amplification reactions to generate the 13+ amplicons suggested by the proposed combination would be readily amenable to parallel PCR,

since “[y]ou could run 20 singleplex PCR wells” for 20 targets, obviating alleged shortcomings of multiplex PCR. EX1078, 186:24-187:2.

C. Claims 10 and 28: Ley discloses the claimed treatment.

1. Anticipation

Personalis contends that Ley cannot anticipate claims regarding therapeutic intervention or treatment because Ley performed its analysis after the patient was deceased. POR26-27. Thus, Personalis seeks to apply a heightened “actual creation or reduction to practice” standard. But anticipation merely requires 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,” so long as, “those suggestions [are] enabling to one skilled in the art.” *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001). Personalis does not otherwise dispute Ley’s treatment/therapy-related disclosures, PET38-40, 43-45, which enable far more than the specification’s “disclos[ure] at a very high level of generality.” DI21.

Ley’s disclosure enabled the development of “methods to discover, monitor, and track mutations in cancer patients,” including to discover mutations “that may respond to targeted therapies.” EX1061, ¶¶82, 95 (quoting Ley); *see also* EX2169, ¶156 (Dr. Furneaux opining that Personalis’s assay “informs a therapy or a change

in therapy” because “[t]he identified genetic variants are used to inform the understanding of the tumor biology and its dynamic response to therapy”). A POSA would have understood Ley’s disclosure to apply to patients during treatment, especially since Ley’s samples were collected contemporaneous with treatment. EX1078, 83:7-14 (Dr. Furneaux confirming that “the patient was alive and receiving treatment for cancer when they took these samples.”). *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,” was anticipatory 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.”).

2. Obviousness

Personalis first argues that “the mutations identified by Ley’s assay have unknown clinical value,” and claims that it is unclear “how a POSA would use mutations of unknown clinical relevance to treat a subject for a disorder.” POR43. Even accepting as true Personalis’s assertions regarding clinical value, 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. EX1061, ¶179.

Additionally, even though Ley's subject was deceased, a POSA would have found it obvious to apply Ley's approach to patients during treatment, as evidenced by the numerous post-Ley and pre-priority studies that utilized Ley's approach. EX1061, ¶¶82-86.

II. Grounds 3 and 4

Personalis disputes only Newman's disclosure of claims 1(a), 1(d), and 1(e)[1], 5, 10, 11, and 28.

A. Claim 1

1. Step 1(a): Newman discloses "sequencing 12 gigabases (GB) or more"

(a) Anticipation

Claim 1 requires a first assay that sequences "12 gigabases (GB) or more," which is met by Newman's WES of more than 12GB. EX1061, ¶189.

Personalis contends that because Newman's option of performing WES with 2x100 paired-end reads would yield less than 12GB of sequencing, Newman does not anticipate. POR45. However, Personalis does not dispute that Newman's alternative option of 2x150 paired-end reads sequences greater than 12GB. Thus, Newman anticipates at least because a POSA "reading the reference, would 'at once envisage' the claimed" 12GB or more of sequencing based on the 2x150 option. *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015).

(b) Obviousness

Sequencing greater than 12GB when performing WES would have involved nothing more than the routine optimization of result-effective variables to select the appropriate number of bases to sequence to determine the sequence of the human exome. *Aller*, 220 F.2d at 456; *see* EX1061, ¶68. Personalis’s argument that a POSA would have been discouraged from performing 2x150 for cost and complexity reasons is not credible. Newman is explicit that it successfully used both options. Moreover, there is no evidence that a POSA would have considered 2x150 too complicated or costly, and Personalis’s suggestion otherwise is inconsistent with the level of skill in the art. *See* I.A.1.(b).

2. Steps 1(d) and 1(e): Newman discloses an “additional biological sample.”

(a) Anticipation

Step 1(d) requires “using said probe set to selectively enrich or amplify sequences...in *an additional biological sample*.” EX1001, cl.1. Newman’s teaching that any given CAPP-Seq selector, such as the GBM and NSCLC selectors, can be applied to serial samples taken over time satisfies step 1(d). PET60-61.

Personalis does not dispute that Newman teaches applying its selectors to serial samples taken over time. Instead, Personalis asserts that the teachings of Newman are confined to the “embodiment” in which they appear. POR46-48.

Such arguments are inconsistent with the law of anticipation, let alone

obviousness. For example, the Board rejected similar arguments in *Unified Patents v. Intellectual Ventures*, IPR2016-01643, Paper 51 at 28-31 (PTAB March 26, 2018).

In finding a claim anticipated based on a reference's disclosure of possible implementations of its methods that would "be immediately apparent to one of ordinary skill in the art," *id.*, 30-31, the Board summarized Federal Circuit law on this issue:

Anticipation occurs when a prior art **reference** discloses each element of the claimed invention, ***not only where a particular embodiment within a reference*** discloses each element of the claimed invention. Instead, a reference may still anticipate if the reference teaches that the disclosed components or functionalities may be combined and one of skill in the art would be able to implement the combination.

Unified Patents, Paper 51 at 28-29 (internal quotations omitted).

In Newman, the CAPP-Seq techniques disclosed for NSCLC and GBM are directly related to each other and a POSA would immediately recognize their functionalities may be combined, given Newman's:

- (i) application of CAPP-Seq to both cancers within the same paragraphs, EX1043.553;
- (ii) suggestion to apply its core workflow to "later blood draws," EX1061, ¶195; and
- (iii) express teaching that its analytical tools apply across cancer-types, EX1043.559 ("[W]e used the same approach described [for NSCLC] to

build a background database for cfDNA from 12 normal controls profiled by a personalized GBM selector.”).

Cf. In re Arkley, 455 F.2d 586, 587-588 (C.C.P.A. 1972) (finding improper “picking and choosing” where chemical structure encompassed “over 230,000 compounds” and arriving at claimed species required “convert[ing] the C-type precursors disclosed...to the CA-type compound claimed by appellants.”).

(b) Obviousness

Personalis argues that Newman teaches away from combining the WES of the GBM tumor samples with subsequent use of the GBM selector to interrogate cfDNA. It relies on Figure 1b’s inclusion of “the proverbial ‘prohibition sign’” as allegedly suggesting the CAPP-Seq technique cannot be used with tissue biopsy samples. POR54. However, Newman expressly discloses that CAPP-Seq can be applied by first performing whole exome sequencing on a tumor biopsy sample and then sequencing cfDNA. EX1043.547; EX1078, 141:11-15 (“Q. [P]rior to performing the CAPP sequencing technique on cfDNA they did sequencing on a tumor biopsy, correct? [Dr. Furneaux.] Yeah[.]”).

3. Step 1(e)[1]: Newman discloses sequencing at a “coverage of 175 kilobases or less.”

(a) Anticipation

Newman discloses applying its 157-kb selector to an additional sample to generate the sequencing library, which is necessarily sequenced such that the

coverage is less than 175kb. PET60-61.

A “coverage of 175 kilobases or less,” refers to the length of the region targeted for sequencing. *See* Section II.A.2.(a) above (discussion of construction of “coverage of 175 kilobases or less”). Since Newman’s 157-kb selector targets less than 175kb of genomic content to create a library, sequencing of said library necessarily has a coverage of less than 175kb. This is consistent with the specification, which suggests that “coverage” as used in step 1(e)[1] can be determined by summing the length of the sequences targeted by the probe set. EX1001, 60:3-12; EX1078, 97:4-10 (175 kb refers “to the extent of the fragments in the genome that we’re going to look at”); EX2169, ¶36 (Dr. Furneaux’s chart indicating that “coverage” in step 1(e) is synonymous with “footprint” in step 1(d) of the ’783 patent); ¶183 (assessing step 1(e)[1] based on gene length). To arrive at 175kb, the specification describes an assay in which probes “whose sequences are designed to capture the regions containing the 500 variants,” “may be done with one capture probe (*an RNA molecule with a sequence complementary to the genomic target*) per variant.” EX1001, 60:3-8; *see also id.*, 35:35 (describing the sequencing “footprint,” which is synonymous with “coverage” in step 1(e), of the exome as 35 million bases). “The genomic region *captured by* each such probe may be at least 350 bases.” *Id.*, 60:9-11. The patent multiplies 500 variants by the 350bp length of the target to arrive at a 175kb footprint. *Id.*, 60:11-12.

Personalis argues that Newman's 157-kb selector has a footprint greater than 175kb because "157-kb" refers to the "the sum of the individual probes." POR49-50; EX2169, ¶260. The basis for that assertion is unclear.⁷ POR49-50 (no supporting citation to Newman); EX2169, ¶260 (same).⁸ In Newman, selector length, such as "157-kb," refers to the length of the genomic regions targeted by the selector, not the length of the capture probes. *See, e.g.*, EX1043.551, 558 (describing a "~300kB NSCLC 'tumor genotyping' selector," that was used to "test[] the performance of iDES for selector-wide ***genotyping across 300 kb of targeted genomic positions***"); *see also, e.g.*, EX2163, 82:3-4 ("What Newman is targeting is 157,000 bases.").

Personalis speculates Newman's 157-kb selector would cover more than 175-kb because it allegedly would pulldown overhanging sequence. POR49-50. However, this directly contradicts the specification, which does not teach how to design a probe set that targets 175-kb of sequence while avoiding off-target enrichment that would exceed the threshold. *See* EX1001, 60:3-12.

⁷ Notably, if it had questions, Personalis could have deposed Dr. Newman, EX1060, but declined.

⁸ Dr. Furneaux's assertion lacks basis and is not entitled to weight given his snarky testimony that Newman presented "a rather tragic experiment," and that he "***tend[ed] not to pay much attention***" following his assessment that he "figure[d] people don't know what they're talking about." EX1078, 146:12-147:1; 150:18.

Finally, Dr. Furneaux's use of the Lander-Waterman equation to calculate the "genome length" allegedly captured is irrelevant because it is based on the mistaken premise that the sum of Newman's probe lengths was 157-kb. EX2169, ¶260. *But see* EX1061, ¶¶66, 198 (Dr. Quackenbush correctly applying the Lander-Waterman equation and using 157kb as "Genome Length (G)" to calculate sequencing depth for Newman step in 1(e)")

(b) Obviousness

Electing to sequence less than 175 kilobases in a targeted assay would also have been obvious in order to increase sequencing depth, reduce the size of the required capture panel, and simplify data analysis. *See* EX1061, ¶¶166-168; EX2163, 82:3-19 (POSA "would understand that 157,000 base selector could easily be reduced in size depending on the application."). Doing so would have involved nothing more than the routine optimization of result-effective variables to select the appropriate number of genes for follow-up with a reasonable expectation of success. *Aller*, 220 F.2d at 456; *see* Section I.A.2.(b) (explaining lack of criticality of 175-kb limitation).

B. Claim 5: Newman discloses the claimed "fixed" and "variable" portions.

1. Anticipation

Personalis does not dispute that Newman discloses a "fixed" and "variable" portion as required by Claim 5. Instead, Personalis accuses Petitioner of improperly

combining embodiments. However, as described in Section II.A.2, a POSA would immediately envision combining Newman's teachings, and thus, Newman anticipates Claim 5.

2. Obviousness

The Petition sets forth numerous reasons why a POSA would have been motivated to include both fixed and variable portions in the probe sets disclosed in Newman. PET72-77. Personalis does not address any of these arguments, but again reiterates its legally incorrect position on "mixing" embodiments. *See* Section II.A.2.(a). Moreover, as described above in Section 1A.1.(b) and 1.B.3, Personalis's analysis of the factors that a POSA might consider in designing an assay does not negate obviousness. *See* PET74.

C. Claims 10 and 28: Newman discloses the claimed treatment.

Newman states that the disclosed sequencing techniques are "likely to play a major role in personalized cancer therapy," and thus anticipate Claims 10 and 28, which require therapeutic intervention or treatment based on the "presence or absence of genetic variants" identified in step 1(e). PET66; EX1043.554. Personalis does not dispute Newman's disclosure, but redoubles its efforts to impose an "actual creation or reduction to practice" standard for anticipation. As discussed in Section II.A.2, that is not the law. *See Gleave*, 560 F.3d at 1334.

D. Claim 11: Newman discloses the claimed tumor sample.

Personalis's arguments for claim 11 are based on the mistaken premise that Newman's teachings represent allegedly distinct embodiments. As described above in Section II.A.2, this misapplies the law of anticipation and obviousness.

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 Dr. Furneaux's reproduction of the conclusory chart submitted with the POPR. POR62; *compare* EX2169, ¶293 with EX2004 (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." POR63-64. 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 the praiseworthy feature of its assay is its overall sensitivity of 1 ppm. POR63. Dr. Furneaux previously confirmed that this is a misleading overstatement, as NeXT Personal's sensitivity for a specific variant is 1,000ppm

(1,000 times less sensitive than the POR claims). EX1083, 56:20-62:21. Critically, no challenged claim recites a sensitivity limitation, rendering irrelevant 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 the claimed probes,” POR64 based on mischaracterizations of Forsheew, which was not part of Grounds 1-4. Personalis did not dispute that Ley and Newman successfully used the claimed “probe set.” Finally, in a 180° about-face, Personalis’s counsel has confirmed a complete lack of skepticism for NGS by 2015 in the *Neogenomics* proceeding. *Compare* POR65 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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Respectfully submitted,

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CERTIFICATE OF WORD COUNT

I hereby certify, pursuant to 37 C.F.R. § 42.24, that the Reply contains 5,595 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: LISTING OF DISPUTED CLAIMS

Claim 1: 1. A method for personalized genetic testing, comprising:

(a) [1] sequencing nucleic acid molecules from at least one biological sample of a subject to generate sequencing data, [2] wherein said sequencing comprises sequencing 12 gigabases (GB) or more;

(b) computer processing said sequencing data to identify a plurality of nucleic acid sequences having a set of genetic variants, wherein said set of genetic variants are identified with respect to a reference;

(c) obtaining a probe set comprising a plurality of nucleic acid probe molecules having said plurality of nucleic acid sequences or complements thereof, wherein said plurality of nucleic acid probe molecules are configured to selectively enrich or amplify sequences comprising said set of genetic variants over other sequences in said at least one biological sample;

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

(e) [1] subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less [2] to identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample from said subject or said at least one biological relative, [3] wherein a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a).

Claim 5: The method of claim 1, wherein each of said plurality of nucleic acid probe molecules includes oligonucleotide-directed genomic content comprising (i) at least one variable portion from a result of said sequencing of (a) and (ii) at least one fixed portion independent of said result of said sequencing of (a).

Claim 10: The method of claim 1, further comprising providing a therapeutic intervention at least based on said presence or absence of said at least said subset of said genetic variants identified in (e).

Claim 11: The method of claim 1, wherein said at least one biological sample includes a tumor sample and said nucleic acids molecules are from cells in said tumor sample.

Claim 28: The method of claim 1, further comprising using said presence or absence of said at least said subset of said set of genetic variants identified in (e) to treat said subject or said at least one biological relative for a disorder.

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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