UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Foresight Diagnostics Inc.,
Petitioner,

v.

Personalis, Inc.,
Patent Owner.

IPR2023-00224
U.S. Patent No. 11,384,394

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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I. Ground 1

A. "whole genome sequencing"

1. Claim Construction

There can be no reasonable dispute that a POSA would have regarded Leary's genome-wide, non-targeted sequencing to be "whole genome sequencing" ("WGS"). Express construction of the WGS term in claim 1(b) is thus not required. Nevertheless, Personalis's application of the Board's preliminary construction raises multiple questions – questions that need not be answered to resolve the dispute – but which in any event confirm that Leary was WGS.

As an initial matter, WGS should be afforded the meaning it would have had to a POSA at the filing date, including the alleged shortcomings of such techniques described in the specification. DI19; Ex1001, 1:23-25. It is undisputed that sequencing "all of the genome" was not achievable at the filing date, which is confirmed by both the patent and Mr. West. Ex1001, 5:38-59; 24:35-62; 28:33-42; Ex1222, 46:15-21, 37:17-24; Ex1225 ¶¶5-10.

Thus, if the preliminary construction is applied, the dispute turns on what a POSA understood sequencing "almost all of the genome" to require. Dr. Furneaux admits that "Leary's sequence coverage was only 0.9x," although elsewhere argues that it was about 53-60%, depending on how it was calculated. Ex2031 ¶¶151, 100; Ex1225 ¶¶64-66. As explained below, such sequence

coverage constitutes WGS under both the Board's construction and Petitioner's proposal.

a) What constitutes "almost all"?

Dr. Furneaux's position on this question changed substantially from his declaration to his deposition. In his declaration, though he offered no opinion regarding the threshold, he was emphatic that sequencing 91% of 3.2 billion base-pairs "will fall substantially short of sequencing all or almost all of the genome." Ex2031 ¶97; Ex1223, 87:9-25. Because Mr. West's intervening testimony contradicted Dr. Furneaux's declaration, at deposition Dr. Furneaux provided an entirely new opinion that "90-percent coverage" was the threshold for "almost all." Ex1223, 88:24-93:24; 97:23-98:5.

The application of this cutoff should involve the straightforward formula below, Ex1210, but Dr. Furneaux's inability (or studied unwillingness) to apply it compounded Personalis's mischief.

<u>Sequence Coverage</u>

"almost all of the genome"

$$90\% = \frac{\text{X basepairs}}{\text{Y basepairs}}$$

While Dr. Furneaux readily used 3.2 billion base-pairs as the denominator in his declaration, Ex2031 ¶97, he would not commit to a denominator under his new opinion. In fact, he suggested that "the Board is…well aware that ***all of this is a moving target***," i.e., both the 90% cutoff and the denominator, and each would vary over time. Ex1223, 94:21-95:23; Ex1225 ¶¶11-12, ¶¶16-19. These opinions contradict a POSA's understanding.

(1) 2.86 Gbp is the correct denominator.

As Mr. West confirmed, the value for "all of the genome" that a POSA would have applied was the size of the known reference genome at the time: "Generally, the goal was to sequence as much as possible of the known reference sequence." Ex1222, 38:3-6. The size of the known reference sequence when the patent was filed (and used in its examples) was 2.86 Gbp. Ex1001, Table 13; Ex1225 ¶¶13-15.

(2) 50% coverage constituted "almost all."

The proper bound for "almost all" of the genome must account for the contemporaneous knowledge of a POSA, which included multiple references that expressly and implicitly referred to Leary's PARE technique as whole-genome sequencing. This literature sets the bar for "almost all" of the genome (in the specific context of defining what is and is not WGS) no higher than 50%.

Personalis's contemporaneous patents, which it did not disclose to the Board or its expert, define WGS as "untargeted sequencing," and affirmatively include within its scope "low coverage" WGS. Ex1211-Ex1214; Ex1211, 1:45-49 ("Methods provided herein advantageously employ ***untargeted (e.g., whole genome) sequencing*** and target-specific sequencing…."). These Personalis patents explicitly characterize "low coverage untargeted sequencing (i.e., single run whole genome sequencing)" that sequences 50% of the genome as WGS, and cite references that would include 10% of the genome within its scope. *E.g.*, Ex1211, 18:33-55. Moreover, Personalis's '058 patent explains that generating sequencing data from mate-pair reads with 1.4 kilobasepair inserts – Leary's method – constitutes WGS. Ex1211, 3:37-49. Ex1225, ¶¶21-24.

Contemporaneous literature expressly recognized that Leary was WGS. Ex1030.10; Ex1112, [0003]. Similarly, non-exhaustive reviews of WGS techniques, such as Meyerson, described the same rearrangement screens as "shallow paired-end whole genome sequencing." Ex1031.687. And other references identified by Dr Furneaux as WGS included "whole-genome sequencing with a shallow sequencing depth of about 0.1x." Ex1214; Ex1225 ¶¶25-32.

Thus, the "almost all" aspect of the Board's construction must account for the literature's acceptance of low-coverage techniques within the scope of WGS,

and must include at least the 50% coverage set forth in Personalis's related patents. This suffices to demonstrate that Leary's WGS satisfies the preliminary construction.

b) Express construction is not required.

Because the contemporaneous literature considered Leary's technique to constitute WGS, no further construction is needed "to resolve the controversy." *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). In light of Personalis's abuse of the Board's construction, to the extent express construction is required, Petitioner believes that the plain meaning of WGS was (and remains) "**a non-targeted approach to generating sequencing reads and mapping those reads back to a reference genome (rather than a genome subset).**" This distinguishes WGS from techniques, like exome sequencing, that targeted subgenomic intervals during library preparation and then mapped reads back only to those regions. Ex1225 ¶¶34-36; DI22.

2. Leary used WGS.

a) "nontargeted sequencing"

Leary's WGS is nontargeted because it results in "[s]equence data [that] were mapped to the human genome" reference, without restriction to preselected loci. Ex1002.05. Leary also clearly determined the relevant sequences and used that sequence information "as target sequences for primer design." Ex1225 ¶63

Personalis's argument that Leary "has a 'targeted nature'" rehashes an already-rejected mischaracterization of Chan. In discussing "the tumor genome ***in the plasma***," Ex1008.212, Chan compares its WGS of such biomarkers to Leary's subsequent targeted capture of circulating DNA. DI39-40; Ex2018.58-63. Chan does not refer to Leary's initial WGS of ***tissue*** DNA as "targeted." Ex1225 ¶¶59-62.

b) "almost all of the genome"

Dr. Furneaux states in his declaration that "Leary's sequence coverage was only 0.9x." Ex2031 ¶151. This satisfies the 90-percent opinion he offered at deposition. Ex1225 ¶¶64-65.

Elsewhere, Dr. Furneaux performs a different mathematical calculation and contends that Leary's WGS sequenced 1.71 Gbp of non-overlapping genomic DNA. Ex2031 ¶100. This yields 60% sequence coverage, which still constitutes "almost all of the genome," as discussed above. Ex1225, ¶66.

3. Leary rendered additional sequencing obvious.

As set forth in the Petition, it also would have been obvious to increase sequencing coverage and depth depending on the needs of the experiment. Pet. 52-53; Ex1020, ¶¶65, 203-205. Personalis's arguments to the contrary, POR10-15 (claim 1(b)), 34-35 (claims 17-18), do not prove otherwise.

a) Increasing coverage

Leary's WGS technique provided high physical coverage, indicating that the sequence reads were broadly distributed across the genome in a nontargeted manner. By October 2010, a POSA would have known how to optimize Leary's mate-pair sample preparation to adjust the physical and sequence coverage depending on the needs of the experiment. Specifically, Meyerson described this routine optimization process in its section "**Whole-genome sequencing**," where it explained that by adjusting the distance between paired reads, one can readily adjust the physical and sequence coverage as needed. Ex1031.688. Meyerson thus confirms that a POSA would have been readily able to increase sequence coverage, for example to increase "sensitivity to observe base changes such as point mutations," by decreasing the distance between mate pairs. *Id.* Ex1225 ¶68.

b) Cost and data burden

Personalis's suggestion that "data burden" and "cost" "demonstrates that WGS was undesirable" is baseless. POR10-14. The Federal Circuit is explicit that a design choice need not be "the best option, only that it be a *suitable* option from which the prior art did not teach away." *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014). Even "[a] statement that a particular combination is not a preferred embodiment does not teach away absent clear

discouragement of that combination," *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005), and none of Personalis's selective quotations come close. In fact, the many articles that Personalis uniformly mischaracterizes consistently promote and encourage the use of WGS. Ex1225 ¶¶69-82.

c) Increasing depth

The Petition established that a POSA would have been motivated to increase coverage depth according to the application using routine techniques. Pet.52-53; Ex1020 ¶65; DI22-23. As Dr. Quackenbush explained, adjusting the depth of coverage and the sequencing parameters, such as read length and number of reads required to do so, would have involved nothing more than "routine optimization of predictable and well-known sequencing techniques." Ex1020 ¶205. Indeed, Meyerson confirmed that adjusting the read lengths "from the end of each fragment" and the "distance between the paired reads" in order to adjust "sensitivity to observe base changes such as point mutations" or "for the detection of structural rearrangements" was well-known by 2010. Ex1031.688; Ex1225 ¶68.

With respect to claims 17 and 18, Personalis contends that selecting 30x coverage "reveals improper hindsight," POR35, even though this was the depth of coverage suggested by Meyerson for detecting single nucleotide variants. Ex1031.687; Ex1020 ¶¶64-65.

Personalis also argues that increasing coverage would not work "with PCR techniques like those used in Leary," POR14, presumably referring to Leary's PCR-based capture probes, which are used ***after*** WGS. Ex1225 ¶60. Personalis then makes unsupported assertions about "saturation limit" but shows neither (i) what the pertinent limit is; nor (ii) how increasing Leary's depth would cross it.

Personalis's speculation about "fragmentation biases and difficulties with tiling," POR14-15, also misses the mark. Even accepting Dr. Furneaux's assertion that Leary's preparation steps would "prevent portions of the genome from being sequenced," this is entirely consistent with the specification's discussion of WGS. Ex1225 ¶8. With respect to tiling, Dr. Furneaux testifies only that "a POSA would ***need to consider*** the number of" mate-pairs needed. Ex2031 ¶131. Dr. Quackenbush explained that a POSA "using Leary's 25 bp read length" would have "conducted 3,600,000,000 sequencing reads" using mate-pairs to achieve a depth of coverage of 30x. Ex1020 ¶¶204-205; Pet.52-53. Dr. Furneaux does not contend that this was unfeasible, impractical, or beyond the level of skill in the art.

B. "second sample"

Personalis argues that "[b]y relying on the same ***tumor sample*** for Leary for both limitations 1(a) and 1(c)(i), Foresight failed to identify a first and second

nucleic acid sample in Leary." POR16. This ignores that different nucleic acid samples can be taken from the same tumor sample. Ex1020 ¶99 ("known DNA extraction technologies extract less than 100% of the nucleic acids present in a tumor biopsy."). This is consistent with the claim language itself, which permits the first and second samples to be taken at the same time point. Ex1001, Claim 1(d) ("wherein said first sample or said second sample is obtained from said subject at a first time point").

C. "capture probes"

1. Leary discloses "capture probes" under the Board's construction.

Personalis does not dispute that, if the Board maintains its correct construction, Leary's PCR primers constitute "capture probes." Personalis's only response is to have its expert to call that construction, "quite simply ridiculous." Ex2031 ¶14, Ex1223, 166:20-168:14.

2. Claim Construction

a) The Board's construction correctly encompasses PCR primers.

The plain and ordinary meaning must be determined in light of the intrinsic record. The specification describes a "capture probe" as a nucleic acid structure that "typically…comprises a nucleic acid binding site," and optionally includes additional features, such as "linkers" and "labels." Ex1020 ¶¶100-106. Personalis contends that "the specification has separate descriptions of capture

probes and primers," POR19, but its cited passages do not treat such nucleic acid structures as mutually exclusive. Ex1001, 23:23-26 (referring to "***capture probes, nucleic acid molecules***, beads, ***primers***, or a combination thereof."). Ex1225 ¶40.

Personalis contends that "capture probes" and "pulldown probes" are synonymous, but the trial record established that a POSA would have understood that a "pulldown probe" refers to a biotinylated oligonucleotide bait used in a "pulldown assay."[1] Ex1222, 83:18-85:22; Ex1225 ¶48. In such an assay, the pulldown occurs from the interaction between biotin and streptavidin. *Id*. The specification is explicit that these separate molecules are considered "linkers" or "labels," Ex1001, 14:22-46, 23:23-36, 31:7-12, which are optional and not necessary components of "capture probes." Thus, molecules that include a nucleic acid binding site but lack any type of label – such as PCR primers – must fall within the scope of a "capture probe" as set forth in the Specification. Ex1225 ¶¶38-39.

The dependent claims reciting "capture probes [that] further comprise barcodes," confirm that the scope of the claim includes PCR primers. There is

[1] Dr. Furneaux provided "facetious" testimony that one could "pull[] down a scalpel" through a filter, "[t]hen you would say, 'Ooh, that's a pull-down probe." Ex1223, 152:4-153:9. This contradicts Mr. West and a POSA's understanding.

not a single example of a barcoded biotinylated olignonucleotide bait in the record. Unsurprisingly, Mr. West confirmed at deposition that this would not make sense because for capture probes that are biotinylated oligonucleotides, "the bar codes are not part of the capture [prob]es, They're part of the molecule that's being sequenced." Ex1222, 170:1-4. But barcoded PCR primers are ubiquitous, and do become part of the molecule that's sequenced. Ex1225 ¶41.

b) Personalis's construction contradicts the record.

Personalis proposes construing "capture probe" as "a nucleic acid sequence that hybridizes to target DNA, either in solution or on a solid support, so that one can physically capture and isolate the ***target DNA***." POR17.

This construction is inconsistent with the specification, which does not require the "capture probe" structure to "physically capture" DNA. Moreover, the relevant claim limitations require only "contacting" a nucleic acid sample with capture probe. Ex1001, claim 1(c). Ex1225 ¶¶42-43.

The specification describes multiple ways to create subsets of nucleic acids with capture probes, and physical separation is only one example. DI25. Indeed, the specification explains that "separation" is an "alternative[] or additional[]" distinct step from "contacting." Ex1001, 32:12-18. Accordingly, one way of defining a subset of molecules is based on whether they are hybridized to capture probes. *Id.*, 32:26-33. Ex1225 ¶¶44-45.

Notably, the physical separation that Personalis now conflates with capture is described in the specification as performing an "elution reaction." Ex1001, 37:5-18. Such separation is not a necessary component of the claimed "contacting," nor is it a requirement of any challenged claim. Ex1225 ¶¶46-47.

Personalis's construction would also ***require*** the inclusion of a "label" on a capture probe (e.g., biotin) even though the Specification is explicit that labels and linkers as optional features of capture probes. Ex1001, 31:7-12; Ex1020 ¶¶100-103.

Personalis's construction also contradicts the extrinsic evidence. For example, it paraphrases language from Mertes to arrive at its construction, but changes the phrase "sequences of interest," Ex1006.375, to "target DNA." The reason for this is to support the argument that "hybrid capture" techniques isolate unmodified, "native" DNA. But the record makes clear that this is a false distinction, because hybrid capture workflows nearly always involve DNA that has been amplified and modified with sequencing adaptors. Importantly, both PCR primers and solution-phase baits are used to preserve sequence information and generate enough DNA for subsequent sequencing. Ex1225 ¶¶49-51.

Personalis also goes to great pains to paint PCR primers and biotinylated baits as divergent techniques because they have different pros and cons. For example, it relies heavily on statements in Mertes and Mamanova that show

differences between PCR, on-array hybrid capture, and in-solution capture probes. POR25-31. Despite these differences, Personalis's proposed construction does not exclude array-based capture. Nor do similar types of differences exclude PCR primers from the scope of the term. Ex1225 ¶¶52-53.

c) PCR primers capture DNA loci for sequencing.

Mr. West twice testified that PCR primers perform the function of capturing DNA loci for sequencing:

> Q. ***Did you ever try to use PCR primers to capture DNA for sequencing?***
>
> A. So in my career, ***yes, I had certainly done that***.

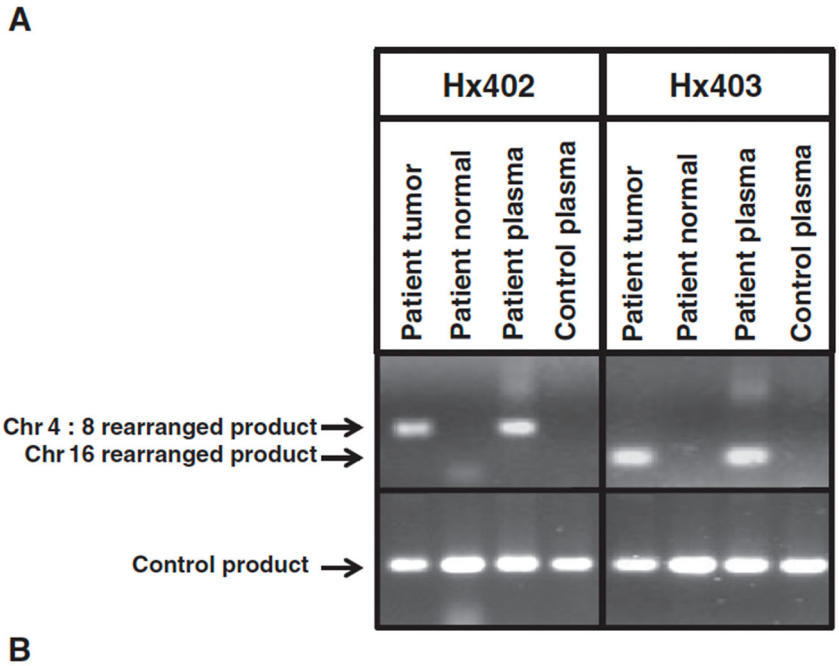
Ex1222, 95:15-18; *id.* 97:4-:21.[2] This testimony is consistent with a POSA's knowledge. For example, Forshew explained that its PCR primers "capture the starting molecules." Ex1030.03. Writing for the interested community, the Head of the Cambridge Institute – lauded by Personalis as a leader in the field at the time – wrote that PCR assays were one of "the different 'capture' mechanisms" available to "capture[] and ampli[y]" loci for sequencing. Ex1216. Similarly, a 2012 editorial described the market for "NGS with Sequence Capture,"

[2] His attempt to undo the damage on re-direct after an hour-long break, claiming he did not "understand that the question did include the term 'capture'" (twice), is not credible. Ex1222, 170:21-24.

observing that "[t]here are two basic approaches to sequence capture: PCR-based and hybridization-based." Ex1217; Ex1225 ¶¶54-57.

3. Leary satisfies Personalis's construction.

In any event, PCR primers capture DNA under Personalis's construction because DNA captured with PCR can be physically isolated, including using gel electrophoresis and well-known physical separation and elution techniques. For example, Dr. Furneaux testified that Southern blot probes are capture probes because the target nucleic acid can be cut out from a filter paper. Ex2031 ¶65. He testified that a similar approach works with PCR: "if you can find and visualize the fragment of a particular size on a gel, then you can physically remove it from the gel." Ex1223, 159:22-25. Leary's Figure 4 shows the visualization of specific nucleic acids on a gel. Ex1002, Fig. 4.



The desired product can be physically collected by cutting out the desired part of the gel and then separating the DNA using a "facile" "extract process." Ex1223, 160:22-161:3. Ex1225 ¶¶84-88.

D. "plurality of capture probes"

Personalis's argument that Leary does not teach "a plurality of capture probes," POR31-32, appears to be based on an implicit claim construction that is not supported by the record. Personalis seemingly reads the phrase to require a "plurality of capture probes <u>with different nucleic acid sequences that bind to different targets</u>." *Cf.* Ex1001, 31:21-22 ("The one or more capture probes…***may be*** different, similar, [or] ***identical***."). But a plurality just means "at least two," and there is no dispute that PCR primers are used in a quantity at great excess to target DNA. Ex1020 ¶72. Even if Personalis's construction were correct, Leary explains that a POSA would have tracked multiple biomarkers – using different pluralities of PCR primers – to mitigate the risk of biomarker escape over time. Ex1005.05; Ex1225 ¶¶89-92.

E. Re-sequencing

As the Petition established, the step of sequencing Leary's PCR products would have been motivated at least by the desire of cancer patients to obtain the most complete and accurate information available, given that sequencing PCR products involved no more than routine skill. Ex1020 ¶¶150, 153. Personalis's

criticism that doing so would be hard and expensive, POR33; 35-36, distorts the record and would not have negated a POSA's motivation to do so. *See* Section I.A.3; Ex2018, 253:3-256:16. Moreover, as set forth in the Petition, a POSA recognized that performing additional sequencing had become, and was becoming, significantly cheaper and more accessible between the publication of Leary and the priority date. Ex1020 ¶151. *See also* Ex1222, 128:23-129:19.

II. Ground 2

The Petition established that a POSA would have found it obvious to supplement the teachings of Leary with Ley, including by detecting SNPs using Ley's deeper, higher coverage WGS (Pet.55-57; Ex1020 ¶¶214, 217), followed by serial monitoring with PCR capture. *Id.* ¶217 ("Ley detected via whole-genome sequencing, and then monitored using probe-based capture techniques….").

Personalis asserts that Ley teaches that "going forward, it would be preferable to use targeted sequencing." POR36-37. This ignores that ***Ley's next sentence*** observes that though targeted sequencing may be an "adjunct to whole-genome sequencing," the WGS approach Ley used had "***several advantages***." Ex1012.71; Ex1225 ¶94.

Personalis argues that a POSA would not have been motivated to use Ley's WGS because of cost and equipment constraints. POR36-37. But as

explained above, Personalis overstates the cost and data issues. It also ignores the fact that sequencing facilities widely available to a POSA in 2012 would have been far better than the facilities available to Ley in 2008 due to the rapid pace of advancement in sequencing technology. Ex1225 ¶¶95-96.

Personalis's allegation that the Petition "provides no specifics about what a combined Leary/Ley assay would entail," POR37-38, ignores the Petition's clear assertions that invalidity was based on the combination of Ley's identification of SNVs using WGS and targeted resequencing with Leary's similar methods. Pet.57. It is "prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose," and the same logic applies to the combination of methods in Leary and Ley. *In re Couvaras*, 70 F.4th 1378-79 (Fed. Cir. 2023). Moreover, the Federal Circuit has repeatedly held that "the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference." *MCM Portfolio LLC v. Hewlett-Packard Co.*, 812 F.3d 1284, 1294 (Fed. Cir. 2015). "Thus, Petitioner is not required," as implied by Personalis, "to show a physical combination of two systems." *Samsung Elecs. Co. v. Netlist, Inc.*, No. IPR2022-00771, Paper 42 at 17 (October 17, 2023).

III. Ground 3

A. Personalis failed to swear behind Chan.

It is Personalis's burden to prove a conception date earlier than its filing date. *Apator Miitors ApS v. Kamstrup A/S*, 887 F.3d 1293, 1297 (Fed. Cir. 2018). It must do so with "corroborating evidence which shows that the inventor disclosed to others [a] completed thought expressed in such clear terms as to enable those skilled in the art to make the invention." *Coleman v. Dines*, 754 F.2d 353, 359 (Fed. Cir. 1985). Personalis has not met its burden.

Personalis contends its NeXT Personal minimum residual disease (MRD) test is coextensive with claim 1, and that every claim of the '394 patent was conceived "by no later than May 8, 2012." POR39. But Personalis was not even working on an MRD assay in 2012—it did not launch NeXT Personal until 2021. Instead, Personalis was working on a project to improve sequencing accuracy, dubbed its "Accuracy Program." Ex1225 ¶¶117-119. Personalis's "Accuracy Program" exhibits do not corroborate the conception of claims of the '394 patent by May 2012.

1. Personalis's conception date should be rejected based on the patent's undisputed inventorship.

The inventorship of the '394 patent contradicts Personalis's proffered May 8, 2012 conception date.[3] Shujun Luo is an undisputed co-inventor of the '394 patent. Ex1001.1. As a co-inventor, Dr. Luo must have contributed to the conception of the claims. *Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352, 1358-59 (Fed. Cir. 2004). But ***co-inventor Luo did not even start working at Personalis until June 18, 2012***. Ex2032 ¶¶35, 337; Ex2016. Named co-inventor Bartha started work at Personalis on May 1, 2012—just a few days before its *latest* proferred bound for conception. It is highly implausible that Dr. Bartha participated in conception within just a few days of starting at Personalis, particularly given that Mr. West's May 8 Board of Directors presentation, which is the basis for Personalis's "no later than" date, was drafted prior to May 8, Ex1222, 51:18-24, and Dr. Bartha is not listed as a participant at the May 3 and May 4 meetings Mr. West discusses.[4] Ex2038-Ex2040; *see* Ex2032 ¶¶63-65.

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[3] Petitioner informed Personalis of this contradiction one week before filing this reply. As of this submission, Personalis has not disclaimed its proffered conception date.

[4] This is particularly true given that Dr. West testified at deposition that he considered "all the pieces that came together to form the basis for the '033 and '394 patent, probably the last of those elements to come together was from a paper that ... came out in ***March of 2012***," more than a month before Dr. Bartha started at Personalis. Ex1222, 48:19-25.

Given the patent's undisputed inventorship, Personalis's proffered conception date cannot be correct.

2. In 2012, Personalis was working on a sequencing project, not an MRD diagnostic project

The "Accuracy Program" that was the subject of Personalis's 2012 efforts was a program to improve sequencing accuracy. *See e.g.,* Ex2046.3, Ex2112; Ex1225 ¶¶116-125. It was not a program to develop an MRD diagnostic test. Hence Personalis's first product – prototypes of which the patent expressly states were the source of its data – was its Exome Plus/Ace Exome product, released in February 2013. Ex1001, 74:60-64. Personalis's NeXT Personal MRD diagnostic test was not launched until 2021. Ex2032 ¶38.

Nonetheless, Personalis contends that claims that the NeXT Personal MRD diagnostic embodies claim 1 and is coextensive with it. POR81. But if NeXT Personal embodies the features of, and is co-extensive with, a claim invented in May 2012, why did it take nine years (until 2021) to launch it?

Further adding to this implausibility is the fact that, in co-pending IPR trials, Personalis argues that NeXT Personal embodies the features of, and is coextensive with, the claims of ***two other challenged Personalis patents whose earliest priority date is May 27, 2016***. IPR2023-00545, Paper 19, 62 IPR2023-00545, Paper 19, 63. Across these four IPRs, then, Personalis is nonsensically arguing that claim 1 was conceived in 2012 and again in 2016.

3. Personalis failed to corroborate the conception of at least steps (c)-(f) of claim 1.

Personalis relies heavily on Slide 5 of EX2112, a CEO Overview presentation to Personalis's Board dated May 8, 2012:

Overview of Personalis Accuracy Program

Characterize errors

Analysis
Rates by variant type & Q-score
Underlying mechanisms
Medical interpretation impact
Regulatory impact

Methods
Comparison with literature
Studies on limited regions
Whole genome analysis:
- Single genome metrics
- Same person twice
- Family inheritance (MIE)
- Platform comparison
  - Arrays
  - ILMN / CGI / Ion T…
  - Sanger capillary

Prioritize solutions
Bio-informatic approaches
Laboratory approaches
Content approaches

Informatic Solutions

Advances in 3rd party alg's
Aligner for > 200bp reads
New versions, current alg's
Other alg's (e.g. lobSTR)

Advances in our alg's:
SV's : Zygocity, accuracy
Combine SV's & SNP's
Broader use of Breakseq

New Personalis alg's
Alignment degeneracy
Genome-aware alignment
VNTR-specific

Advances in reference
Ethnic major-allele ref's
Iterative
Admixed
InDel's / SV's

Flag or Filter Out
For problems not yet solved

Lab, Content Solutions

Combine technologies
WGS + exome
Longer reads and/or inserts
Multi-vendor
Arrays (genotypes & SV's)
Electrophoretic sizing
Sanger validation

Content-based semi-custom
Array (genotypes & SV's)
Pullout

Custom sample preps
Problematic motifs
Degenerate regions
Phasing

Content
Gold standard genomes
Known healthy genomes

Personalis Confidential May 8, 2012 5

Personalis EX2112

Petitioner has submitted unrebutted expert testimony from Dr. Quackenbush that a POSA would have understood this slide to refer to Personalis's program to improve sequencing accuracy, ***not*** to a program to develop a diagnostic assay. Ex1225 ¶¶117-125.

Step (b) recites an initial whole genome sequencing assay on a "first subset" of nucleic acids. Step (c) recites "generating a second subset of nucleic acid molecules" from a "second sample" by contacting that sample with a "plurality of capture probes" that hybridize to "one or more polymorphisms" that

are based on "databases of polymorphisms" or "observed in a population of one or more samples." Personalis relies exclusively on Ex2112, Slide 5 for the "plurality of capture probes" limitation of step 1(c). POR, 17-19.[5] But slide 5 has just a bare reference to "Pullout." A POSA would have insufficient information on how Personalis intended to use such "Pullout." Ex1225 ¶125. There is no corroboration that, as of May 8, 2012, Personalis's co-inventors conceived of a diagnostic assay involving the use of capture probes as claimed in step 1(c). Ex1225 ¶126.

A peculiar feature of claim 1 is that the "first result" from WGS is not explicitly used or even referred to in any of the following steps, including for the "biomedical report." The WGS result could be immediately discarded and the claim could still be met. In the district court litigation, Personalis took subtle steps to mask this, undoubtedly aware that it was improperly recasting its sequencing patent as an MRD diagnostic patent. In particular, to give the appearance that the claims relate to a tumor-informed MRD assay (i.e., tracking a tumor based on a mutation signature identified in an initial WGS step, as in Leary), Personalis put a gloss on the claim language in its infringement contentions to emphasize capture probes that "hybridize to one or more

[5] Personalis refers to Ex2044 to demonstrate that it had corporate "computer processors and servers" by May 8, but Ex2044 does not reference capture probes. POR, 17-18.

polymorphisms . . . ***observed in a population of one***" sample identified in the initial WGS step (element 1(b)). Ex1011, 3-4 (claim 1(c)). The reason for the convoluted claim language and the lack of explicit relationship between the WGS step 1(b) and the capture probe design step 1(c) is because the Specification itself has no disclosure of designing personalized probe sets that hybridize to polymorphisms identified in an individual's DNA through an initial WGS step. And certainly, nothing in Slide 5 suggests designing a personalized "pullout" set based on patient-specific, WGS-identified polymorphisms. Ex1225 ¶125. There is thus no corroboration for the full scope of step 1(c) as applied by Personalis in the district court litigation. *Id.* ¶126.

Finally, there is no corroboration for steps 1(d)-(g), which require assaying a sample obtained from the same individual obtained at a different time point. None of Personalis's conception exhibits disclose assaying different samples from an individual obtained at different time points. Ex1225 ¶¶120-121, 126-127.

4. Personalis failed to prove constructive reduction to practice.

Personalis relies solely upon its January 17, 2013, provisional for a constructive reduction to practice. But Personalis failed to prove that the provisional provides written description support for the claims under § 112. *Bigham v. Godtfredsen*, 857 F.2d 1415, 1417 (Fed. Cir. 1988). It has not even attempted to do so. Nor can it. Personalis's provisional is directed to the Accuracy Program, not to an MRD assay. *See* Ex2098; Ex2032 ¶ 390. It does not provide written description support of steps 1(c)-(d). This is a separate and independent reason that its attempt to swear behind Chan fails.

B. The Leary/Chan/Liao Combination renders the claims obvious.

With respect to element 1(b), Personalis asserts that Chan's shotgun sequencing is not WGS. POR77-78. This is contradicted by Newman, which Personalis injected into this proceeding. Specifically, Dr. Furneaux pointed to Newman's page 11 as containing "a list of exemplary whole genome sequencing references," and did not dispute its veracity. Ex2031 ¶107. Reference 32 in Newman's list is Chan. Ex2152.07. Moreover, Chan discloses performing initial WGS on a tissue sample, and a POSA would have been motivated to use that sequencing protocol in instances where high depth of coverage was desirable,

for example to identify SNPs for subsequent monitoring. Ex1008.218; Ex1225 ¶¶97-98.

With respect to element 1(c), the Petition explains that a POSA would have been motivated to use "solution-phase hybridization probes targeting polymorphisms such as SNPs and SNVs," (Leary's PCR capture probes targeted rearrangements), including because such information could be used to order "a kit from a vendor" containing the desired capture probes. Pet. 64-73; Ex1020 ¶69. Thus, Personalis ignored that the Petition in fact evaluated the majority of its concocted-for-this-proceeding "seven parameters and seven metrics." To the extent Personalis purports to require bodily incorporation, that is the wrong standard, as set forth above. The Petition also explains that the use of solution-phase baits followed by NGS "would have provided similar information about the patient's cancer" to Leary's "PCR followed by sequencing." Pet.71.

Personalis's argument that "Chan's supposed use of solution-phase hybridization capture is conducted ***before*** the sequencing—not after" is not credible. POR79. The Petition explains that the proposed combination performs an initial WGS step followed by targeted resequencing using capture probes; thus capture probes are used after WGS and before resequencing. Ex1225 ¶¶99-100.

With respect to element 1(e), the Petition expressly references its analysis of element 1(c) regarding the selection of an appropriate enrichment technique, which Personalis ignores. Pet.74.

With respect to element 1(f), repeating an assay multiple times is not inventive, as set forth with respect to Ground 1.

IV. No Secondary Considerations

A. Lack of Nexus

Personalis failed to show that its "Next Personal" assay embodies the claims. POR81. Though the Board invited the "development of a full trial record" on this issue, DI33, Dr. Furneaux performed no investigation and merely pasted in his declaration the same conclusory attorney-created chart (including the same typos) that Personalis submitted with its POPR. Ex1223, 35:15-38:24; Ex1208. *See Microsoft Corp. v. Synkloud Technologies, LLC*, No. 2020-00316 (P.T.A.B. Jun. 14, 2021) (finding no nexus because "Patent Owner has left it up to us to figure out how the various screen shots meet the limitations.").

B. No Cognizable Industry Praise

Personalis trumpets its assay's alleged selection as "the top innovation of 2022" in *The Scientist* magazine throughout its papers, including on secondary considerations. POR81-82. This, it turns out, was an overstatement, Ex1220, 112:18-114:19, and its witnesses confirmed that *The Scientist* carries little weight in the relevant community. For example, Personalis's former Board

Chairman Dr. MacQuitty dismissed *The Scientist* and its Top 10 listing as not "important" compared to other life sciences industry magazines. Ex1221, 44:19-45:10. Underscoring *The Scientist's* irrelevance, Dr. Furneaux knew "embarrassingly, not very much at all" about Personalis when he was first engaged in 2023. Ex1223, 12:11-21.

Nevertheless, Personalis argues that the praiseworthy feature of its 2023 assay is its overall sensitivity of 1 ppm. POR82. But no challenged claim recites a sensitivity limitation. This defect in Personalis's argument also renders irrelevant its allegations of praise based on sensitivity-focused industry collaborations. POR82; *see Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1342 (Fed. Cir. 2020) (affirming Board's rejection of argument that invention was praiseworthy because it was selected for presentation at a conference: "Genentech fails to establish a nexus between the objective indicia and the claimed method because there was no evidence that the presentation was selected due to the claimed method.")

Furthermore, as Dr. Quackenbush explains, Personalis's sensitivity-based arguments paint a false picture by comparing the Next Personal assay's sensitivity for detecting any one of 1,800 variants with Leary's sensitivity for detecting a specific variant ("**V**ariant **A**llele **F**raction"). POR82-83; Ex2012.15-17. The Next Personal assay's VAF is reported as 1,000 ppm (1,000 times less

sensitive than the POR claims), and at best 3 times more sensitive than Leary's 2010 assay. Ex1225 ¶¶108-112; Ex1223, 56:20-62:21.

C. No Cognizable Skepticism

Finally, Personalis's arguments concerning supposed skepticism of using genome sequencing and capture probes repeat the same generic mischaracterizations raised in its responses to the Grounds. POR83-84. None of the alleged "problems" equate to skepticism that the claimed invention could be achieved. Ex1225 ¶113.

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Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I hereby certify, pursuant to 37 C.F.R. section 42.24, that the foregoing Petitioner's Reply to Patent Owner Response contains 5,562 words, excluding the words in the table of contents, table of authorities, mandatory notices under section 42.8, this certificate of word count, certificate of service or exhibit list. The word count is based on the word count of the Microsoft Word program used to prepare the Petitioner's Reply to Patent Owner Response.

/Andrew E. Krause/
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CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. section 42.6, that on December 22, 2023, a complete copy of the foregoing document **PETITIONER'S REPLY TO PATENT OWNER RESPONSE** and **Exhibits 1033, 1070, 1112, 1208-1218, 1220-1223** and **1225** were served upon the following, by ELECTRONIC MAIL:

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CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. section 42.6, that on January 22, 2024, per the Board's email today, a complete copy of the corrected version of Paper 32, **PETITIONER'S REPLY TO PATENT OWNER RESPONSE** and the corrected version of **Exhibit 1223** were served upon the following, by ELECTRONIC MAIL:

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