

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS INC.,

Petitioner,

v.

PERSONALIS, INC.

Patent Owner.

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

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

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2003	Swanton, C., “Plasma-Derived Tumor DNA Analysis at Whole-Genome Resolution,” <i>Clinical Chemistry</i> 59:1 6-8 (2013)
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2006	Mardis, E., et al., “Cancer genome sequencing: a review,” <i>Human Molecular Genetics</i> , 2009, Vol. 18, Review Issue 2
2007	Declaration of Dr. Henry Morrice Furneaux
2008	Feldman, A., et al., “Discovery of recurrent t(6;7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genomic sequencing,” <i>Blood</i> , January, 20 2011 Volume 117, Number 3
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2011	“Whole Genome Sequencing,” NIH National Cancer Institution, Genetics Dictionary, available at https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/whole-genome-sequencing (last accessed Mar. 23, 2023)
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2013	“Whole Genome Sequencing,” Centers for Disease Control and Prevention, available at https://www.cdc.gov/pulsenet/pathogens/wgs.html (last accessed Mar. 23, 2023)
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2015	Transcript of the deposition of John Quackenbush, Ph.D., taken on January 31, 2018 in <i>Guardant Health, Inc. v. Foundation Medicine, Inc.</i> , Case IPR2017-01170, IPR2017-01447, IPR2017-01448
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2031	Declaration of Henry Morrice Furneaux
2032	Declaration of John West
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2034	Declaration of Doug Zeman
2035	Declaration of Dan Norton
2036	April 2, 2012 Email from John West to Christian Haudenschild re Personalis Laboratory plans
2037	May 3, 2012 Email from John West to Mark Pratt re Comparing methods to determine SNP error rate with attachment
2038	May 3, 2012 Google calendar reminder re Dev Group Weekly Mtg
2039	May 4, 2012 Google calendar reminder re Pipeline timeline walk through
2040	May 4, 2012 Google calendar reminder re Personalis Weekly Team Meeting

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2041	May 8, 2012 Email from John West to Carol Tillis re J West Board slides with one slide revised (#8 of 14) with attachment
2042	May 8, 2012 Email from Richard Chen to John West, et al. re Final Board Slides with attachment
2043	May 8, 2012 Minutes of a Meeting of the Board of Directors of Personalis, Inc.
2044	April 24, 2012 Email from Hugo Lam to John West, et al. re Personalis Servers (with new storages)
2045	Presentation, Update from Ashley Lab
2046	January 6, 2012 Email from John West to Mark Pratt, et al., re Draft Framework for Personalis accuracy-related product development with attachment
2047	May 11, 2012 Google Calendar reminder, Personalis Weekly Team Meeting
2048	Google Calendar reminder re Accuracy review / brainstorm on May 5, 2012
2049	May 25, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
2050	May 25, 2012 Email from Carlos Bustamente to Mark Pratt re Founder meeting schedule change for this PM
2051	May 14, 2012 Email from Richard Chen to Founders, et al. re Founder Working Group Proposal with attachment

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2052	May 15, 2012 Email from Mark Pratt to John West re accuracy strategy notes with attachment
2053	May 15, 2012 Email from Scott Kirk to Richard Chen, et al., re Sprint 0 sprint backlog
2054	May 22, 2012 Email from John West to Richard Chen, et al., re Spreadsheet for 2pm discussion of Accuracy Differentiation with attachment
2055	May 22, 2012 Email from John West to Mark Pratt re My slides for meeting with Mike Snyder yesterday with attachments
2056	May 29, 2012 Email from John West to Scott Kirk re Accuracy documents to convert into project plan format with attachments
2057	June 1, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
2058	June 15, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
2059	June 22, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
2060	June 29, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
2061	June 7, 2012 Email from John West to Richard Chen re Accuracy next steps, spreadsheet to organize the discussion with attachment
2062	June 11, 2012 Email from Richard Chen to John West, et al. re updated board slides with attachment

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2063	June 11, 2012 Email from John West to Richard Chen, et al. re Draft Board slides for your comments with attachment
2064	June 12, 2012 Minutes of a Meeting of the Board of Directors of Personalis, Inc.
2065	June 17, 2012 Email from John West to Scott Kirk re Sprint 2 overview
2066	July 6, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
2067	July 13, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
2068	July 20, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
2069	July 27, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
2070	July 17, 2012 Email from Richard Chen to John West, et, al. re Final Board Slides with attachment
2071	July 18, 2012 Email from John West to Carol Tillis, et, al. re JW Board slides for printing with attachment
2072	July 18, 2012 Google calendar reminder re 2012 Personalis BOD Meeting
2073	July 18, 2012 Minutes of Meeting of The Board of Directors of Personalis, Inc

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2074	July 24, 2012 Quick Notes on Lab Sequencing From Discussion with JW
2075	August 6, 2012 Email from Mark Pratt to John West re Lab Projects with attachment
2076	August 6, 2012 Email from John West to Mark Pratt re Lab Projects
2077	August 10, 2012 Email from Richard Chen to John West re Sprint 4 pre planning =JW Questions & Input
2078	August 28, 2012 Email from Nan Leng to Hugo Lam re MiSeq 2x250 run completed over the weekend
2079	August 3, 2012 Google calendar reminder re Personalis Weekly Team Meeting
2080	August 10, 2012 Google calendar reminder re Personalis Weekly Team Meeting
2081	August 17, 2012 Google calendar reminder re Personalis Weekly Team Meeting
2082	August 20, 2012 Email from John West to Russ Altman re USE THIS ONE: my edits/slides v2 with attachment
2083	September 4, 2012 Email from Richard Chen to John West, et al. re Final Board Slides with attachment
2084	September 4, 2012 Email from John West to Carol Tillis re Personalis Board meeting preview

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2085	September 5, 2012 Google calendar reminder re 2012 Personalis BOD Meeting
2086	September 5, 2012 Email from John West to Carol Tillis and Eliane Sousa, et al. re John West's Board Slides with attachment
2087	September 5, 2012 Minutes of A Meeting of The Board of Directors of Personalis, Inc.
2088	September 7, 2012 Google calendar reminder re Personalis Monthly Team Meeting
2089	September 27, 2012 Purchase Order to Agilent
2090	October 5, 2012 Google Calendar reminder re Personalis Monthly Team Meeting
2091	October 9, 2012 Google Calendar reminder re accuracy requirements walk through
2092	October 10, 2012 Google Calendar reminder re Accuracy Bi-weekly
2093	October 24, 2012 Google Calendar reminder re Accuracy Bi-weekly
2094	October 4, 2012 Email from Scott Kirk to John West re Notes from the runs discussion
2095	October 10, 2012 Email from Scott Kirk to John West, et al., re PGS v1 Requirements draft (rev 1.10) with attachment

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2096	October 9, 2012 Email from John West to Richard Chen, et al., re Slide for accuracy requirements walkthrough meeting 3-5pm today with attachment
2097	October 12, 2012 Email from John West to Christian Haudenschild, et al., re Prioritization of Ops Sequencing projects with attachment
2098	October 19, 2012 Email from John West to Richard Chen, et al., re Applying for a patent on our idea of panels reflecting to exome / WGS
2099	November 1, 2012 Email from John West to Carol Tillis re Board slides from John West, ready to print with attachment
2100	October 31, 2012 Email from Richard Chen to John West, et al., re final board slides, ready to print with attachment
2101	November 1, 2012 Google Calendar reminder re Personalis BOD Meeting – Breakfast will be served between 8:15am and 9am
2102	November 1, 2012 Email from Shujun Luo to John West re Re: Can you please email me a copy of your slides from this afternoon? with attachment
2103	November 21, 2012 Google Calendar reminder re Accuracy Bi-weekly
2104	December 7, 2012 Google Calendar reminder re Accuracy Bi-weekly
2105	December 12, 2012 Email from Richard Chen to John West, et al., re Final board slides with attachment
2106	December 13, 2012 Email from John West to Carol Tillis re CEO Update presentation for Board meeting with attachment

Exhibit No.	Description
2107	December 14, 2012 Minutes of a Meeting of the Board of Directors of Personalis, Inc.
2108	January 16, 2013 Google Calendar reminder re Accuracy Bi-weekly
2109	January 13, 2012 Email from John West to Richard Chen re Draft of what we might offer as Laboratory Assays with attachment
2110	July 26, 2011 Minutes of a Meeting of the Board of Directors of Personalis, Inc.
2111	November 01, 2012 Minutes of a Meeting of the Board of Directors of Personalis, Inc.
2112	May 08, 2012 CEO Overview Board of Director Presentation by John West
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2119	January 14, 2013 Email from John West to Carol Tillis, et al. re Product naming decisions from staff meeting today
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2122	Dewey, et al., Phased Whole-Genome Genetic Risk in a Family Quartet Using a Major Allele Reference Sequence, PLoS Genetics, September 2011, Vol. 7(9)
2123	November 2, 2012 Google calendar reminder re Personalis monthly team meeting
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2151	Foresight Diagnostics, About, https://foresight-dx.com/about
2152	Newman, et al., An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage, HHS Public Access Author Manuscript
2153	“Personalis MRD Assays to Support UK’s TRACERx ctDNA Monitoring Study,” Precision Medicine Online, April 5, 2023
2154	“Personalis, AstraZeneca Extend Collaboration Around Residual Cancer Detection Test,” GenomeWeb, March 7, 2023

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2156	Labrousse, “MATRIX plasma-in-plasma contrived samples assessment and detection of MRD using the Personalis NeXT Personal assay,” American Society of Clinical Oncology, e15056, 2023.
2157	DeRienzo and Quackenbush et al., “Gender-Specific Molecular and Clinical Features Underlie Malignant Pleural Mesothelioma,” Cancer Research, 76:319-28, 2015
2158	Sathirapongsasuti and Quackenbush et al., “Exome sequencing-based copy-number variation and loss of heterozygosity detection: ExomeCNV,” Bioinformatics 27:2648-2654, 2011
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2160	Excerpt from Sambrook, et al., Molecular Cloning, Vol. 1, 2001
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2162	Stephens et al., Complex landscapes of somatic rearrangement in human breast cancer genomes, Nature, 462:1005-1010 (2009) supplementary figures
2163	<i>Personalis, Inc. v. Foresight Diagnostics Inc.</i> November 29, 2022 Stipulated Protective Order, Case No. 1:22-cv-01913-CNS-NRN (D. Colo.)
2164-2177	RESERVED
2178	The Chicago Manual of Style, 16th ed., University of Chicago Press, Chicago IL, 2010

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2179-2180	RESERVED
2181	Dudley and Diehn, “Detection and Diagnostic Utilization of Cellular and Cell-Free Tumor DNA,” <i>Annu. Rev. Pathol. Mech. Dis.</i> 16:199-222 (2021), Exhibit 2166 from <i>Foresight v. Personalis</i> , IPR2023-00545
2182	RESERVED
2183	Leary et al., “Detection of Chromosomal Alterations in the Circulation of Cancer Patients with Whole-Genome Sequencing,” <i>Science Translational Medicine</i> , 4:1-12 (2012)
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I. INTRODUCTION

Personalis identified numerous deficiencies with each of Grounds 1-3. The most glaring deficiency is Foresight's construction of "capture probes" as encompassing "PCR primer capture probes." Dr. Quackenbush admitted that there is no such thing as a "PCR primer capture probe," and Foresight's Reply abandons this term. Foresight failed to identify a single instance where a PCR primer is referred to as a "capture probe." Foresight correctly quoted Dr. Furneaux's explanation of Foresight's construction as being "quite simply ridiculous." Reply 10. This sentiment accurately reflects Personalis's belief that it would suffer severe prejudice if Foresight's construction of "capture probes" were adopted in the Board's final written decision.

Foresight takes an equally unreasonable position regarding the Board's construction of "whole genome sequencing" (WGS) as requiring sequencing of no higher than 50% of the genome. Foresight's construction grossly deviates from the "almost all" aspect of the Board's construction and should be rejected. Likewise, Foresight's newly-proposed construction of WGS is untimely and incorrect.

Leary's PARE assay fails to teach or suggest five limitations of claim 1. The remaining references—Ley, Chan, and Liao—fail to correct these deficiencies. Foresight has not met its burden of proving that the claims are obvious by a preponderance of evidence. Further, even "if the fact trier of the issue is left

uncertain, the party with the burden [the petitioner] loses,” which is the only reasonable outcome of this proceeding. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378-79 (Fed. Cir. 2015).

II. GROUND 1

Foresight failed to prove that Leary teaches or suggests the “capture probes” of limitation 1(c), the WGS of limitation 1(b), the “second nucleic acid sample” of limitation 1(c), the “plurality of capture probes” of limitation 1(e), and the “third sequencing assay” of limitation 1(f).

A. Limitation 1(c): capture probes

The Board preliminarily adopted Foresight’s construction of “capture probe” as encompassing “PCR primer capture probes and solution-based hybridization capture probes.” Institution Decision (“Decision”) 23-29. Foresight’s construction cannot stand.

First, Dr. Quackenbush admitted “PCR primer capture probe” does not exist in the literature. EX2018 166:10-169:1. Foresight’s Reply makes no defense of this term. Foresight’s construction must be rejected for at least this reason.

Second, the record shows that the term “capture probe” is used exclusively to refer to hybridization capture. EX1007 115-16. *Foresight fails to identify any prior art instance of “capture probe” referring to PCR primers.*

Third, Foresight’s exhibits explain that hybridization capture has a different core reaction principle than PCR primers: capture probes can *physically capture and isolate* target DNA, while PCR primers *amplify/copy*. EX1006 375; EX2031 ¶¶67-68; Patent Owner Response (“POR”) 22-23. Foresight concedes that “Wagle’s [capture probe] approach enriches *by isolating the targets and removing them* from non-targeted nucleic acids in the sample. Forshew’s [PCR primer] approach *copies* the targets and thereby enriches them over non-targeted nucleic acids.” *Foresight v. Personalis*, IPR2023-00317, Paper 1 at 48.¹

Foresight incorrectly believes that PCR primers fall within the scope of “capture probe” simply because PCR primers contain a nucleic acid binding site. Reply 11. A molecule does not qualify as a capture probe merely because it contains a nucleic acid hybridization binding site. Dr. Quackenbush admitted that “it would be hard for me to think of any technology where capture would simply occur the moment hybridization occurred.” EX2018 116:1-117:8. He also admitted that PCR and hybridization capture are “different approaches” with different “pros and cons” that need to be evaluated “depending on the needs of their experiment.” EX1225 ¶52. A POSA would not conflate PCR primers with capture probes.

¹ All emphasis supplied unless otherwise noted.

1. Personalis’s construction is consistent with the specification

The parties agree that the specification does not define the term “capture probe.” Foresight incorrectly argues that “capture probes” must encompass PCR primers because the specification does not state that “capture probes” and PCR primers are mutually exclusive, Reply 10-11, and because the claims do not explicitly require physically capturing DNA, *id.* 12. Foresight ignores that the term “capture probe” has a plain meaning in the art that includes the functional requirement that one must be able to physically capture the target DNA. POR 16-27.

Foresight incorrectly asserts that this functional requirement is inconsistent with alternative embodiments described in the specification. Reply 12-13. Such alternative embodiments are not inconsistent with Personalis’s construction. POR 17, 21-24. “The mere fact that there is an alternative embodiment disclosed in the asserted patent that is not encompassed by our claim construction does not outweigh the language of the claim.” *August Technology Corp. v. Camtek, Ltd.*, 655 F.3d 1278, 1285 (Fed. Cir. 2011). The term should be given its plain meaning. *V-Formation, Inc. v. Benetton Group SpA*, 401 F.3d 1307, 1311 (Fed. Cir. 2005).

Foresight’s objection to the term “target DNA” in Personalis’s construction, Reply 13, is baseless. Foresight and Dr. Quackenbush repeatedly refer to “target DNA” as the type of DNA captured by capture probes. Petition 13-14; EX1020

¶¶76, 105; EX1225 ¶¶100, 103. The prior art uses “target DNA” and “targeted DNA” with capture probes. EX1007 112, 115. Personalis consistently referred to “target DNA” with “capture probes” throughout this proceeding without previous objection by Foresight. POPR 22, 37.

Foresight distorts the West transcript to argue that a “pulldown probe” refers only “to a biotinylated oligonucleotide bait.” Reply 11. Mr. West explained that a pulldown probe includes any chemical modification that allows the capture probe to be pulled. EX1222 83:18-84:12.

Foresight argues that capture probes must include ubiquitous PCR primers because the record does not contain an example of a “barcoded biotinylated oligonucleotide bait.” Reply 11-12. Personalis provided an appropriate example of the claimed barcoded capture probe, which is distinct from a PCR primer. POR 24; EX2028 251; EX2031 ¶70.

Foresight confusingly argues that because the proposed construction does not exclude array-based capture, the construction must be so broad as to include PCR primers. Reply 14. The literature describes on-array hybrid capture and in-solution capture as using “capture probes,” but places PCR primers in a separate category. EX1006 Table 1; EX1007 112, 115.

2. PCR primers are not equivalent to capture probes

Foresight fails to identify a single instance of PCR primers being referred to as “capture probes.” Instead, Foresight identifies three instances where the words “PCR” and “capture” were used in the same sentence. Reply 14. Two instances come from the same laboratory—the author of EX1216 was a co-author of Forshew (EX1030). EX2188 16:1-17:14. More importantly, EX1216 places the word “capture” in scare quotes, which indicates that “capture” was used in a nonstandard manner. EX2178 7-55 (“scare quotes”); EX2188 32:9-33:8, 49:1-50:9 (“his definition with the scare quotes that you referred to earlier are a way of alerting us to the fact that this is a broad definition”). These isolated, nonstandard uses of “capture” in the same sentence as “PCR” fail to establish that a POSA would have viewed PCR primers as “capture probes.”

Foresight improperly truncates a portion of Mr. West’s transcript to assert that PCR primers qualify as “capture probes,” which is a noun. Reply 14. Foresight slipped the verb “capture” into the tail end of a question. Mr. West appropriately clarified under oath on redirect that he did not hear the word “capture” during questioning. EX1222 170:15-171:10. Redirect examination is appropriate “to clarify facts that were not made sufficiently clear” during cross examination. *Taskett v. Dentlinger*, 344 F.3d 1337, 1343 (Fed. Cir. 2003). Foresight failed to directly ask

Mr. West if he considers PCR primers to be “capture probes” during cross or re-cross examination.

3. Leary’s PCR primers are not capture probes

A POSA would not confuse Leary’s PCR primers with capture probes. Foresight has no reply to Dr. Quackenbush’s articles that consistently recognize capture probes and PCR primers as different, non-overlapping types of nucleic acids. POR 23 (quoting EX2158, EX2157); EX2188 116:7-118:19.

Dr. Quackenbush admitted that PCR primers were preferable for Sanger sequencing, EX2188 121:10-13, which was performed on Leary’s amplicons, EX1002 3, 6. He admitted that if a POSA were to use capture probes for Sanger sequencing, they would additionally “have to do targeted PCR on whatever was captured to allow the Sanger sequencing reactions.... So it would be an additional step, after which one would have to do targeted PCR with additional primers.” EX2188 123:22-124:16; *id.* 120:1-123:21. There was no motivation to complicate Leary’s workflow with capture probes because a POSA would still need to perform PCR. Further, Leary uses PCR as its detection method (not as an enrichment technique for subsequent sequencing), POR 30-31, and Foresight has no reply regarding how Leary’s workflow could be modified to use capture probes as a detection method.

Foresight argues that Leary's PCR primers must be capture probes because amplicons can be physically isolated in subsequent assay procedures. Reply 15-16. Foresight fails to acknowledge that Leary's PCR primers operate via a fundamentally different "core reaction principle" from capture probes. EX1006 375. PCR can only copy DNA to preserve sequence information—it cannot physically isolate the target DNA molecules. POR 26; EX2031 ¶¶71-74. While PCR primers and capture probes are both "enrichment" techniques, Foresight has no reply to:

- Its own exhibit's explanation that PCR and capture probes have different "operational characteristics" that makes them "vary in their suitability for different fields" and give "very divergent" results. *Id.* 375, 383; POR 24-25.
- Its own exhibits and expert's repeated explanations that a POSA would evaluate seven parameters/metrics to weigh pros and cons before selecting either PCR primers or capture probes for any given experiment. POR 25-26, 28-29; EX1225 ¶52; EX2188 51:19-54:3, 64:12-65:15, 70:13-71:8, 105:19-108:1.
- Its own Founder's admission that "hybrid capture-based workflows" are limited because they "typically have longer turnaround times, since the target enrichment process often takes days (instead of hours with PCR), and are more expensive, since they involve sequencing a larger genomic space," which "may provide diminishing additional value." EX2181 203.

These many distinctions between PCR primers and capture probes are unrebutted by Foresight, and Foresight has failed to prove that Leary's PCR primers meet the claimed capture probes.

B. Limitation 1(b): WGS

Leary (EX1002) does not refer to its PARE method as WGS. If the authors had considered their PARE method to be WGS, they would have so stated. It was not until two years later that the Leary authors published their first article describing a "whole-genome sequencing" method. EX2183 1. The 2012 article switched to Illumina's sequencing-by-synthesis paired-end approach to achieve WGS, EX2183 8, which is different than the Applied Biosystem SOLiD sequencing-by-ligation mate-pair approach used by Leary. EX1002 5; EX2018 216:3-19.

Foresight's Founders and exhibits excluded Leary from their lists of WGS references, POR 9, which correctly reflects the POSA's understanding that Leary's PARE is not WGS.

1. Claim construction of WGS

The Board construed WGS as "a non-targeted approach to sequencing all or almost all of a genome" based on the intrinsic record. Decision 19-23.

Foresight asserts that no construction of WGS is required because it believes a POSA would have regarded Leary's PARE approach to be WGS. Reply 1, 5. Foresight's position is illogical, contrary to the law, and the epitome of hindsight.

The first step of a validity determination “involves the proper interpretation of the claims,” and only thereafter does it proceed to the second step of “determining whether the limitations of the claims as properly interpreted are met by the prior art.”

TI Group Automotive Sys. v. VDO N.Am., 375 F.3d 1126, 1139 (Fed. Cir. 2004).

a) Sequence coverage

Foresight attempts to reduce sequence coverage to a “straightforward formula” of “X basepairs / Y basepairs.” Reply 2-3. This equation cannot be used unless the X basepairs are randomly distributed across the entire genome in a non-targeted manner. EX2022 121 (coverage requires “the assumption that reads are randomly distributed across an idealized genome”); EX2188 194:2-8, 178:11-179:10; EX1223 97:21-99:3. For example, if the X basepairs were located only on chromosome 6, then dividing by 2.86 GBP as the degapped genome would not provide a sequence coverage across the entire human genome. EX2188 188:8-189:14.

b) “Almost all”

Foresight asked Mr. West and Dr. Furneaux to provide a threshold cutoff for “almost all,” and they testified that 90% sequence coverage was the accepted cutoff at the time of the invention. EX1222 42:25-44:10; EX1223 97:23-98:5. Their testimony is well supported. EX2122 2 (“We used the Illumina GAII sequencing platform to sequence genomic DNA from peripheral blood monocytes from four

individuals in this nuclear family, providing 39.3x average coverage of 92% of known chromosomal positions in all four family members (Figure S1).”); EX1012 67 (“We performed 98 full runs on the Illumina Genome Analyser to achieve the targeted level of 90% diploid coverage as determined by coverage of the high-quality SNP set.”). Their testimony is consistent with the Board’s construction that “whole” in WGS for purposes of the ’394 patent requires sequencing “all or almost all of the genome” in accordance with the specification. Decision 19-23; EX2031 ¶52.

Foresight, however, takes an extreme position that “the bar for ‘almost all’” must be “no higher than 50%.” Reply 3-5. Foresight fails to point to any intrinsic evidence supporting its position. Foresight cites a variety of extrinsic evidence that, at best, confirms Dr. Quackenbush’s testimony that the term WGS has “taken on many different flavors of meaning,” EX2018 155:15-21, and has been used in different ways by different individuals in different contexts, *id.* 157:9-22, 161:21-162:1.

The specification provides the appropriate intrinsic evidence for construction of WGS. Decision 19-23; *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (en banc). The use of certain terms in “different patents, in entirely different patent families, with different specifications” does not govern construction. *SIPCO, LLC v. Emerson Elec. Co.*, 980 F.3d 865, 870 n2 (Fed. Cir. 2020). Foresight’s

position grossly deviates from the intrinsic evidence because it fails to give meaning to the term “whole” in WGS.

c) Foresight’s construction should be rejected

Foresight refused to construe WGS during the preliminary phase, and now belatedly asserts that WGS should be interpreted as “a non-targeted approach to generating sequencing reads and mapping those reads back to a reference genome (rather than a genome subset).” Reply 5. First, Foresight fails to cite any intrinsic evidence supporting its construction. Second, Foresight’s construction is inappropriate because it evades the significance of “almost all” that gives meaning to “whole” in WGS. Third, it raises new questions, such as how to interpret “a reference genome” versus “a genome subset.”

2. Leary does not teach WGS

Foresight has not proven that Leary’s PARE approach is (a) non-targeted and (b) sequences almost all of the genome.

a) Leary’s targeted nature

Leary’s PARE approach intentionally sequences only the 25-bp mate-paired tags at the ends of the original fragments, while the 1,400 bases in the middle of the fragments are intentionally discarded. EX1002 1; EX2031 ¶¶93-96. This approach was selected to target only “rearrangement” mutations rather than, e.g., “copy number alterations (duplications, amplifications, and deletions), inversions, insertions,” EX1002 1, or “single-base alterations,” *id.* 5. Dr. Quackenbush

correctly admitted that Leary has “a targeted nature, and thus may provide only a partial glimpse of the tumor genome.” EX1020 ¶227. Foresight has not proven that Leary’s PARE approach is non-targeted.

b) Leary does not sequence almost all of the genome

Leary’s PARE approach only yields “high *physical* coverage of breakpoints provided by the ~40 million mate-paired sequences per sample.” EX1002 1. *Physical* coverage is not the same as *sequence* coverage. EX2031 ¶¶14, 102; EX2188 164:10-165:16. Leary does not attempt to sequence all or almost all of the genome because PARE does not sequence the middle 1,400 bases from every original DNA fragment. Leary deliberately omits 1,400 bases from every fragment *because* they did not want to sequence anything close to almost all of the genome—that is the entire benefit of Leary’s approach, as admitted by Dr. Quackenbush. EX2188 206:19-208:10 (explaining that sequencing all the bases would require “28 times more sequencing”); EX2018 245:1-11 (Leary “is a very cost-effective strategy” because it didn’t “hav[e] to sequence every base”).

Foresight takes an intermediate snippet of Dr. Furneaux’s analysis of Leary out of context to allege that he was “emphatic that sequencing 91% of the 3.2 billion base-pairs will fall substantially short of sequencing all or almost all of the genome,” Reply 2, and that “Leary’s sequence coverage was only 0.9x,” *id.* 6. Dr. Furneaux’s complete analysis included an explanation that Leary’s mate-pair tags are

overlapping, EX2031 ¶¶98-99, which means that “in reality, the mate paired analysis for Co84 normal covers, in a best-case scenario, only about 1.71 Gb” of the genome. *Id.* ¶100. Dr. Quackenbush admitted that Leary’s mate-pairs overlapped, EX2188 198:17-199:3, and that his opinions failed to account for that overlap, *id.* 202:20-203:2. Dr. Furneaux performed the appropriate overlap analysis. EX2031 ¶100. The parties agree that this overlap amounts to sequencing only 60% of the genome using 2.86 Gbp as the denominator in Foresight’s “sequence coverage” equation, or just 53% using 3.2 Gbp as the denominator. EX1225 ¶66. Foresight failed to prove that Leary’s best-case 53-60% sequence coverage meets the claimed WGS.

3. Leary does not suggest WGS

Foresight failed to prove that a POSA would have been motivated to transform Leary’s PARE approach to a WGS approach for several reasons discussed below.

a) No motivation to increase coverage/depth

A POSA would need to modify Leary to sequence 64 million *non-overlapping* mate-pairs to cover all the base pairs in the human genome. POR 7; EX2031 ¶96. Foresight mistakenly believes it proved obviousness by simply showing that such a modification was not “unfeasible, impractical, or beyond the level of skill in the art.” Reply 9. Foresight’s supposed proof merely goes to whether a POSA *could* have modified Leary’s assay to be WGS, not whether a POSA *would* have done so. “[O]bviousness concerns whether a skilled artisan not only *could*

have made but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.” *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (emphases in original).

As discussed above, Dr. Quackenbush admitted that the benefit provided by Leary’s PARE approach was to provide high *physical* coverage without having to sequence the middle 1,400 bases from each DNA fragment. A POSA would not have discarded this advantage to instead sequence all or almost all of the bases because it would defeat the very aspect of Leary’s PARE approach that made it beneficial for detecting rearrangements.

Foresight generically asserts that a POSA would modify Leary to sequence the discarded 1,400 bases from each fragment to adjust the sequence coverage “as needed,” Reply 7, or “according to the application,” *id.* 8. Foresight fails to specify what level of adjustment would convert Leary’s PARE approach to WGS. Leary explains that its approach was already “expensive for general clinical use” as “a consequence of the high physical coverage and the inefficiencies associated with stringent mapping of 25-bp sequence data to the human genome.” EX1002 5. Foresight’s proposed modification would make Leary’s assay even more expensive and inefficient by requiring more mapping of sequence data, which would defeat the advantage provided by Leary’s omission of 1,400 bases from each fragment. Here, “[a]n inference of nonobviousness is especially strong [because] the prior art’s

teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements” of Leary’s PARE and WGS. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009).

b) Data burden and cost constraints

A POSA would not have modified Leary’s PARE approach to use WGS based on the data burden and cost constraints imposed by WGS. POR 10-14. Foresight mistakenly believes that it need not provide a rationale why a POSA would take on these disadvantages so long as WGS was a “design choice” that was “a suitable option from which the prior art did not teach away.” Reply 7. Merely being “a design choice does not make it obvious.” *Polaris Indus. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1069 n.4 (Fed. Cir. 2018). Foresight must do “more than merely show that the prior art does not preclude” altering the prior art to arrive at the claimed invention and must instead “affirmatively demonstrate that a skilled artisan would have been motivated to” arrive at the invention. *Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1380-81 (Fed. Cir. 2018).

Foresight cannot prove obviousness by ignoring the real-world data burden and cost constraints associated with WGS that pervade its references. “[I]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of

other parts necessary to the full appreciation of what such reference fairly suggests” to a POSA. *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986). Foresight cannot refuse to engage on these issues because “[t]he benefits, ***both lost and gained***, should be weighed against one another.” *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019) (emphasis in original). Here, the inventors persisted against known disadvantages to combine WGS with capture probes, which provides significant evidence of nonobviousness that cannot be ignored. *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 958 (Fed. Cir. 1997).

C. Limitation 1(c): second nucleic acid sample

Foresight does not dispute that it relies on the same tumor sample from Leary to supposedly meet the “first nucleic acid sample” of limitation 1(a) and the “second nucleic acid sample” of limitation 1(c)(i). Reply 9-10. Instead, Foresight proffers an untimely new theory that “different nucleic acid samples ***can be*** taken from the same tumor sample.” *Id.* 10. This theory fails to prove obviousness because “[a]n assertion that something ***could*** be done does not articulate a reason why something ***would*** be done” and “raises a specter of impermissible hindsight bias.” *Nautilus Hyosung Inc. v. Diebold, Inc.*, IPR2016-00633, Paper 9 at 21 (PTAB 2016). Foresight’s invocation of limitation 1(d), Reply 10, does not save the Petition because claim 1 still requires first and second nucleic acid samples.

D. Limitation 1(e): plurality of capture probes

Leary's PCR primers are not "capture probes," and Leary fails to teach limitation 1(e) for at least this reason.

E. Limitation 1(f): third sequencing assay

Foresight argues that a POSA would have conducted an undisclosed re-verification of Leary's PCR products to obtain "the most complete and accurate information available" and arrive at the third sequencing assay of limitation 1(f). Reply 16. Leary, however, already had the complete and accurate sequence of Leary's PCR products from the verification sequencing Foresight relied upon to supposedly meet limitation 1(d). Foresight fails to articulate how sequencing Leary's PCR product was incomplete or inaccurate such that a POSA would conduct additional re-verification sequencing. Without reason to believe that Leary's PCR product sequencing was incomplete or inaccurate, there was no such motivation. Foresight's argument that someone *could* re-sequence the PCR products, Reply 17, does not provide any reason why they *would* have done so. This is especially true given that Leary's workflow was already "difficult to implement on a routine basis." EX1030 10.

F. Claims 17 and 18

Foresight misrepresents Meyerson as exclusively teaching 30x coverage. Reply 8. Meyerson also teaches "less than 30-fold coverage." EX1031 687. Foresight fails to provide a reasoned analysis why a POSA would have modified

Leary's 18x *physical* coverage to 30x *sequence* coverage when Dr. Quackenbush explained that selecting sequence coverage "depends on your application" and that 10x and 18x can be sufficient. EX2018 95:6-97:4. Further, Leary's *physical* coverage was an advantage of its PARE method. Performing WGS *sequence* coverage at 30x would discard the advantage of Leary's method. *Supra* Section II.B.3.a.

III. GROUND 2

Leary and Ley suffer the same fatal flaw—they disclose PCR primers that are not the "capture probes" required by limitations 1(c) and 1(e). Ground 2 fails for this reason.

Ley took on the cost and data burden of performing WGS to discover single-base alterations. EX1002 6-7. Two years later, Leary designed its new PARE approach that omitted 1,400 bases from each fragment to target structural chromosomal rearrangements instead of single-base alterations. *Supra* Section II.B.3.a. As discussed, a POSA would not discard Leary's PARE approach for the cost and data burden associated with Ley's WGS because doing so would defeat the advantage provided by Leary's approach. *Id.*; *DePuy Spine*, 567 F.3d at 1326.

Foresight vaguely asserts that Ley discloses "several advantages" of WGS, but fails to articulate how the unspecified advantages would motivate a POSA to change Leary's PARE assay. Reply 17. Foresight tries to sidestep the data burden

and cost constraints of WGS by asserting that there was a “rapid pace of advancement in sequencing technology.” Reply 18. Post-filing references by Foresight’s expert and Founders admit these issues remained years after the priority date. POR 11-14. Those admissions remain unrebutted.

Third, Foresight vaguely alleges that combining Leary and Ley “form a third composition” for “the same purpose.” Reply 18. Leary and Ley have different purposes—detecting chromosomal rearrangements versus single-nucleotide variants. Foresight asserts that it need not show how Leary and Ley are “bodily incorporated.” *Id.* However, “[a] petitioner may not rely on a vague, generic, and/or meandering petition.... it is the petitioner’s burden to present a clear argument.” *Netflix, Inc. v. DivX, LLC*, 84 F.4th 1371, 1377 (Fed. Cir. 2023); 35 U.S.C. 312(a)(3). Foresight failed to present a clear position on its Leary/Ley combination. Leary fails to teach limitations 1(b), 1(c), 1(e), and 1(f). POR 34. Foresight fails to explain how Ley rectifies these many deficiencies to arrive at the claimed invention.

IV. GROUND 3

“In an IPR, the petitioner bears the ultimate burden of persuasion on invalidity, which never shifts to the patent owner.” *Medtronic, Inc. v. Teleflex Innovations SARL*, 68 F.4th 1298, 1303 (Fed. Cir. 2023). When a patent owner antedates a reference, “the patent owner takes on a temporary burden of production.” *Id.* “Once that burden is met, the burden shifts back to the petitioner.” *Id.*

Personalis produced overwhelming evidence of conception by May 8, 2012 and diligence through filing its provisional application, which was corroborated by two witnesses and over 80 exhibits. POR 38-76. Foresight fails to rebut the compelling evidence of prior invention, and therefore fails to establish that Chan is prior art.

A. Antedation

1. Inventorship

Foresight speculates that it is “implausible” that Dr. Bartha participated in conception by May 8, 2012. Reply 20. Mr. West explained that Dr. Bartha joined Personalis on May 1 and “was immediately tasked with working on the Accuracy Program under Mark Pratt.” EX2032 ¶34. Mr. West’s testimony is undisputed, and it is supported. EX2042 Slides 3, 27. Foresight’s unsupported speculation does not carry its burden. *Medtronic*, 68 F.4th at 1303.

Foresight seeks a broad rule against antedation because Ms. Luo was not hired until June 18, 2012. However, “[t]he determination of whether a person is a joint inventor is fact specific, and no bright-line standard will suffice in every case.” *Vanderbilt Univ. v. ICOS Corp.*, 601 F.3d 1297, 1308 (Fed. Cir. 2010). “***All inventors, even those who contribute to only one claim or one aspect of one claim of a patent, must be listed on that patent.***” *Vapor Point LLC v. Moorhead*, 832 F.3d 1343, 1348-49 (Fed. Cir. 2016).

As of May 8, 2012, all of the inventors (minus Ms. Luo) had conceived of claim 3. EX2032 ¶¶264-266. In August of 2012, Ms. Luo improved the “variable length tandem repeat” aspect of claim 3 by “identif[ying] a DNA sequencing chemistry which could provide enough reads in regions of certain difficult VNTR’s (variable length tandem repeats) that the lobSTR algorithm could correctly call them.” *Id.* ¶369; EX2075 1, 7, 27. Thus, claim 3 was conceived by May 8, and further improved in August 2012. Ms. Luo’s contribution in August makes her a joint inventor of the ’394 patent. *Ethicon, Inc. v. U.S. Surgical Corp.*, 937 F.Supp. 1015, 1036 (D.Conn. 1996) (“If a prior invention of one inventor is modified as a result of the collaborative effort of joint inventors, the modified invention may become a joint invention.”), *aff’d* 135 F.3d 1456 (Fed. Cir. 1998).

2. NeXT Personal

Foresight irrelevantly disputes the inventors’ 2012 conception based on NeXT Personal being launched in 2021. Reply 21. Conception does not require a commercial product. *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994) (“courts have not required commercial perfection nor absolute replication of the circumstances of the invention’s ultimate use”).

Foresight argues that NeXT Personal cannot embody the claims of multiple patents. Reply 21. Foresight is wrong. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 526 F. Supp.2d 162, 176 (D.Mass. 2007) (“The defendants argue that

because the plaintiffs' products reflect other patents, in addition to the '678 patent, the plaintiffs cannot prove that these devices' commercial success is attributable to the '678 patent. The Court disagrees."), *aff'd-in-part, rev'd-in-part, and rem'd on other grounds* 567 F.3d 1314 (Fed. Cir. 2009). Expert testimony demonstrates that the NeXT Personal assay embodies the claims of each patent. Thus, nexus is presumed, which "cannot be rebutted with mere argument." *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000).

3. Limitations 1(c)-1(f)

Foresight submits immaterial testimony about what it believes *a POSA* would have understood by reviewing Slide 5 of EX2112. Reply 22-23. "For conception, we look not to whether one skilled in the art could have thought of the invention, but whether the alleged inventors actually had in their minds the required definite and permanent idea." *Burroughs Welcome Co. v. Novopharm, Inc.*, 40 F.3d 1223, 1232 (Fed. Cir. 1994). The presentation "is not itself a conception, for conception occurs in the inventors' minds, not on paper." *Id.* 1230. The presentation corroborates Mr. West's testimony. *Id.* More importantly, Mr. West's testimony regarding capture probes for limitation 1(c) is corroborated by several exhibits. *See* EX2032 ¶¶223-246 (citing EX2112, Slides 4, 5; EX2036; EX2109).

Foresight incorrectly states there is no corroboration for assaying the same individual at different time points for limitations 1(d)-1(g). Reply 24. Mr. West's

testimony is corroborated. EX2032 ¶¶249, 252-254, 258 (citing EX2109 Slide 3; EX2112 Slides 3, 5, 13; EX2036). Further, corroboration is evaluated under “the rule of reason,” which does not require “that every point of a reduction to practice be corroborated by evidence having a source totally independent of the inventor.” *Fleming v. Escort Inc.*, 774 F.3d 1371, 1377 (Fed. Cir. 2014).

4. Constructive reduction to practice

Foresight incorrectly cites *Bigham* (an interference case) to assert that Personalis must prove written description. Reply 25. In an IPR, antedation requires “(1) conception prior to the filing date of the asserted reference and (2) reasonably continuous diligence” through the constructive reduction to practice. *Medtronic, Inc. v. Teleflex Innovations SARL*, 86 F.4th 902, 906 (Fed. Cir. 2023). Personalis has met those two requirements.

Foresight untimely asserts—without any explanation—that there is no written description for limitations 1(c)-1(d) in the provisional application. Reply 25. Foresight and Dr. Quackenbush previously conceded the January 2013 provisional priority date. Petition 7, 43, 59; EX1020 ¶¶31, 34-35, 37, 151-152, 223. Foresight cannot reverse course on Reply, and its conclusory assertions cannot carry its burden. Regardless, limitations 1(c)-1(d) are supported by EX2113 ¶¶[0008], [0042], [0049], [0108]-[0109], [0127], [0324].

B. Leary/Chan/Liao

Leary/Chan/Liao fail to render obvious limitations 1(b), 1(c), 1(e), and 1(f).

1. Limitation 1(b)

Personalis explained that Chan’s *plasma* sample does not constitute WGS because it lacks the whole genome, which Foresight does not dispute. POR 77. Foresight now argues that Chan performs WGS on a *tissue* sample. Reply 25. Foresight cannot change its obviousness theory on Reply. *Henny Penny*, 938 F.3d at 1330-31. Foresight still fails to establish that a POSA would discard Leary’s omission of 1,400 bases from every fragment—which is the aspect that made Leary’s approach beneficial for detecting rearrangements—for WGS in view of the unrebutted data burden and cost issues discussed above.

2. Limitation 1(c)

Foresight argues that it was obvious to modify Leary’s PCR approach to use capture probes because such probes “could be used to order a kit from a vendor.” Reply 26. Even if a POSA *could* have ordered a kit from a vendor, Foresight has not established that a POSA *would* have been so motivated. PCR primers and capture probes have different core reaction principles, and different pros and cons, that must be evaluated according to the unique needs of each experiment. *Supra* Section II.A. Foresight asserts that the seven metrics/parameters are “concocted-for-this-proceeding.” Reply 26. But these metrics/parameters are set forth in Foresight’s exhibits. POR 24-31. Foresight fails to articulate why a POSA would

modify Leary's PCR-based workflow to instead use capture probes, especially in view of Leary's detection mechanism requiring PCR.

3. Limitation 1(e)

Foresight does not dispute that it mistakenly alleged that Chan suggests "tuning the capture technique." POR 80.

4. Limitation 1(f)

Foresight relies on Ground 1 for limitation 1(f). Reply 27. Ground 3 does not cure the deficiencies of Ground 1 regarding 1(f).

V. OBJECTIVE INDICIA OF NONOBVIOUSNESS

A. Nexus

Dr. Furneaux provided a detailed explanation of nexus that confirmed the pre-institution evidence submitted in this case, which Foresight does not substantively address. Reply 27. Nexus is therefore un rebutted. *Brown & Williamson*, 229 F.3d at 1130.

B. Industry Praise

Foresight asserts that the Scientist's praise of NeXT Personal is an "overstatement." Reply 27. The recognition is clear from EX2001. Foresight's argument that the industry praise lacks nexus, Reply 28, fails to rebut Personalis's showing of nexus. POR 81; EX2031 ¶178.

C. Skepticism

Foresight provides no substantive response to the real-world evidence of skepticism.

Respectfully submitted,

WEIL, GOTSHAL & MANGES LLP

Dated: February 13, 2024

/Derek C. Walter/

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), Counsel for Patent Owner Personalis, Inc. hereby certifies that this document complies with the type-volume limitation of 37 C.F.R. § 42.24(b). This document contains approximately 5,588 words, including any statement of material facts to be admitted or denied in support, and excluding the table of contents, table of authorities, mandatory notices under § 42.8, exhibit list, certificate of service or word count, or appendix of exhibits or claim listing.

Dated: February 13, 2024

/Derek C. Walter/

Derek C. Walter,
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CERTIFICATE OF SERVICE

I hereby certify that, pursuant to 37 C.F.R. § 42.6(e) and with the agreement of counsel for Petitioner, a true and correct copy of **PATENT OWNER'S SUR-REPLY TO PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE AND EXHIBITS 2178, 2181, 2183, AND 2188** is being served electronically on February 13, 2024, to the e-mail addresses shown below:

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