

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

Foresight Diagnostics Inc.,
Petitioner,

v.

Personalis, Inc.,
Patent Owner.

IPR2023-00317
U.S. Patent No. 11,408,033

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

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<u>PETITIONER’S EXHIBIT LIST</u>	
EX1001	U.S. Patent No. 11,408,033 issued to Bartha <i>et al.</i>
EX1002	Rebecca J. Leary <i>et al.</i> , “Development of Personalized Tumor Biomarkers Using Massively Parallel Sequencing,” <i>Science Translational Medicine</i> (2010) (Leary)
EX1003	Stephen R. Quake <i>et al.</i> , WO 2011/057061 (Quake)
EX1004	Matthew W. Anderson & Iris Schrijver, “Next Generation DNA Sequencing and the Future of Genomic Medicine,” <i>Genes</i> (2010) (Anderson)
EX1005	Andreas Gnirke <i>et al.</i> , “Solution hybrid selection with ultra-long oligonucleotides for massively parallel targeted sequencing,” <i>Nature Biotechnology</i> (2009) (Gnirke)
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EX1007	Lira Mamanova <i>et al.</i> , “Target-enrichment strategies for next-generation sequencing,” <i>Nature</i> (2010) (Mamanova)
EX1008	K.C. Allen Chan <i>et al.</i> , “Cancer Genome Scanning in Plasma: Detection of Tumor-Associated Copy Number Aberrations, Single-Nucleotide Variants, and Tumoral Heterogeneity by Massively Parallel Sequencing,” <i>Clinical Chemistry</i> (2013) (Chan)
EX1009	Reserved
EX1010	<i>Personalis v. Foresight</i> , First Amended Complaint, D. Colo., Case No. 1:22-v-01913, Dkt. 9, filed August, 17, 2022 (“FAC”)
EX1011	Reserved
EX1012	Timothy J. Ley <i>et al.</i> , “DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome,” <i>Nature</i> (2008) (Ley)
EX1013	Jay Shendure and Hanlee Ji, “Next-generation DNA sequencing,” <i>Nature Biotechnology</i> (2008) (Shendure)

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EX1014	Jeffrey S. Ross and Maureen Cronin, “Whole Cancer Genome Sequencing by Next-Generation Methods,” <i>American Journal of Clinical Pathology</i> (2011) (Ross)
EX1015	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)
EX1016	David M. Kurtz, et al., “Enhanced detection of minimal residual disease by targeted sequencing of phased variants in circulating tumor DNA,” <i>Nature Biotechnology</i> (2021) (Kurtz) (EXJ to FAC)
EX1017	Dennis Lo, “Cancer Genome Scanning in Plasma, Clinical Chemistry Journal,” Jan. 3, 2013 https://www.aacc.org/science-and-research/clinical-chemistry/clinical-chemistry-podcasts/2013/cancer-genome-scanning-in-plasma-detection-of-tumor-associated-copy-number-aberrations
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EX1025	Reserved
EX1026	Leary Supplemental Information
EX1027	Hugo Lam, et al., "Performance comparison of whole-genome sequencing platforms," <i>Nature Biotechnology</i> (2012) (Lam)
EX1028	Illumina, Technical Note: Sequencing
EX1029	Illumina, Specification Sheet: Illumina Sequencing
EX1030	Tim Forshew, et al., "Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA," <i>Science Translational Medicine</i> (2012) (Forshew)
EX1031	Matthew Meyerson, et. al., "Advances in understanding cancer genomes through second-generation sequencing," <i>Nature Reviews</i> (2010) (Meyerson)
EX1032	Forshew Supplemental Information
EX1033 (New)	Nikhil Wagle et al., "High-Throughput Detection of Actionable Genomic Alterations in Clinical Tumor Samples by Targeted, Massively Parallel Sequencing," <i>Cancer Discovery</i> (2012) (Wagle)
EX1034	Andreas Untergasser <i>et al.</i> , "Primer3—new capabilities and interfaces," <i>Nucleic Acids Res.</i> (2012) (Untergasser)
EX1035	Simon Forbes <i>et al.</i> , "COSMIC: mining complete cancer genomes in the Catalogue of Somatic Mutations in Cancer," <i>Nucleic Acids Res.</i> (2011) (Forbes)
EX1036	Y. Kohara, "DNA probes on beads arrayed in a capillary, 'Bead-array', exhibited high hybridization performance," <i>Nucleic Acids Res.</i> (2002) (Kohara)

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EX1037	Infringement Claim Chart for U.S. Patent No. 11,408,033; EXO to Patent Owner’s FAC
EX1038	C. Vale <i>et al.</i> , “Does anti-EGFR therapy improve outcome in advanced colorectal cancer? A systematic review and meta-analysis.” Cancer Treat Rev. (2012) (<i>Vale</i>)
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EX1210 (New)	90% Chart (Furneaux Deposition EX1210)
EX1211 (New)	U.S. Patent No. 11,456,058, issued to West <i>et al.</i>
EX1212 (New)	U.S. Patent No. 11,584,968, issued to West
EX1213 (New)	Pasaniuc, <i>et al.</i> , “Extremely low-coverage sequencing and imputation increases for genome-wide association studies”
EX1214 (New)	(Personalis) U.S. Patent No. 11,640,405 issued to Chandratillake
EX1215 (New)	Jain, <i>et al.</i> , “Single molecule pull-down for studying protein interactions” https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3654178/
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EX1217 (New)	Biocompare Editorial Article, “Maximize Your NGS with Sequence Capture”
EX1218 (New)	Heitzer, <i>et al.</i> , “Tumor-associated copy number changes in the circulation of patients with prostate cancer identified through whole-genome sequencing”
EX1219 (New)	Reserved
EX1220 (New)	[Redacted] Norton Deposition Transcript, Nov. 21, 2023, and [Sealed] Norton Deposition Transcript, Nov. 21, 2023
EX1221 (New)	[Redacted] MacQuitty Depo Transcript, Dec. 1, 2023, and [Sealed] MacQuitty Depo Transcript, Dec. 1, 2023

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EX1222 (New)	[Redacted] West Depo Transcript, Dec. 8, 2023, and [Sealed] West Depo Transcript, Dec. 8, 2023
EX1223 (New)	Furneaux Depo Transcript, Dec. 12, 2023
EX1224 (New)	U.S. Patent No. 11,384,394 to Bartha <i>et al.</i>
EX1225 (New)	Declaration of John Quackenbush, Ph.D. iso Petitioner’s Reply

I. Personalis Failed to Swear Behind Forshew and Chan.

Personalis attempts to swear behind Forshew and 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) (affirming Board's finding that patentee failed to prove earlier conception). Personalis 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 each of the patent's 23 claims was conceived "by no later than May 8, 2012." POR1, 2, 79-80. The evidence shows that PO 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," which was itself just a research project as of May 2012. Ex1225 ¶¶119, 128. As explained below, the reams of "Accuracy Program" exhibits submitted with the POR do not corroborate conception because Personalis has overclaimed its disclosure to try to cover an MRD diagnostic assay that it did not invent in 2012. Personalis's

proffered conception date lacks credibility and is uncorroborated. Personalis's attempt to swear behind Forshew and Chan should be rejected.

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

The inventorship of the '033 patent contradicts Personalis's proffered May 8, 2012 conception date. Shujun Luo is a co-inventor of the '033 patent. Ex1001.01. 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) (A "person is a joint inventor only if [s]he contributes to the conception of the claimed invention."). But *co-inventor Luo did not even start working at Personalis until June 18, 2012*. Ex2032 ¶35. On that same day, Mr. West sent an email to two other named co-inventors "regarding Shujun Luo *beginning employment* at Personalis," Ex2032 ¶337, stating "[w]ith Shujun starting, I wonder if she can *begin coming up to speed* on our accuracy analysis [the Accuracy Program]." Ex2016; Ex2032, ¶337. Thus, the claims of the '033 patent must have been conceived *no earlier* than *June 18, 2012*, when Dr. Luo first began working the Accuracy Program. "[L]ogic dictates that the earliest date of conception among a claim invented by joint inventors is the date that the last of the joint inventors began to work on creating the invention." 4 Annotated Patent Digest § 26:122; *see Samson v. Crittenden*, 14 U.S.P.Q.2d 1810 (B.P.A.I. 1989) ("Since [joint inventor] did not become involved with the project until late

November 1984, only activities which occurred after that time may be relied upon by [inventive entity] to establish joint conception and reduction to practice on their behalf.”).

Personalis does not contest that Dr. Luo was properly named a co-inventor.¹ Indeed, the POR includes a photograph of “co-inventor Shujun Luo.” POR49-50; *id.*, 9 (including Dr. Luo as among the patent’s “co-inventors”). Mr. West testified that “when we submitted the patent application we included the people that we felt contributed to that invention,” Ex1222, 144:14-16, and did not see any “corrections that needed to be made” to the patent. *Id.*, 26:10-13.

Mr. West’s testimony on conception is also inconsistent with Gabor Bartha’s co-inventorship. Dr. Bartha started work at Personalis on May 1, 2012—just a few days before its *latest* proffered bound for conception (“by *no later than* May 8, 2012”). But 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. Ex2038-Ex2040; *see* Ex2032 ¶¶63-65.

¹ Petitioner informed Personalis of this contradiction one week before filing this reply. As of this submission, Personalis has not disclaimed its proffered conception date.

These facts make it highly implausible that Dr. Bartha participated in conception within just a few days of starting at Personalis.²

Mr. West states in his declaration:

The '033 patent issued with 23 claims. *My co-inventors and I formed a definite and permanent idea of the complete and operative invention described in each of these claims by no later than May 8, 2012.*

Ex2032 ¶82. But Mr. West and his “*co-inventors*” (which include Drs. Bartha and Luo, as Mr. West confirmed under oath) could *not* have conceived the claims by May 8, 2012. For this reason alone, Personalis’s proffered conception date fails any “rule of reason” scrutiny.

B. 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 (“We have developed all three of these

² 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.

libraries and have preliminary data combining standard TruSeq Exome and ESP to produce what we call Exome+, Extended Exome or ACE[] Exome (Tables 13-14).”); Ex2032 ¶¶378, 329, 406; Ex1222, 126:1-127:19, 151:17-20. Consistent with the patent having been filed to support that product release, the contemporaneous Specification of the ’033 patent focuses on accuracy in sequencing. Ex1001. And Personalis’s NeXT Personal MRD diagnostic test was not launched until 2021. Ex2032 ¶ 38.

Nonetheless, Personalis claims that the NeXT Personal MRD diagnostic “embodies the features” of claim 1, and is “coextensive with them.” POR79-80 (arguing for presumption of nexus under *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018)). Personalis’s argument on nexus renders its conception story even more far-fetched. There is no corroborating evidence that Personalis’s co-inventors conceived any invention coextensive with an MRD diagnostic assay by May 2012. And Personalis offers no answer to this question: If NeXT Personal embodies the features of, and is co-extensive with, a claim invented in May 2012—and a claim that, by May 2012, was allegedly disclosed to others in enabling terms—why did it take nine years (until 2021) to launch it? *Coleman*, 754 F.2d at 359 (standard for corroboration); EX2032 ¶38 (NeXT Personal launch date).

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 (arguing for presumption of nexus between NeXT Personal and USPN 11,299,783, citing *Polaris Indus.*); IPR2023-00545, Paper 19, 63 (same for USPN 10,450,611). Across these four IPRs, then, Personalis is essentially arguing that claim 1 was conceived in 2012 and again and anew in 2016. This is nonsensical.

C. Personalis failed to corroborate the conception of any steps in 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	Informatic Solutions	Lab, Content Solutions
<u>Analysis</u> Rates by variant type & Q-score Underlying mechanisms Medical interpretation impact Regulatory impact	<u>Advances in 3rd party alg's</u> Aligner for > 200bp reads New versions, current alg's Other alg's (e.g. lobSTR)	<u>Combine technologies</u> WGS + exome Longer reads and/or inserts Multi-vendor Arrays (genotypes & SV's) Electrophoretic sizing Sanger validation
<u>Methods</u> 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	<u>Advances in our alg's:</u> SV's : Zygosity, accuracy Combine SV's & SNP's Broader use of Breakseq	<u>Content-based semi-custom</u> Array (genotypes & SV's) Pullout
<u>Prioritize solutions</u> Bio-informatic approaches Laboratory approaches Content approaches	<u>New Personalis alg's</u> Alignment degeneracy Genome-aware alignment VNTR-specific	<u>Custom sample preps</u> Problematic motifs Degenerate regions Phasing
	<u>Advances in reference</u> Ethnic major-allele ref's Iterative Admixed InDel's / SV's	<u>Content</u> Gold standard genomes Known healthy genomes
	<u>Flag or Filter Out</u> For problems not yet solved	

Petitioner has submitted un rebutted 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 ¶¶116-125.

The first phase of PO's Accuracy Program, reflected in the left-hand column, was to "Characterize errors" in 2012 sequencing technology. Ex1225 ¶120; Ex1222, 65:6-10. The middle and right-hand columns refer vaguely to some of the "Informatic Solutions" and "Lab, Content Solutions" Personalis contemplated "for addressing problems in sequencing accuracy." Ex2112.5; Ex1222, 99:12-100:4; Ex1225 ¶¶122-125. A POSA would have viewed the slide as referencing these "solutions" at a very high level of generality, devoid of any meaningful (much less novel or innovative) details. Ex1225 ¶¶123-125.

No wonder, then, that Personalis's conception documents fail to corroborate that its co-inventors conceived of the '033 patent's claims by May 8, 2012. Personalis relies exclusively on Ex2112, Slide 5 for the "plurality of capture probes" limitation of step 1(a). POR, 17-19.³ But slide 5 has just a bare reference to "pullout." At most, this suggests that by May 2012, Mr. West contemplated that a particular type of capture probe could be one among many

³ Personalis refers to Ex2044 to demonstrate that PO had corporate "computer processors and servers" by May 8, but Ex2044 does not reference capture probes. POR17-18.

other “lab solutions” for addressing sequencing accuracy. Ex1225 ¶¶123-125. But Ex2112 provides no details at all on how he contemplated designing and/or using these “pullout” probes. Ex1225 ¶127.

The bare reference to “pullout” on Ex2112, Slide 5 does not corroborate that, as of May 8, 2012, Personalis’s co-inventors conceived of (a)(i) producing, with a computer processor, a plurality of capture probes that (a)(ii) hybridize to a plurality of polymorphisms in sequences encoding genes with known biomedically interpretable variants, (a)(iii) based on or extracted from databases of polymorphisms, as claimed in step 1(a).⁴ Ex1225 ¶¶125-126. Personalis has provided even less corroborating evidence for step 1(a) than the patentee in *Sprint Spectrum, L.P v. General Access Solutions LTD*, IPR2017-01885. There, the Board rejected the patentee’s attempt to swear behind a reference because the patentee could not corroborate conception of one particular claim limitation (“determining an optimum modulation configuration”). Paper No. 57, 13-14. The patentee’s evidence was insufficient because it did “not describe what the optimum modulation is or how such optimum modulation is determined.” *Id.* Here, there is no remotely sufficient description of step 1(a) in Ex2112, Slide 5, which simply lists a number of various conventional lab, content and informatics

⁴ This claimed use of capture probes also has no connection to improving sequencing accuracy.

technologies without providing any details on how they would be used. Ex1225 ¶¶125-127. As Dr. Quackenbush explains, “a POSA reviewing Slide 5 in light of the overall record on conception would have insufficient information to determine how, specifically, Personalis intended to use the ‘Pullout,’ other than that their purpose was to provide one of a number of potential laboratory solutions to improve the accuracy of 2012 sequencing technology.” Ex1225 ¶125.

Steps 1(b) and 1(c) are predicated on the use of the capture probes produced in step 1(a), and hence there is no corroboration for these steps, either. PO also fails to corroborate the conception of step 1(d), “(d) repeating steps (b)-(c) on a *subsequently obtained* biological sample from said individual.” None of Personalis’s conception exhibits disclose assaying different samples from an individual obtained at different time points, much less contacting those samples from different time points with sets of the claimed capture probes. Ex1225 ¶¶120-121, 126-127. Personalis’s corroborating evidence for this step is limited to two exhibits. POR22-23. The first is Ex2112, Slide 3, which references a paper from a Stanford group published in March 2012. But there is no evidence that Personalis’s co-inventors contemplated incorporating this group’s work into Personalis’s Accuracy Program, nor is there any disclosure of step 1(d) in the Stanford paper in any event. EX2112, Slide 5; Ex1225 ¶127.

The other exhibit Personalis relies on is EX2046.14:

**Categories of experimental data to assess
error types, mechanisms, frequencies**

- Repeatability :
 - Same person twice (or more ?), trying to keep everything else constant
 - Alternatives: Genomes of identical twins, or children where identical
- Controlled process experiments :
 - Same person sequenced multiple times, each time varying just one parameter of the process (many of these can be done computationally)
- Concordance of other technology platforms on the same sample
- Compare process QC metrics from many sources of raw genome data, even low coverage (e.g. 1,000 Genomes)
- Mendelian inheritance errors (MIE's) determined from family genome sets
- Absolute accuracy :
 - Genomes of individuals known to have clear Mendelian diseases
 - Sequencing of complex synthesized oligo sets (synthetic genome)
 - Targeted modifications of DNA from a naturally occurring genome

Personalis EX2046.14

Here, Personalis contemplated sequencing the *same sample* twice to assess sequencing errors. The objective was “to keep everything else constant” to determine whether the sequence results would be “repeatable.” *Id.*; Ex1222, 121:20-122:16; EX1225 ¶120-121. This slide does not contemplate taking samples from an individual at different time points. It certainly does not disclose contacting samples taken at different time points with a set of capture probes as described in step 1(a), as claimed. Ex1225 ¶¶120-121, 126.

The concerns behind the corroboration requirement—that “inventors ... would be tempted to remember facts favorable to their case by the lure of protecting their patent or defeating another's patent,” *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1577 (Fed. Cir. 1996)—are fully applicable here. Mr. West,

a named inventor and Personalis's former CEO who advocated for its lawsuit against Petitioner, Ex1222, 32:17-33:8, has been "tempted to remember facts favorable" to Personalis's case. One example is his testimony to demonstrate diligent reduction to practice in August 2012. In paragraph 372 of his declaration, as if testifying from his own independent recollection, Mr. West stated that a Personalis Board of Directors meeting "took place on Tuesday, August 14, 2012, from 9am-11am. During the Board of Directors meeting, we discussed updates on the Accuracy Program." Ex2032 ¶372. But he admitted at deposition that no such meeting took place. Ex1222, 17:15-18:17; 20:23-21:2. He simply assumed that there was such a meeting based on a Google Calendar invitation he reviewed in 2023 as he was working on his declaration, *id.*, and then worded his declaration as if he had a current, independent recollection of such a meeting. There is thus good reason for the Board to insist on sufficient corroborating evidence and not to credit Mr. West's attempt to bridge the gulf between Personalis's conception exhibits and the claimed subject matter.

In sum, Personalis has fallen far short of presenting corroborating evidence "expressed in such clear terms as to enable those skilled in the art to make the invention." *Coleman*, 754 F.2d at 359; Ex1225 ¶¶124, 126, 128. Personalis's attempt to swear behind Forshew and Chan fails because it has not established a conception date by May 8, 2012.

D. Personalis failed to prove constructive reduction to practice.

Personalis also failed to establish reduction to practice. It relies solely upon an alleged constructive reduction to practice on January 17, 2013, based on the filing of U.S. Provisional Application No. 61/753,828. POR2, 6, 39, 53-54. Where, as here, a patentee seeks to rely on a priority application such as a provisional for constructive reduction to practice, the patentee must prove that the priority application meets the requirements of § 112. *Bigham v. Godtfredsen*, 857 F.2d 1415, 1417 (Fed. Cir. 1988). In *Bigham*, the Federal Circuit reversed the Board's ruling that the appellee's British application constituted a constructive reduction to practice of the count at issue because that application did not contain an adequate written description of the count under § 112. *Id.* at 1417-18.

Here, Personalis has not even attempted to establish that the '828 Provisional Application provides adequate written support for any claim of the '033 patent. Personalis simply included, without any discussion, that provisional application (Ex2113) among the reams of exhibits it interjected into this trial. Notably, a provisional application does not enjoy any presumption of written description support. "[B]ecause the PTO does not examine priority claims unless necessary, the Board has no basis to presume that a reference patent is necessarily entitled to the filing date of its provisional application." *Dynamic*

Drinkware, LLC v. Nat'l Graphics, Inc., 800 F.3d 1375, 1380 (Fed. Cir. 2015).

Personalis's provisional is directed to the Accuracy Program, not to an MRD assay. *See* Ex2098, Ex2032, ¶390 (describing what became the '033 patent family's provisional application as "a patent application for Exome Plus (formerly referred to as the Accuracy Program)."). Unsurprisingly, it does not support multiple claim limitations. For example, there is no disclosure of step 1(d), contacting samples taken at different time points to a set of capture probes produced per step 1(a).

Personalis's attempt to swear behind Forshew and Chan fails for the separate and independent reason of a failure of proof to establish reduction to practice.

II. Ground 1

A. "capture probes"

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

Personalis does not dispute that, if the Board maintains its correct construction, Forshew's PCR primers constitute "capture probes." Its 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,” POR58, 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.”⁵ 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

⁵ 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, 151:25-153:9. This contradicts Mr. West and a POSA’s understanding.

“labels,” Ex1001, 14:22-46, 23:23-36, which are optional and not necessary components of “capture probes.” *Id.*, 31:7-12. 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 not a single example of a barcoded biotinylated oligonucleotide in the record. Consistent with the Petition, 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.” Ex1022:16-22. 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*.” POR56.

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(b). 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 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 depict 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. POR63-66 (“Mamanova identifies numerous differences between “PCR,” “[o]n-array hybrid capture,” and “[i]n-solution hybrid capture.”). Despite these differences, Personalis’s proposed construction would include array-based capture within its scope. Nor is there reason to exclude PCR primers from the construction based on such differences. 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.

Ex2122, 95:15-18; *id.* 97:4-:21.⁶ 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 amplif[y]" loci for sequencing. Ex1216. Similarly, a 2012 editorial described the market for "NGS with Sequence Capture," observing that "[t]here are two basic approaches to sequence capture: PCR-based and hybridization-based." Ex1217. Ex1225, ¶¶54-57.

3. Forshew Satisfies Personalis's Construction

In any event, PCR primers capture DNA under Personalis's construction because DNA captured with PCR can be physically isolated, for example 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 nucleic acid can be cut out of 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. The desired product can be physically collected by

⁶ 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.

cutting out the desired part of the gel, and separating the DNA using a “facile” “extract process.” Ex1223, 160:22-161:3, Ex1225, ¶¶84-88.

B. Element 1(c)

Personalis argues that Forshew does not meet limitation 1(c) “because its sequencing assay is conducted on molecules that result from PCR amplification.” POR67-68. To the extent this argument can be understood, it appears that Personalis has construed “generated from” to require the direct sequencing of an original “nucleic acid molecule” from the sample. The Board rejected this exact argument under the plain meaning of “generated from” in its Institution Decision, and Personalis did not propose further construction. DI27-28. Moreover, the inventor Mr. West disclaimed this argument, testifying that “the claims of the ’033 patent and the ’394 patent *do not call for sequencing the original molecules* from the sample.” Ex1222, 174:22-24.

The plain meaning of “generated from” does not require direct sequencing. Indeed, Personalis does not impose this requirement on the claims of the ’394 patent, which recite “generating” subsets from nucleic acid samples. Ex1224, claim 1. Nor does the specification suggest – let alone compel – Personalis’s narrow implicit construction. Ex1225 ¶¶101-102.

Intermediate steps such as amplification are entirely consistent with the claim, which recites “comprising.” Indeed, even when using the pulldown

probes to which Personalis contends the claims are limited, the molecules that are ultimately sequenced are typically amplicons. Ex1225 ¶103.

C. Elements 1(b) and 1(d)

Personalis's arguments for these elements are entirely based on its "capture probe" argument and thus fail when the correct construction is applied. POR67-68.

III. Ground 2

A. The Petition provided ample motivation to modify Forshew.

Contrary to Personalis's contention, the Petition established motivation to combine Forshew and Wagle using Wagle's capture probes, including because Wagle suggested, consistent with the background art, that "its exon capture approach" is a "related technique suitable for the capture portion" of a targeted sequencing workflow that might improve on "PCR-capture based techniques" in certain circumstances. Ex1020, ¶¶182-183; Pet.47-48. "It's enough for [Petitioner] to show that there was a known problem [] in the art, that [Wagle's capture probes] helped address that issue, and that combining the teachings of [Forshew] and [Wagle] wasn't beyond the skill of an ordinary artisan." *Intel Corp. v. PACT XPP Schweiz AG*, 61 F.4th 1373, 1381 (Fed. Cir. 2023).

Personalis imposes a heightened burden on the motivation analysis, contending that a POSA would have needed to proceed through its convoluted and concocted-for-this-proceeding "seven parameters" framework. POR73-74.

Even though this asks the wrong questions, Personalis ignores that Dr. Quackenbush *did* address these parameters, explaining in detail why certain circumstances may favor the selection of hybridization baits over PCR primers, and why they were considered interchangeable in other circumstances. Ex1020, ¶¶182-183 (citing *id.* ¶¶68-80) (evaluating considerations for selection of particular enrichment techniques). At deposition, Mr. West testified that “PCR primer methods” are mostly used to capture “a small number of genomic targets,” Ex1222, 95:15-22, but the ’033 claims only require capture probes that hybridize to as few as two polymorphisms (a “plurality”). So even according to Mr. West, PCR primers could readily be used in the method as claimed.

B. Personalis’s DNA quantity arguments are contradicted by Forshew and Wagle.

Personalis argues that “[b]ecause capture probes do not amplify DNA they can only capture the incredibly small amounts of DNA that are already present in the microliters of plasma used in Forshew’s TAm-Seq samples.” POR70-71. This is pure misdirection.

For example, Personalis relies heavily on the volume of plasma used in individual assays to suggest that a POSA would not have been able to obtain sufficient DNA from plasma samples generally. POR69-70. Forshew used very small fractions of the plasma it collected in part because a goal of its method was to show that it could work on samples containing “even single copies of ctDNA.”

Ex1030.1. Forshew clearly collected ample volumes of plasma, given that it describes collecting multiple 1 *milliliter* aliquots. Ex1030.10. Moreover, obtaining additional plasma would have merely involved a routine blood draw. Ex1225 ¶105.

Personalis's brief gives the impression that Wagle's 3.6 micrograms of DNA constituted the mass of native DNA present in its samples. POR70-71. But in fact, Wagle's tumor DNA was PCR-amplified, modified by adding sequencing adaptors and barcodes, and then pooled together before being subjected to hybridization capture probes. Ex1033.91. In other words, Wagle generated sufficient DNA by *amplifying* source DNA using PCR and then pooled together multiple different samples to yield the 3,600 ng of DNA it used for hybrid capture. Ex1225 ¶¶106-107.

C. Forshew does not teach away.

Personalis asserts that "Forshew itself recommends not using Wagle's capture probes." POR71. False. The quoted passage at most suggests that "[t]argeted sequencing...*has not been applied* for analysis of circulating tumor nucleic acids," but in no way discourages doing so. Indeed, Forshew goes on to demonstrate that targeted sequencing could be applied to circulating tumor nucleic acids. Ex1030.9. Nor does Forshew's mention of cost considerations negate motivation to combine. Confirming Wagle's baits were neither

unnecessarily costly nor difficult to obtain, Wagle purchased them from a commercial vendor. Pet.47 (citing Ex1033.10) (describing “Agilent SureSelect” probes). *Intel Corp. v. Qualcomm Inc.*, 21 F.4th 784, 800 (Fed. Cir. 2021) (“Our caselaw is clear. It’s not necessary to show that a combination is ‘the best option, only that it be a suitable option.’”). Personalis’s similar mischaracterizations of Forshew, POR75, should be rejected for the same reasons.

Personalis also claims that “PCR amplification has a ‘negative influence’ on hybrid capture, that combining them should be avoided,” and if used at all, only ‘after hybridization.’” POR76. This characterization overstates the quoted passage from Mamanova, which refers only to potential effects on “uniformity of enrichment.” The claims do not require any particular uniformity of enrichment. Moreover, as discussed above, this “incompatibility” is belied by the fact that *Wagle’s hybrid capture is performed on PCR-amplified DNA*. Ex1033.91; Ex1225 ¶¶106-107.

D. Petitioner did not need to show how to bodily incorporate Wagle into Forshew.

Personalis’s allegation that the combination is “hopelessly vague,” POR74-75, ignores the Petition’s clear explanation that Wagle’s “RNA bait hybridization probes” would be used in the same claim steps as “Forshew’s PCR primers.” Pet.47. Personalis’s subsequent complaints dig deep into the nuances of Forshew’s protocol at a level of specificity far beyond what is required by the

claims and purports to require the Petition to set forth a laboratory manual. But “[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). Indeed, 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. IPR2022-00711, Paper 42 at 17 (October 17, 2023).

IV. Ground 3

Personalis does not dispute that Wagle teaches elements 1(a)-(c). Its only response on the merits is that it would not have been obvious to repeat Wagle’s assay on additional samples. POR77.

As explained in the Petition, a POSA would have been motivated to repeat Wagle’s assay on subsequently obtained tumor samples, and Personalis’s identification of convenience and cost issues would not negate that motivation in the context of cancer treatments. For example, Personalis gives great weight to Forshe’s statement that “biopsies are invasive and costly,” POR78, but

ignores that Forsheew nevertheless discloses obtaining multiple biopsies from patients. Ex1030.07 (Fig. 4); *see also* Ex1008.219. Claim 11 of the '033 patent even recites, “said subsequently obtained biological sample is a tissue biopsy sample,” and Personalis does not argue that this “innovation” was separately patentable.

Moreover, the Petition explained that a POSA would have been motivated to repeat Wagle’s assay on a plasma sample. Personalis’s sole argument against that motivation is that “cell-free tumor DNA is not present in sufficient quantities.” POR78-79. But this is (a) based on Personalis’s mischaracterization of Forsheew’s highly subdivided plasma samples, discussed above; and (b) ignores that Wagle teaches to amplify DNA before hybrid capture. Ex1033.91; Ex1225 ¶¶106-107. That argument is further belied by the Petition’s explanation that motivation is based on Chan’s report that “solution-phase hybridization based capture approaches *have already been successfully used to enrich plasma DNA*.” Pet.63-64; Ex1020 ¶213.

V. No Secondary Considerations

A. Lack of Nexus

Personalis failed to show that its “Next Personal” assay embodies the claims. POR79. Though the Board invited the “development of a full trial record” on this issue, DI35, Dr. Furneaux performed no investigation and merely

pasted in his declaration the same conclusory attorney-created chart (including the same typos) Personalis submitted with its POPR. Ex1223, 35:15-38:24, 41:16-46:14; Ex1208. *See Microsoft Corp. v. Syncloud 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. POR79-80. 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. POR80-81; *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 (“Variant Allele Fraction”). POR82-83; Ex2008.015-17. 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. POR82-83. None of the alleged “problems” equate to skepticism that the claimed invention could be achieved. Ex1225 ¶113.

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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 5,545 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'S RESPONSE** and **Exhibits 1070, 1112, 1208-1218, 1220-1223 and 1225** were served upon the following, by ELECTRONIC MAIL:

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