

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 RESPONSE

TABLE OF CONTENTS

	Page No.
I. INTRODUCTION	1
II. OVERVIEW OF THE '394 PATENT	3
III. GROUND 1: NONOBVIOUSNESS OVER LEARY	5
A. Claim 1	5
1. Limitation 1(b)	5
a) Leary does not teach WGS	6
b) Leary does not suggest WGS	10
(1) Data burden	10
(2) WGS is an order of magnitude more expensive than targeted approaches	13
(3) Simply increasing Leary's coverage depth would not convert Leary's PARE to WGS	14
2. The "second nucleic acid sample" of limitation 1(c)(i)	15
3. The "capture probes" of limitation 1(c)(i)-(ii)	16
a) Claim construction of "capture probes"	16
(1) The preliminary construction does not comply with the plain meaning of "capture probes"	18
(2) The specification does not contradict the plain meaning of "capture probe"	21

TABLE OF CONTENTS
(*cont'd*)

	Page No.
(3) Foresight incorrectly treats PCR primers as being interchangeable with capture probes	24
(1) Conclusion regarding claim construction.....	27
b) Leary does not teach or suggest “capture probes”	27
4. The “plurality of capture probes” of limitation 1(e).....	31
5. The “third sequencing assay” of limitation 1(f)	33
6. No motivation to modify Leary	34
B. Claims 17 and 18.....	34
C. Claim 19	35
IV. GROUND 2: NONOBVIOUSESS OVER LEARY AND LEY	36
V. GROUND 3: NONOBVIOUSESS OVER LEARY, CHAN, AND LIAO	38
A. Chan is not prior art.....	39
1. Conception	40
a) Genesis of the Accuracy Program	40
b) The Accuracy Program: November 2011 through May 8, 2012	42
c) Summary of Mr. West’s Presentation	43
d) The Accuracy Program and the '394 patent claims	45

TABLE OF CONTENTS
(cont'd)

	Page No.
(1) Claim 1 - Preamble.....	45
(2) Limitations 1(a)-(b)	47
(3) Limitation 1(c).....	48
(4) Limitation 1(d)	50
(5) Limitations 1(e)-(f).....	51
(6) Limitation 1(g)	52
e) Claim 2.....	53
f) Claims 3-4.....	53
g) Claim 5.....	54
h) Claim 6.....	55
i) Claim 7.....	55
j) Claim 8.....	55
k) Claim 9.....	55
l) Claim 10.....	56
m) Claim 11.....	56
n) Claim 12.....	57
o) Claim 13.....	58
p) Claim 14.....	58
q) Claim 15.....	59

TABLE OF CONTENTS
(cont'd)

	Page No.
r) Claim 16.....	60
s) Claims 17-18.....	60
t) Claim 19.....	60
u) Conclusion	61
2. Diligence	61
a) May	61
b) June	64
c) July.....	68
d) August.....	69
e) September	70
f) October	70
g) November	71
h) December	75
i) January	75
B. Chan and Liao do not cure the deficiencies of Leary	76
1. Limitation 1(b)	77
2. Limitation 1(c)	78
3. Limitations 1(e) and 1(f).....	80
VI. OBJECTIVE INDICIA OF NONOBVIOUSNESS	81

TABLE OF CONTENTS
(cont'd)

	Page No.
A. Nexus.....	81
B. Industry Praise.....	81
C. Skepticism	83
VII. CONCLUSION	84

TABLE OF AUTHORITIES

	Page No(s).
<i>Arctic Cat Inc. v. Bombardier Recreational Prod. Inc.</i> , 876 F.3d 1350 (Fed. Cir. 2017)	81
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TABLE OF AUTHORITIES
(cont'd)

Page No(s).

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2009	Murphy, S., et al., “Mate Pair Sequencing of Whole-Genome-Amplified DNA Following Laser Capture Microdissection of Prostate Cancer,” DNA Research 19, 395–406, (2012)

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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)
2012	Embodying Product Claim Chart for U.S. Patent No. 11,384,394
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
2033	Declaration of Jonathan MacQuitty
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
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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

Exhibit No.	Description
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
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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
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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
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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

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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
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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
2113	U.S. Provisional Patent Application No. 61/753,828
2114	January 19, 2010 Illumina Individual Genome Sequence Report
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2153	“Personalis MRD Assays to Support UK’s TRACERx ctDNA Monitoring Study,” Precision Medicine Online, April 5, 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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Patent Owner Personalis submits this Response to Petitioner Foresight Diagnostic Inc. (“Foresight”) regarding U.S. 11,384,394 (“the ‘394 patent”).

I. INTRODUCTION

Personalis is recognized as an undisputed leader in developing innovative personalized genomic assays. The ‘394 patent claims recite a novel and nonobvious process that uses whole genome sequencing to query the entire genome of an individual coupled with a subsequent targeted sequencing assay using capture probes to collect nucleic acids associated with particular polymorphisms that may be associated with, for instance, cancer. The targeted assay is then repeated using capture probes on an additional sample from the patient at an additional time point. Personalis’ NeXT Personal[®] detection and monitoring assay practices the ‘394 patent and has been hailed by *The Scientist* magazine as the top scientific innovation in 2022. EX2001 1-2.

Personalis’ successful approach has been adopted by Foresight. EX1010 ¶¶52-57; EX1011. Through this proceeding, Foresight seeks to reap the benefits of Personalis’ claimed invention before it is dedicated to the public.

Foresight challenges the claimed invention as being obvious over the Leary reference. Leary, however, discloses a targeted PARE assay that is nothing like the claimed invention because it fails to teach or suggest at least five limitations of claim 1:

- the “whole genome sequencing” (WGS) required by limitation 1(b),
- the “second nucleic acid sample” required by limitation 1(c),
- the “capture probes” required by limitation 1(c),
- the “plurality of capture probes” required by limitation 1(e), and
- the “third sequencing assay” required by limitation 1(f).

Foresight asserts that it would have been obvious to make a wholesale redesign of Leary to arrive at the claimed invention, but its assertions are repeatedly and consistently contradicted by its own exhibits, statements by its own founders,¹ and its own expert witness (Dr. Quackenbush). The Board should reject Foresight’s petition-inspired arguments that are overwhelmingly at odds with the rest of the record.

Foresight’s remaining references—Ley, Chan, and Liao—fail to correct the numerous deficiencies with Leary. For example, Ley and Liao teach a person of ordinary skill in the art (POSA) that transforming Leary’s targeted PARE assay into a WGS assay would be undesirable due to the data burden and economic challenges associated with WGS, particularly at the time of the claimed invention. Nothing in

¹ Foresight was founded by Ash Alizadeh, Maximilian Diehn, David Kurtz, and Jake Chabon. EX2151.

Chan fixes any of these references at least because Chan is not prior art to the '394 patent.

The patentability of Personalis' claims is further confirmed by objective indicia of nonobviousness including industry praise and skepticism in the field. After considering all of the relevant evidence, there is only one reasonable conclusion—Claims 1-19 of the '394 patent would not have been obvious at the time of the invention.

II. OVERVIEW OF THE '394 PATENT

The '394 patent relates to methods for processing and data analysis of nucleic acid samples. EX1001 Abstract. Claim 1—the only independent claim—recites seven steps:

1. A method for analyzing nucleic acid samples isolated from an individual, comprising:
 - (a) generating a first subset of nucleic acid molecules from a first nucleic acid sample obtained from said individual;
 - (b) conducting a first sequencing assay on said first subset of nucleic acid molecules to yield a first result comprising a first nucleic acid sequence wherein said first sequencing assay comprises whole genome sequencing;
 - (c) generating a second subset of nucleic acid molecules from a second nucleic acid sample of said individual by contacting said second nucleic acid sample with a plurality of capture probes, wherein said plurality of capture probes hybridize to one or more polymorphisms which are

based on or extracted from one or more databases of polymorphisms, observed in a population of one or more samples, or a combination thereof, wherein said first sample or said second sample is obtained from said subject at a first time point;

(d) conducting a second sequencing assay on said second subset of nucleic acid molecules to yield a second result comprising a second nucleic acid sequence;

(e) using said plurality of capture probes to generate an additional subset of nucleic acid molecules from an additional nucleic acid sample isolated from an additional sample obtained from said subject at an additional time point different from said first time point;

(f) conducting a third sequencing assay on said additional subset of nucleic acid molecules from said additional nucleic acid sample to yield a third result comprising a third nucleic acid sequence; and

(g) generating a biomedical report that includes biomedical information of said subject, which biomedical information identifies the presence or absence of said one or more polymorphisms identified by said second result or said third result.

The '394 Patent explains that prior art methods based on whole genome sequencing alone were not only costly, but could “fail to capture many biomedically important variants.” EX1001 1:23-34. The inventors of the '394 Patent overcame these problems by coupling whole genome sequencing with a subsequent targeted sequencing assay according to the claimed method. The inventors of the '394 Patent developed an enrichment pulldown process and customized sample preparation

methods that use sequencing protocols to specifically improve performance over the prior art.

III. GROUND 1: NONOBVIOUSNESS OVER LEARY

Leary does not render obvious independent claim 1, and therefore fails to render obvious any of dependent claims 2-19. Leary further fails to render obvious dependent claims 17, 18 and 19 for additional reasons discussed herein.

A. Claim 1

Obviousness requires proof “that all claimed limitations are disclosed in the prior art.” *Par Pharms., Inc. v. Twi Pharms., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014). Leary fails to render claim 1 obvious because it does not teach or suggest at least five limitations of the claim:

- the “whole genome sequencing” (WGS) required by limitation 1(b),
- the “second nucleic acid sample” required by limitation 1(c),
- the “capture probes” required by limitation 1(c),
- the “plurality of capture probes” required by limitation 1(e), and
- the “third sequencing assay” required by limitation 1(f).

1. Limitation 1(b)

Leary does not teach or suggest the “whole genome sequencing” (WGS) required by limitation 1(b). The Board construed WGS to mean “a non-targeted approach to sequencing all or almost all of a genome.” Institution Decision

(“Decision”) 19-23. The Board found it “pertinent that Leary’s PARE studies... *presumably* resulted in non-targeted, randomly-distributed sequencing reads throughout the genome,” and requested a more complete record on whether a POSA² would have understood that Leary’s PARE approach teaches or suggests “sequencing all or almost all of the genome.” *Id.* 22. The Board’s presumption is incorrect, and Leary does not teach or suggest sequencing all or almost all of the genome for reasons discussed below.

a) **Leary does not teach WGS**

Foresight concedes that Leary has a “targeted nature” that only provides a “partial glimpse of the tumor genome.” Petition 61. Leary’s “partial glimpse” does not “sequence all or almost all of the genome” and therefore fails to teach WGS. Leary teaches a *physical mapping* approach that evaluates the relative *location* of genomic markers; it does *not* report the actual *sequence* (i.e., the order of nucleotides) of a polymorphism. EX2031 ¶¶89, 108.

Foresight’s expert, Dr. Quackenbush, admits that “[t]he human genome consists of approximately 3.2 billion nucleotides of DNA.” EX1020 ¶47. He further admits “[t]o obtain highly accurate sequencing information of the whole genome, it

² For purposes of the trial phase of this proceeding only Personalis does not contest Foresight’s description of a POSA. Decision 15-19.

is necessary to sequence each base in the genome multiple times.” *Id.* ¶63. Leary’s PARE approach does not sequence each of the 3.2 billion bases in the human genome, much less each base multiple times. As Dr. Furneaux explains, “PARE” is an acronym for Leary’s “personalized analysis of rearranged ends” approach in which only the “[e]nd sequences” comprising “25-bp mate-paired tags were sequenced.” EX1002 1; EX2031 ¶¶92-95. This means that each mate-paired tag contains about 50 bases of DNA sequence (2 times 25-bp mate-paired tags) and one would need to sequence about 64 million ***non-overlapping*** mate-pairs (3.2 billion divided by 50) to sequence all of the human genome. *Id.* ¶96. Leary reports a maximum value of 59,019,031 mate-paired tags matching the human genome, which is a maximum of only 2.9 billion bases (59,019,031 times 50-base pairs)—far less than the 3.2 billion bases in a human genome. EX1002, Table 1; EX2031 ¶97. Also, Leary’s mate-paired tags ***overlap*** each other by a factor of approximately 1.7 such that only about 1.71 Gb of the genome was potentially covered by Leary’s maximum value of 59,019,031 tags. EX2031 ¶¶98-100.

Leary’s statement that its PARE analysis provides “53.6 Gb per sample, or an 18-fold physical coverage of the human genome,” EX1002 1, does not mean Leary sequenced all or almost all of the genome. Each of Leary’s 25-bp tags were separated by “~1.4 kb” of ***non-sequenced*** bases such that only 3-4% of each sheared DNA strand in Leary’s sample was sequenced, leaving 96-97% of each strand

unsequenced. EX2031 ¶¶101-103. Given Leary's report that it *physically* covered the genome 18x, and given that only about 3% of each strand in Leary's sample was sequenced, at most about half (0.03×18) of the genome was sequenced. *Id.* This is not WGS.

During deposition, Dr. Quackenbush admitted that he did not consider or know how Leary's PARE assay works when he prepared his declaration, EX2018 234:13-17, 232:15-233:16. His unsupported conclusion that Leary teaches WGS is entitled to no weight. 37 C.F.R. § 42.65(a). What little he did know about Leary's assay confirms that it is not WGS. Dr. Quackenbush admitted that Leary's assay did not "sequence the entire genome" because Leary was "actually using something that's much more informative for her particular application, translocations[, b]ecause what she's looking for are two pieces of DNA, each 25 bases in length, that should be 1,400 bases apart." EX2018 242:11-243:13. He admitted that the 1400 bases are in the middle of the fragments and are "not carried through the rest of the sequencing assay." *Id.* 236:15-237:1, 238:19-22. He explained that not sequencing these 1400 bases was a "very cost-effective strategy" precisely because Leary didn't "hav[e] to sequence every base." *Id.* 245:1-11.

The Board found it pertinent that Forshew described "Leary's PARE approach as [WGS]." Decision 22. Forshew's description of Leary is not controlling here. Dr. Quackenbush admits that the term "WGS" has "taken on many different flavors

of meaning,” EX2018 155:15-22, and has been “used in different ways by different individuals in different contexts,” *id.* 157:9-22, 161:21-162:1. As discussed above, Leary’s PARE approach does not sequence all or almost all of the human genome, and therefore fails to meet “WGS” as construed in this proceeding.

Further, Forshe’s description of Leary is at odds with the body of literature that consistently excluded Leary’s PARE approach from WGS. *See* EX2008 918 (“Whole genome sequencing currently demands resources beyond the reach of most cancer investigators.... Therefore, we used a mate-pair genomic DNA sequencing approach....”). Foresight’s exhibits specifically exclude Leary from WGS. *See* EX1031 687, Table 1 (excluding Leary, which is cited elsewhere in EX1030 as reference 99, from the seven “complete sequences of cancer genomes” that had been reported up to the date of publication); EX1015 9 (explaining that Leary and McBride use similar “primary paired-end screen[s] require[ing] only low coverage sequencing of the cancer cell genome”). Two of Foresight’s founders reviewed WGS references and specifically did not classify Leary as teaching WGS. EX2152 7 (citing several references as “whole genome sequencing,” but excluding Leary, which is cited elsewhere as reference 5); EX2031 ¶¶104-108. Based on the foregoing, Leary does not teach WGS as construed by the Board.

b) Leary does not suggest WGS

A POSA would not have been motivated to modify Leary's targeted PARE approach to use WGS based on at least (1) the large data burden imposed by WGS, and (2) the constraining expenses levied by WGS.

(1) Data burden

Foresight's exhibits uniformly demonstrate that WGS was undesirable at the time of the claimed invention because it imposes a large data burden that is orders of magnitude larger than targeted approaches such as Leary's PARE approach. For example, Foresight's Meyerson exhibit teaches that WGS requires "the 3 billion bases of the human genome [to be] covered at least 30-fold on average, requiring the generation of 90 billion bases of sequence data per sample." EX1031 688. The data burden is even higher for cancer samples "to account for the decreased purity and often increased ploidy of each sample." *Id.* WGS at 30-fold coverage requires "90 Gb of sequence," which is nearly two orders of magnitude higher than the "3 Gb of sequence" required for targeted approaches. *Id.* 690. Meyerson explains that the "computational issues" caused by "the huge quantity of experimental data," *id.* 692, results in a "*major challenge... to make biological sense of the mountains of genomic data.*" *Id.* 694.³

³ All emphasis supplied unless otherwise noted.

Foresight's Mertes exhibit teaches that targeted exome sequencing, as opposed to WGS, provides "simpler data interpretation" that is a "***crucial consideration*** as it is generally much more challenging to find the functional impact of variants in noncoding regions." EX1006 382. Foresight's Mamanova exhibit teaches that a POSA would pursue targeted methods because the demands "on laboratory time and funding" required by WGS "would place a substantial burden on a research center's informatics infrastructure." EX1007 111. Foresight's Shendure exhibit explains that large quantities of sequencing data raises "new challenges for experimental design, data analysis and interpretation." EX1013 1143.

The list goes on. Foresight's Ross exhibit teaches that large amounts of sequencing data present "significant data management and interpretation challenges." EX1014 537. Foresight's Forshew exhibit disparages WGS for "generat[ing] a large amount of data on genomic regions that do not, at present, inform clinical decisions." EX1030 9. Foresight's Anderson exhibit recommends "sequencing targeted subsets of the genome" over WGS. *Id.*

Dr. Quackenbush wrote in 2019—years after the '394 patent was filed—that "the greatest barrier to obtaining scientific insights is more related to data storage, analysis, and interpretation than its generation." EX2019 7. He elsewhere wrote "[t]he pace of acquisition of genomic data for cancer patients far outstrips the utility of that information for choosing specific therapeutic avenues for individualized

patient care... [t]here are both conceptual and technical challenges to assessing the wealth of information for individual tumors obtained with next-generation sequencing (NGS) technologies,” EX2020 580, and “[t]he cost and analytical complexity of sequencing still limit the number of whole genomes that can be sequenced in any single project.... Thus, whole-exome sequencing presents an effective alternative to whole-genome sequencing and provides an unbiased, cost-effective and time-efficient tool for the study of the genetic basis for disease.” EX2158 2648.

Foresight’s founders wrote that Leary was undesirable because it was more “technically challenging and expensive” than targeted approaches. EX2021 2688.

Others agree. Blighe criticizes WGS for being “expensive” and “generating tremendous amounts” of useless data. EX2155 230.

Foresight provides no reason why a POSA would have been motivated to reconfigure Leary’s targeted PARE assay to use WGS, particularly in a routine clinical context, in the face of its own exhibits, expert, and founders uniformly teaching that WGS should be avoided, even in a research setting, due to the substantial burden of processing the mountains of “useless” data associated with WGS. EX2031 ¶¶110-120. Foresight fails to prove obviousness for at least this reason.

(2) **WGS is an order of magnitude more expensive than targeted approaches**

Foresight’s exhibits demonstrate that WGS was undesirable because it is significantly more expensive than targeted approaches, such as Leary’s targeted PARE approach. The difference in expense is not trivial. Foresight’s Sims exhibit from IPR2023-00545 explains that the difference in expense “can be an order of magnitude.” EX2022 123. Indeed, the expenses were “*substantial*” and “*often set limits* to the amount of sequences that can be generated” such that investigators sought experimental designs “for the lowest sequencing cost.” *Id.* 121. Foresight’s Mertes exhibit teaches that targeted approaches allow “costs and efforts [to] be reduced significantly compared with whole-genome sequencing.” EX1006 374. Foresight’s Gnirke exhibit teaches that there is a “substantial economy in targeting” that “substantially lower[s] the sequencing costs of a project.” EX1005 182. Faced with the real-world constraints imposed by sequencing costs being an order of magnitude greater for WGS than for targeted approaches, Foresight’s Liao exhibit teaches that it was logical for a POSA to avoid WGS. EX1009 92 (“Rather than nonselectively sequencing the genome, target enrichment provides a logical approach for more efficient and cost-effective massively parallel sequencing because it increases the proportion of informative data from the targeted region(s).”).

Even today, Foresight’s founders admit that “the amount of sequencing required for the much larger targeted genomic space makes the per sample costs of

WGS significantly higher” than other approaches. EX2023 2969. Foresight’s founders repeatedly criticized Leary as having “limitations” due to “high cost” among other things. EX2152 2; EX2031 ¶¶121-127. Yet in this proceeding, Foresight failed to provide any reason why a POSA would have been motivated to switch Leary’s admittedly cost-limited targeted approach to a WGS approach that would increase sequencing costs by at least an order of magnitude. Foresight’s own exhibits and writings demonstrate that a POSA would have avoided such a modification.

**(3) Simply increasing Leary’s coverage depth
would not convert Leary’s PARE to WGS**

The Board cited Dr. Quackenbush’s “discussion of increasing coverage depth when required by an experiment” as potentially motivating a POSA to modify Leary to sequence all or almost all of a genome. Decision 22-23. A POSA would not have been so motivated. First, Dr. Quackenbush explains that “[d]espite widespread perceptions to the contrary (5), increasing the number of reads generally does not improve the signal-to-noise ratio or lower the detection limit” with PCR techniques like those used in Leary. EX2020 587.

Second, increasing coverage depth would not, by itself, be expected to sequence all or almost all of a genome due to real world saturation limits. Foresight’s Sims exhibit from IPR2023-00545 explains that “[s]aturation” is the “point at which the addition of extra reads to an analysis yields no improvement in

the number of significant effects identified.” EX2022 126. Foresight’s founders explain “due to assay background error rates, there are diminishing returns of increasing the number of tracked mutations past a certain point.” EX2023 2969.

Third, Dr. Furneaux explains that simply increasing the coverage depth of Leary’s PARE would not be expected to sequence all or almost all of the genome due to fragmentation biases and difficulties with tiling millions of mate-pair tags across the genome. EX2031 ¶¶131-132.

Fourth, Foresight’s petition was based on a theory that Leary teaches WGS, which is incorrect for reasons discussed above, *see supra* Section III.A.1.a. The petition contains no explanation why a POSA would have modified Leary to increase coverage depth to the point of sequencing all or almost all of the genome in view of the data burden and real-world expense constraints associated with WGS, particularly at the time of the claimed invention.

2. The “second nucleic acid sample” of limitation 1(c)(i)

Limitation 1(c)(i) requires “generating a second subset of nucleic acid molecules from a second nucleic acid sample of said individual.” Foresight, however, relies on the *same* tumor sample from Leary to supposedly meet the “first nucleic acid sample” required by limitation 1(a) and the “second nucleic acid sample” required by limitation 1(c)(i). Specifically, Foresight relies on Leary “obtaining a nucleic acid sample from a patient’s tumor sample” for limitation 1(a).

Petition 32. Foresight relies on the *same* tumor sample for limitation 1(c)(i). *See* Petition 34 (asserting Leary “generate[s] a second subset of DNA from *the* tumor sample). By relying on the same tumor sample for Leary for both limitations 1(a) and 1(c)(i), Foresight failed to identify a first and second nucleic acid sample in Leary, as required by the claims. EX2031 ¶¶133-136.

Foresight provides no explanation why a POSA would have been motivated to obtain a second tumor sample to use in Leary’s method. A POSA would have been dissuaded from obtaining a second tumor sample from Leary’s patient because it would have involved an invasive procedure. Indeed, Foresight’s founders admit that tumors “cannot be repeatedly sampled without invasive procedures.” EX2152 2.

3. The “capture probes” of limitation 1(c)(i)-(ii)

Limitation 1(c)(i)-(ii) requires “capture probes.” The Board’s preliminary construction of “capture probes” does not comply with how a POSA would have understood this term, and Leary fails to disclose “capture probes” under the appropriate construction of this term.

a) Claim construction of “capture probes”

The specification “provides no express definition of ‘capture probes.’” Decision 23. This term should therefore be accorded its plain and ordinary meaning. *See Luminara Worldwide, LLC v. Liown Elecs. Co.*, 814 F.3d 1343, 1353 (Fed. Cir.

2016) (“Absent lexicography or disavowal, we do not depart from the plain meaning of claims.”); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-16 (Fed. Cir. 2005) (en banc).

The Board preliminarily construed “capture probes” as encompassing “at a minimum, PCR primer capture probes and solution-based hybridization capture probes (e.g., biotinylated oligonucleotide baits).” Decision 23-29, 42. The concurring opinion would have construed “capture probes” as “encompassing nucleic acid structures as small [as] one nucleotide that may but are not required to include linkers and labels.” *Id.* 45. The Board’s preliminary constructions do not comply with how a POSA would have understood the plain meaning of “capture probes.”

The specification describes several features of capture probes, *see e.g.*, EX1001 31:4-32:5, but appropriately refrains from describing all known aspects of capture probes because “a patent need not teach, and preferably omits, what is well known in the art.” *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

Foresight’s exhibits consistently demonstrate that a POSA would have understood the plain meaning of “capture probes” to be “***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.***” Foresight’s Mamanova exhibit

teaches that “capture probes” are the specific type of probes used in “hybrid capture” techniques. EX1007 115-16 (exclusively using the term “capture probes” in describing hybrid capture techniques, and at 112-14 avoiding the term in describing PCR primer amplification techniques). Foresight’s Mertes exhibit explains “hybrid capture” techniques as follows:

‘Hybrid capture’: wherein *nucleic acid strands derived from the input sample are hybridized specifically to preprepared DNA fragments* complementary to the targeted regions of interest, either in solution or on a solid support, *so that one can physically capture and isolate the sequences of interest.*

EX1006 375. Dr. Quackenbush selected Mamanova and Mertes as “representative” examples from the “vast” biomedical literature because “they provide complementary sources of information” about the “background on capture technology.” EX2018 142:18-143:15, 150:11-155:3. Personalis’ construction stays true to the plain meaning of capture probes described in Mamanova and Mertes as representative examples of the background knowledge of a POSA regarding this term. EX2031 ¶¶55-57.

(1) **The preliminary construction does not comply with the plain meaning of “capture probes”**

The Board’s preliminary construction departs from the plain meaning of “capture probe” because it includes “PCR primer capture probe.” First, “PCR primer capture probe” is not found in any of Foresight’s prior art exhibits. Dr. Quackenbush

confessed that the term “PCR primer capture probe” doesn’t exist in the literature. EX2018 166:10-169:1. It is a new term fabricated by Foresight for this proceeding. Dr. Quackenbush was unable to explain what types of primers are excluded (or included) by the term “PCR primer capture probe” because he “wouldn’t want to limit” the term and its meaning would “depend on how one uses” the term. *Id.* 171:16-175:2. “Capture probe” should not be construed to include “PCR primer capture probe” because it would improperly inject ambiguity into the claim. *Liquid Dynamics Corp. v. Vaughan Co.*, 355 F.3d 1361, 1367 (Fed. Cir. 2004) (a construction should “assign a fixed, unambiguous, legally operative meaning to the claim”).

Second, “capture probes” should not be construed to include “PCR primer capture probes” because it would unreasonably expand the term beyond its plain meaning. The intrinsic record treats capture probes and PCR primers as different types of nucleic acids. For example, the specification has separate descriptions of capture probes and primers. EX1001 31:4-32:5, 40:29-41:36, 23:23-26, 32:56-60. Several embodiments describe the use of capture probes as a separate and distinct step from using PCR primers. *Id.* 64:29-43, 65:38-50, 66:53-67.

Foresight argues that a “capture probe” merely needs to hybridize to target DNA. *See* Petition 21; EX1001 31:4-34. Foresight overlooks that capture probes must also physically capture sequences of interest, as conceded by Dr.

Quackenbush's testimony 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.

The Board preliminarily determined that it was unclear whether a "pulldown probe" is synonymous with a "capture probe." Decision 27-28. However, "capture probes" are indeed synonymous with "pulldown probes." The parties and experts agree that "capture probes" refers to "nucleic acid fragments" that "catch" target nucleic acid sequences of interest through hybridization so that target DNA can be physically "pulled down" or "fished out." Petition 69; EX1020 ¶¶77, 238, 67 (describing "physically pulling certain pieces of DNA out of a mixture for further analysis"). Foresight's Gnirke exhibit treats "pull-down" as synonymous with "capture." EX1005 182, 186-87; EX2031 ¶¶58-64.

The prosecution history evidences that "pulldown probes" and "capture probes" are synonymous. For example, the Examiner used "capture" and "pulldown" synonymously when conducting prior art searches during prosecution of the '394 patent and related U.S. 11,408,033. EX2024 3-8 ("((enrich\$5 captur\$5 pull-down pulldown) with probe"); EX2025 3-25 (same). The Examiner did not include "primers" or "PCR" in the search terms. *Id.* The Examiner agreed during prosecution of two related applications that "pulldown probes" are not PCR primers. EX2005 19, 24, 31; EX2004 14, 17, 25.

The Board took issue with Patent Owner’s proposed construction based on a hypothetical set of capture probes used with a solid support gel that supposedly “cannot be physically collected or separated.” Decision 25 n.11 (citing EX3003). Dr. Furneaux explains that capture probes can be physically separated from such gels by cutting out the strip of nitrocellulose containing the captured nucleotides of interest and eluting the captured nucleotides. EX2031 ¶65; EX2026.

The Board took issue with Patent Owner’s proposed construction because one part of the specification “suggests that physical separation is an independent method of producing a subset [of nucleic acids].” Decision 25 (citing EX1001 32:12-18, 32:26-34). The cited portion of the specification appropriately discloses one method of producing a subset of nucleic acids. However, “the claims of the patent need not encompass all disclosed embodiments. Our precedent is replete with examples of subject matter that is included in the specification, but is not claimed.” *TIP Systems, LLC v. Phillips & Brooks/Gladwin Inc.*, 529 F.3d 1364, 1373 (Fed. Cir. 2008).

(2) The specification does not contradict the plain meaning of “capture probe”

The Board preliminarily determined that PCR primers and capture probes have similar physical characteristics, Decision 26-27, and that the specification “provides no indication as to whether the categories [of primers and capture probes] are overlapping, *id.* 25. First, a POSA would recognize important physical differences between PCR primers and capture probes. PCR requires *two* primers (a

pair of primers) to exponentially amplify DNA. EX1020 ¶¶72-75; EX2018 112:18-115:11. In contrast, only *one* capture probe is required to physically pulldown a target DNA strand. EX1020 ¶76 (depicting a single type of probe); EX2031 ¶66.

Second, a POSA would understand that capture probes and PCR primers have very different *functions*. There is nothing wrong “with defining some part of an invention in functional terms” and a functional term must be considered for what it fairly conveys to a POSA. *In re Swinehart*, 439 F.2d 210, 212 (CCPA 1971).

Foresight’s exhibits go to great lengths to explain the differences in function between capture probes and PCR primers. Foresight’s Mertes exhibit teaches that capture probes and PCR primers are two different enrichment techniques that are “categorized according to the nature of their *core reaction principle*.” EX1006 375. As discussed above, the core reaction principle of capture probes involves hybridizing to “targeted regions of interest, either in solution or on a solid support, *so that one can physically capture and isolate the sequences of interest*.” *Id.* In contrast, the core reaction principle of PCR primers is “*amplification*” of targeted regions by a “polymerase chain reaction (PCR)” that *copies* target regions. *Id.*; *see also id.* 376, Fig. 1. Dr. Quackenbush explains “[i]n PCR, DNA molecules are replicated,” EX1020 ¶70, using “PCR ‘primers’ or ‘probes,’” *id.* ¶72, and “results in the *exponential amplification* of target DNA sequences,” *id.* ¶75. Dr. Quackenbush explains that PCR primers function to prime a reaction by allowing a DNA

polymerase enzyme to bind and start a catalytic polymerization reaction to generate amplicons. *Id.* ¶¶71-75. Dr. Quackenbush’s own articles also treat capture probes and PCR primers as different types of nucleic acids. EX2158 2650 (“All samples were captured using the same probe set (*Agilent SureSelect Human All Exon* G3362)... an individual[’s] exons deletion/duplication status would be more powerfully observed by including additional flanking intronic sequence in the *capture probe* design.”); EX2157 320 (“*Selected candidate SNVs were further characterized using PCR* and conventional Sanger sequencing to confirm tumor-specific single-nucleotide mutations... [l]ibrary construction and *custom exome capture* were performed using the *SureSelectXT2* for Illumina protocol (*Agilent*) according to the manufacturer’s instructions[.]”); EX2031 ¶¶67-68.

The Board noted that a capture probe can be one nucleotide long. Decision 26 n.12, 43-44. The specification correctly includes capture probes having a length of one nucleotide because there are instances where a single nucleotide can function as a capture probe. EX2031 ¶¶69; EX2027 2013-2014. However, limitation 1(c) further clarifies that the claimed capture probes must specifically hybridize to “polymorphisms.” A POSA would be able to discern an appropriate length for these claimed capture probes. EX1006 378; EX1007 115; EX1005 187; EX2018210:4-211:16; EX2031 ¶¶69. The mere fact that the specification describes an alternative embodiment of one nucleotide does not outweigh the language of the claim that

further clarifies that the capture probes hybridize to polymorphisms. *August Tech Corp. v. Camtek, Ltd.*, 655 F.3d 1278, 1285 (Fed. Cir. 2011).

The Concurrence explains that the capture probes “may but are not required to include linkers and labels.” Decision 45. Personalis agrees that capture probes may include linkers and labels, EX1001 31:7-12, and would not object to adding this language to its proposed construction.

The Board found that claim 13’s recitation of “barcode” weighs moderately in favor of Foresight’s construction because barcodes are typically used on PCR primers. Decision 24. A “barcode” is a type of “sample identifier.” EX1001 55:14-18. It was known that barcodes can also be used on capture probes. EX2031 ¶70; EX2028 251. Thus, claim 13 does not expand “capture probes” beyond its plain meaning to include “PCR primer capture probes.”

(3) **Foresight incorrectly treats PCR primers as being interchangeable with capture probes**

Foresight incorrectly treats capture probes and PCR primers as being interchangeable. Foresight’s exhibits, however, go to great lengths to describe the different benefits and drawbacks of these different techniques. Foresight’s Mertes exhibit has entirely different sections discussing “enrichment by hybrid capture” and “enrichment by PCR” with primers, EX1006 378-80, and explains that “[g]iven the operational characteristics of these different targeted enrichment methods, they naturally vary in their suitability for different fields of application,” *id.* 375.

Mertes demonstrates “how very divergent the results of” hybrid capture and PCR primer amplification can be, as they “produce very different average coverage, evenness and specificity.” EX1006 383. Similarly, Mamanova identifies numerous differences between “PCR,” “[o]n-array hybrid capture,” and “[i]n-solution hybrid capture.” EX1007 114, Table 1.

Based on the differences in core reaction principles of the techniques, Foresight’s exhibits explain that there are many factors that a POSA must weigh when selecting either capture probes or PCR primers for a given experiment. Mamanova teaches “[t]here are several enrichment approaches, each with unique advantages and disadvantages” such that a user must “find the best compromise between sensitivity, specificity and uniformity for their particular project.” EX1007 111. Mamanova further teaches that there are *seven* “parameters” by which a POSA should evaluate capture probes or PCR primers before selecting one over the other:

- (i) sensitivity, or the percentage of the target bases that are represented by one or more sequence reads;
- (ii) specificity, or the percentage of sequences that map to the intended targets;
- (iii) uniformity, or the variability in sequence coverage across target regions;
- (iv) reproducibility, or how closely results obtained from replicate experiments correlate;
- (v) cost;

- (vi) ease of use; and
- (vii) amount of DNA required per experiment, or per megabase of target.

Id.

Similarly, Mertes teaches that a POSA must “rationally decide which technologies are most suitable when designing a research project” by weighing the following *seven* “series of metrics” to evaluate each “method’s innate enrichment capability” for each experiment:

- (i) Region of interest (size): ROI;
- (ii) Average read depth (in ROI): D;
- (iii) Fraction of ROI sufficiently covered (at a specified D): F;
- (iv) Specificity (fraction of reads in ROI): S;
- (v) Enrichment Factor (D for ROI versus D for rest of genome): EF;
- (vi) Evenness (lack of bias): E and
- (vii) Weight (input DNA requirement): W.

EX1006 380. Further, PCR cannot truly “capture” DNA, it can only copy it. For example, PCR cannot “capture” methylated cytosine, but capture probes can. EX2031 ¶¶71-74. Therefore, a POSA would understand that capture probes and PCR primers are different enrichment techniques, and selecting one or the other is a compromise that involves evaluating numerous parameters/metrics for each experimental design.

(1) Conclusion regarding claim construction

In sum, the Board should adopt Personalis’ construction of “capture probes” because it stays true to the plain meaning of the term. In contrast, the Board should reject a construction that includes “PCR primer capture probe” because it is a new term made-up by Foresight that has no basis in the literature and improperly imbues the claim with ambiguity. Foresight’s exhibits consistently teach that a POSA would have understood capture probes and PCR primers to be two different enrichment techniques each having unique drawbacks and potential advantages that should be carefully weighed before selecting one technique over the other in view of the specific requirements of each experimental design.

b) Leary does not teach or suggest “capture probes”

Foresight’s entire challenge to the ’394 patent hinges on a POSA conflating Leary’s PCR primers with the claimed “capture probes.” Petition 33-36. A POSA would not have considered Leary’s PCR primers to be “capture probes” because Leary’s PCR primers do not hybridize to target DNA so that one can physically capture the target DNA. Instead, Foresight asserts that Leary’s PCR primers meet the claimed capture probes simply because they “‘hybridize to’ the complementary sequences on the polymorphic nucleic acid comprising the breakpoint.” Petition 35. Dr. Quackenbush admitted, however, 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.

A POSA would not confuse Leary’s PCR primers with the claimed capture probes as evidenced by Foresight’s own exhibits, which consistently and repeatedly distinguish these two enrichment techniques according to their very different core reaction principles. *Supra* Section III.A.3.a; EX2031 ¶¶138-139. Accordingly, Leary fails to teach the “capture probes” required by limitation 1(b).

Foresight provides no reason why a POSA would have been motivated to reconfigure Leary’s PCR primer-based PARE assay to use the hybridization capture technique of capture probes. As discussed above, a POSA would have needed to evaluate seven parameters and seven metrics associated with the disadvantages of capture probes before discarding the core reaction principle of Leary’s PCR primer PARE assay and replacing it with capture probes. The vast majority of these parameters would have counseled a POSA to avoid attempting to redesign Leary’s experiment. For example, Mamanova teaches that “[t]he *specificity* of PCR will almost certainly always exceed that of hybrid capture, and its *uniformity* may never be matched by either hybrid capture or MIPs.” EX1007 111. Further, Mamanova teaches that PCR has higher *reproducibility* of “up to 100%” than capture probes. *Id.* Table 1. Leary already had a working assay, so switching the core reaction principle to capture probes would entail more *costs* for redesigning the experiment

(and adding a different detection mechanism), and risk making the assay *harder to use*. EX2031 ¶140. The *sensitivity* and *amount of DNA required* are parameters that would, at best, be considered neutral; but the risks associated with modifying Leary's already-working assay could very well cause the assay to lose sensitivity or even worse, not work at all.

Further, Foresight failed to describe what the workflow of Leary's PARE assay would look like if a POSA were to somehow have been motivated to use capture probes instead of PCR primers. Leary's PARE approach requires DNA from each patient sample to be "purified, sheared, and used to generate libraries with mate-paired tags ~1.4 kb apart" followed by the libraries being "digitally amplified by emulsion polymerase chain reaction (PCR) on magnetic beads," and then sequencing 25-bp mate-paired tags "using the sequencing-by-ligation approach." EX1002 1. Two incredibly complex multistep methods are then "used to identify somatic rearrangements from these data (fig. S1)" with multiple PCR steps:

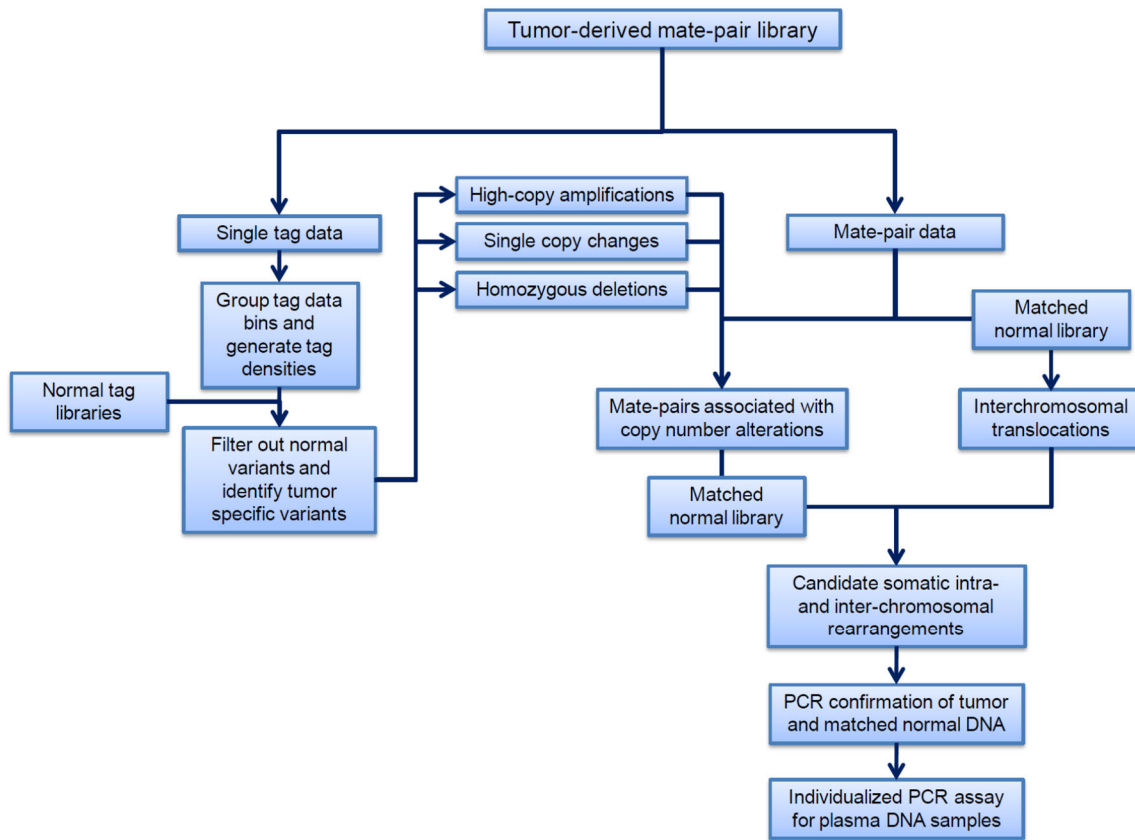


Fig. S1. Flow chart of approach used to identify rearranged sequences

EX1002, 1; EX1026, Fig. S1. Foresight leaves the Board and Personalis guessing as to which PCR portion of the PARE approach a POSA would have been motivated to change to capture probes, and which steps in the PARE workflow would need to be kept, jettisoned, or rearranged to accommodate such a change in the core reaction principle of Leary’s assay with a reasonable expectation of success.

Further, Leary’s assay uses PCR *as its detection method* for identifying chromosomal rearrangements. EX1002 4 (“we designed PCR assays to detect” rearranged sequences”); *id.* (“Digital PCR analyses... indicated that rearranged

tumor DNA was detectable....”); Petition 40 (“Leary shows the detection of tumor specific rearrangements... using digital PCR....”). Foresight fails to explain how capture probes could conceivably replace PCR to serve as the detection method for Leary’s assay. EX2031 ¶141.

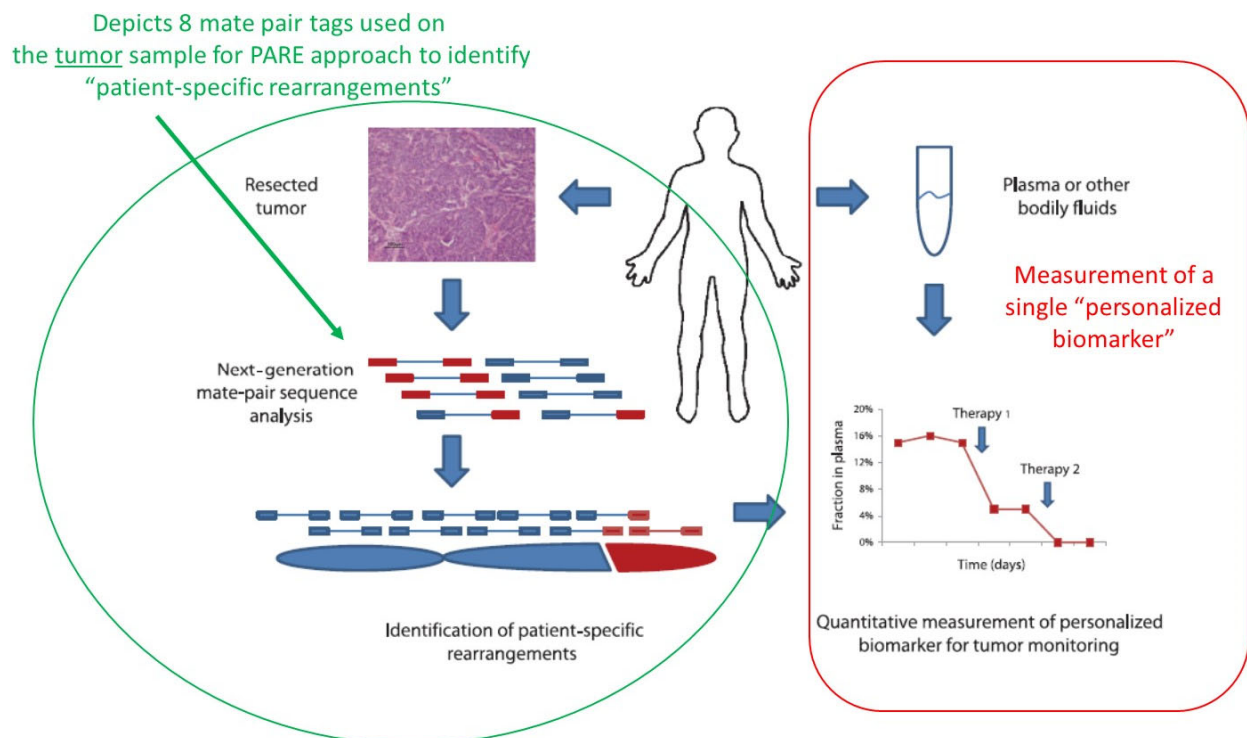
4. The “plurality of capture probes” of limitation 1(e)

Limitation 1(e) requires a “plurality of capture probes.” As discussed above, Leary’s PCR primers are not “capture probes,” and Leary fails to teach limitation 1(e) for at least this reason. However, even if Leary’s PCR primers were to be considered “capture probes”—which they should not—Leary fails to disclose a *plurality* of PCR primers that would meet limitation 1(e).

Foresight relies on Leary Figure 4 for limitation 1(e). Petition 40. However, only a single chromosomal rearrangement was analyzed for each patient in Leary Figure 4. That is, patient Hx402 was only analyzed with a single primer pair designed to amplify the fragment spanning the Chr 4:8 rearrangement. EX1002 4, 6. Patient Hx403 was only analyzed with a single primer pair designed to amplify the fragment spanning the Chr 16 rearrangement. *Id.*; EX2031 ¶¶143-145. Each primer pair functions as a *single unit* because amplification “is achieved only when each member of a primer pair anneals in a stable fashion to its target sequence.” EX2160; EX1006 380 (“distinct pairs of primers”); EX2018 114:21-115:11.

Foresight fails to explain how Leary's single primer pair that function as a single unit constitutes a plurality of capture probes.

Foresight also relies on the "monitoring of plasma samples or other bodily fluids" depicted in Leary Figure 1 for limitation 1(e). Petition 38-39. Leary Figure 1, which is reproduced below with green and red annotations, shows that multiple mate-pair tags are prepared only for the tumor sample to identify "patient-specific rearrangements," which Foresight relies on for the first sample required by claim limitation 1(a). Leary's Figure 1 depiction of only monitoring a single biomarker is consistent with the actual experiment conducted by Leary that monitored just one chromosomal rearrangement in each of the Hx402 and Hx403 patients.



EX1002, Fig. 1 (green and red annotations added); EX2031 ¶146. As a result, Foresight fails to establish that Leary teaches a “plurality” of capture probes that meets limitation 1(e), and Foresight fails to provide any reason that a POSA would have been motivated to modify Leary with a reasonable expectation of success to arrive at limitation 1(e).

5. The “third sequencing assay” of limitation 1(f)

Foresight argues that Leary “discloses, and at a minimum renders obvious, conducting a sequencing assay on PCR products generated from each plasma sample” for the purpose of “verify[ing] that the selected PCR primer capture probes selectively bind the tumor sequences they were intended to target.” Petition 41-44. Foresight, however, previously relied on Leary’s verification sequencing to supposedly meet limitation 1(d). Petition 37-38. Leary does not disclose conducting an additional *re*-verification sequencing step, and there is no reason a POSA would have been motivated to modify Leary to conduct such unnecessary *re*-verification sequencing. Foresight’s exhibit criticizes Leary’s existing workflow as being “difficult to implement on a routine basis,” EX1030 10, and not “widely adopted,” *id.* 8; EX2031 ¶¶147-148. Foresight’s speculation that a POSA would want to add even more sequencing steps to Leary’s already complicated assay would only have made the process even more difficult to implement and less adopted. A POSA would not have been motivated to convolute Leary’s method with even more data analysis,

cost, and time to conduct an undisclosed and unnecessary *re*-verification sequencing step.

6. No motivation to modify Leary

As discussed above, a POSA would not have been motivated to completely redesign Leary's PCR primer-based targeted PARE assay to (1) increase sequencing by at least an order of magnitude to cover all or almost all of the genome, (2) conduct a second sequencing assay on a second tumor sample, (3) change the core reaction principle from PCR primers to capture probes, (4) use a plurality of capture probes on an additional sample, and (5) include a third sequencing assay. Foresight fails to articulate a convincing motivation for any one of these modifications, much less the total overhaul required to do all of them, absent improper hindsight. *Cheese Systems, Inc. v. Tetra Pak Cheese and Powder Systems, Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013). Accordingly, Foresight failed to prove obviousness of independent claim 1 and all dependent claims.

B. Claims 17 and 18

Dependent claims 17 and 18 require that the "whole genome sequencing produces at least [750,000,000 or 1,000,000,000] sequencing reads."

Foresight argues that a POSA would have been motivated to increase Leary's 18x physical coverage to a depth of "30x," which it alleges would result in 3,600,000,000 sequencing reads. Petition 52-53. First, Foresight confuses physical

coverage with sequencing coverage. Dr. Quackenbush admittedly did not know how Leary's PARE assay actually works. EX2018 234:13-234:17, 232:15-233:16. Leary's sequence coverage could not simply be increased to 30x for reasons discussed above. *Supra* Section III.A.1.b.3.

Second, Foresight selection of a "30x" depth inappropriately "[d]efin[es] the problem in terms of its solution," which "reveals improper hindsight." *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015). Dr. Quackenbush concedes that selecting a depth of coverage "depends on your application" and that 10x and 18x can be sufficient, but "[t]here are examples like Leary where the sequence coverage was lower" at about "onefold" coverage. EX2018 94:8-97:4. Foresight provides no reasoned analysis why a POSA would select 30x as opposed to 18x, 10x, or any other multiplier besides a hindsight-driven reconstruction of the claimed invention. EX2031 ¶¶151-152.

C. Claim 19

Dependent claim 19 requires "repeating said third sequencing assay one or more times" on "a fourth nucleic acid sequence."

Foresight relied on Leary's verification sequencing to supposedly meet limitation 1(d), Petition 37-38, and also asserted that a POSA would conduct additional *re*-verification sequencing to meet limitation 1(f). Petition 41-44; *supra* Section III.A.5. Foresight alleges that a POSA would conduct another re-

verification (i.e., a *re-re*-verification) to meet dependent claim 19. Petition 53-55. A POSA would not have been motivated to complicate Leary’s already “difficult to implement” method with even more data analysis, cost, and time to conduct an undisclosed and unnecessary *re-re*-verification sequencing step. EX1030 10; EX2031 ¶154.

IV. GROUND 2: NONOBVIOUSNESS OVER LEARY AND LEY

The Petition relies on Ley as supposedly rendering obvious limitation 1(c)(ii), which requires observing polymorphisms “in a population of one or more samples.” Petition 54-55.

Ley does not cure any of the deficiencies with Leary discussed above. Instead, Ley reinforces that a POSA would not have been motivated to modify Leary’s assay to perform WGS. Ley’s authors are from The Genome Center at Washington University—one of the most sophisticated sequencing laboratories in the world. A POSA would not have access to such resources and would not pursue WGS because Ley teaches that, going forward, it would be preferable to use targeted sequencing because it would be “faster, cheaper, and more efficient.” EX1012 71 (“Although we performed whole-genome sequencing on this cancer sample, we restricted our initial validation studies to the 1-2% of the genome that encodes genes. This raises the issue of whether sequencing the complementary DNA transcriptome of this

tumor would have been a faster, cheaper and more efficient way of finding the mutations.”); EX2031 ¶¶158-162.

Ley’s method is not “feasible” without performing WGS *twice*: once on the patient’s normal genome, and again on the tumor genome. *Id.* 71 (“We cannot overemphasize the importance of parallel sequencing of the patient’s normal genome to determine which variants were inherited; the identification of the true somatic mutations in this tumour genome would not have been feasible without this approach.”); EX2018 87:11-13 (“what Ley did was a whole-genome sequence analysis, *actually two*”). A POSA would have avoided a method that performs WGS twice for routine clinical purposes at the time of the claimed invention for reasons discussed above regarding data burden and expense constraints.

Like Leary, Ley uses PCR primers, which fails to teach or suggest the recited “capture probes” for reasons discussed above. *Supra* Section III.A.3; EX1012 69, 71.

Further, Foresight provides no specifics about what a combined Leary/Ley assay would entail to result in an assay that meets limitations 1(b), 1(c), 1(e) and 1(f). Leary discloses a PARE approach. EX1002 1. Ley discloses a different approach that involves identifying “putative variants” with “validation using custom PCR and capillary sequencing” as well as sequencing of “validated somatic mutations” “by Roche/454 sequencing of PCR-generated amplicons made from

primary genomic DNA.” EX1012 71. These approaches have significantly different workflows, and Foresight fails to explain with any degree of particularity which steps of Leary’s PARE assay would be retained, replaced, or discarded by something from Ley’s assay to utilize WGS with capture probes that meets all limitations of the claim. Foresight’s lack of particularity is insufficient to prove obviousness. *Intelligent BioSys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) (“It is of the utmost importance that Petitioners in the IPR proceedings adhere to the requirement that the initial petition identify with particularity the evidence that supports the grounds for the challenge to each claim.”). Further, a POSA would have expected replacing Leary’s PCR-based approach with capture probes would cause Leary’s assay to undesirably lose specificity and uniformity because “[t]he specificity of PCR will almost certainly always exceed that of hybrid capture, and its uniformity may never be matched by either hybrid capture of MIPs.” EX1007 117.

V. GROUND 3: NONOBVIOUSNESS OVER LEARY, CHAN, AND LIAO

Ground 3 fails to prove obviousness of the claims for several reasons. First, Chan is not prior art to the ’394 patent. Second, Chan and Liao do not cure Leary’s many deficiencies.

A. Chan is not prior art

Inventors may antedate a reference by showing that the invention was conceived before the effective date of the reference, followed by reasonably continuous diligence until constructive reduction to practice. *ATI Techs. v. Iancu*, 920 F.3d 1362, 1369-70 (Fed. Cir. 2019). Inventor testimony must be corroborated, which is governed by a “rule of reason.” *Id.*

Here, the inventors conceived of the claimed invention by no later than May 8, 2012 and diligently worked towards its reduction to practice via filing the provisional application on January 17, 2013. EX2113. Chan did not publish until October 2012. Thus, Chan is not prior art.

Personalis submits the following evidence showing prior invention:

- Declaration of John West, EX2032. Mr. West is an inventor of the '394 patent. He co-founded Personalis and served as its founding CEO from August 2011 through December 2022.
- Declaration of Jonathan MacQuitty, EX2033. Dr. MacQuitty is a partner at Lightspeed Management Company. He served on the Personalis Board of Directors from 2011 until 2022. He provides testimony corroborating Mr. West's declaration.
- Declaration of Doug Zeman, EX2034. Mr. Zeman is the Associate Director of Scientific Computing and Information Technology at

Personalis. He confirms that certain exhibits referenced in Mr. West's declaration were made, retained, and maintained in the regular course of Personalis' business.

- Supporting and corroborating Exhibits 2036-2123.

1. Conception

The inventors conceived of the claimed invention no later than May 8, 2012, as demonstrated below.

a) Genesis of the Accuracy Program

The claimed invention was developed by the "Accuracy Program" at Personalis, the genesis of which dates back to November 2009, when Mr. West paid \$160,000 to have his family of four's whole genomes sequenced. Mr. West found the data had systematic gaps, and it occurred to him that supplementing whole genome sequencing (WGS) data with additional assays could lead to more complete and accurate results. Mr. West and the four faculty members decided to found Personalis, which was incorporated in February 2011, and closed its initial Series A financing for \$20 million in August 2011. EX2032 ¶¶20-28.

Dr. Sara Garcia joined Personalis as its first employee (besides Mr. West) in November 2011. She earned her Ph.D. in Genetics from Stanford University. EX2032 ¶29.

Dr. Richard Chen joined Personalis in November 2011. He earned his M.D. from Stanford University. EX2032 ¶30.

Dr. Hugo Lam joined Personalis in November 2011. He earned his Ph.D. from Yale University. EX2032 ¶31.

Dr. Mark Pratt joined Personalis in January 2012. He earned his Ph.D. from the University of California, Santa Barbara. EX2032 ¶32.

Dr. Gemma Chandratillake joined Personalis in February 2012. She earned her Ph.D. from The Open University . EX2032 ¶33.

Dr. Gabor Bartha joined Personalis on May 1, 2012. He earned his Ph.D. from the University of Southern California. EX2032 ¶34.

Ms. Shujun Luo joined Personalis on June 1, 2012. She earned her M.S. from Columbia University. EX2032 ¶35.

Personalis had assembled a world-class team of scientists by mid-2012. A photo of the Personalis team as of May 4, 2012 is shown below, including co-inventors of the '394 patent:

Company photo May 4, 2012



Left to right : Michael Clark, Rich Chen, Carol Tillis, Christian Haudenschild, Russ Altman, Carlos Bustamante, Euan Ashley, Gemma Chandratillake, Atul Butte, John West, Sarah Garcia, Hugo Lam, Rong Chen, Scott Kirk, Gabor Bartha, Namhai Nguyen, Mark Pratt, Eliane Sousa, Nan Leng

EX2032 ¶¶36, 327.

b) The Accuracy Program: November 2011 through May 8, 2012

The inventors met many times between November 2011 and May 8, 2012 to develop assays for the Accuracy Program. On January 6, 2012, the inventors were working on “augment[ing] NGS [next-generation sequencing] with other technologies to determine key variants,” and “conduct[ing] follow-up genetic & non-genetic testing to validate results.” EX2046 3, 10, 14; EX2032 ¶¶57-59.

On January 13, 2012, Mr. West planned to supplement whole genome sequencing using hybrid capture “oligo-based pullouts.”. EX2032 ¶¶53-56; EX2109 2-3; EX2102 2.

On April 2, 2012, Mr. West describe Personalis’ laboratory plans. EX2036; EX2032 ¶61.

Inventors met and exchanged ideas on May 3 and 4, 2012. EX2037; EX2038; EX2039; EX2040; EX2032 ¶¶62-65.

On May 8, 2012, Mr. West presented his “CEO Overview” slides to the Personalis Board of Directors. The meeting was attended by Jonathan MacQuitty (from Abingworth), Chris Schaepe (from Lightspeed), Carol Tillis, Richard Chen, Christian Haudenschild, James Kitch (from the law firm of Cooley LLP), Alex de Winter (from Mohr Davidow Ventures), and John West. EX2043. Dr. MacQuitty attests to having been present at the meeting and that EX2112 is a true and correct copy of Mr. West’s presentation to the best of his recollection, and further that the Meeting Minutes provide a true and correct summary of the meeting. EX2033 ¶¶20-26.

c) Summary of Mr. West’s Presentation

Slide 5 of Mr. West’s May 8, 2012 CEO Presentation (“Presentation”) provides an overview of the Accuracy Program. It includes several acronyms and short-hand names that were understood by the Personalis Board members:

Overview of Personalis Accuracy Program

Characterize errors <u>Analysis</u> Rates by variant type & Q-score Underlying mechanisms Medical interpretation impact Regulatory impact <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>Prioritize solutions</u> Bio-informatic approaches Laboratory approaches Content approaches	Informatic Solutions <u>Advances in 3rd party alg's</u> Aligner for > 200bp reads New versions, current alg's Other alg's (e.g. lobSTR) <u>Advances in our alg's:</u> SV's : Zygosity, accuracy Combine SV's & SNP's Broader use of Breakseq <u>New Personalis alg's</u> Alignment degeneracy Genome-aware alignment VNTR-specific <u>Advances in reference</u> Ethnic major-allele ref's Iterative Admixed InDel's / SV's <u>Flag or Filter Out</u> For problems not yet solved	Lab, Content Solutions <u>Combine technologies</u> WGS + exome Longer reads and/or inserts Multi-vendor Arrays (genotypes & SV's) Electrophoretic sizing Sanger validation <u>Content-based semi-custom</u> Array (genotypes & SV's) Pullout <u>Custom sample preps</u> Problematic motifs Degenerate regions Phasing <u>Content</u> Gold standard genomes Known healthy genomes
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Personalis Confidential May 8, 2012

5

EX2112 5. This slide concisely describes the Accuracy Program in three panels. The bottom of the first panel describes three approaches for reducing errors: “bio-informatic approaches” (such as improved algorithms in computer software), “laboratory approaches” (assays to provide more accurate results), and “content approaches” (including using genetic data to create “custom” or “semi-custom” assays). The center panel describes bioinformatic solutions using “alg’s” (algorithms) for genetic variants such as “SNP’s” (single nucleotide polymorphisms), “InDel’s” (insertions/deletions), “VNTR” (variable number tandem repeats), and “SV’s” (structural variants). The third panel describes “Lab” assays and “Content Solutions.” This included supplementing genome sequencing

with additional data created by using capture probes to “pullout” three types of content: targets outside the coding regions of genes, longer molecule targets to resolve alignments, and targets to fill in coverage gaps. EX2033 ¶¶71-76. The inventors were focused on improving WGS with custom or semi-custom capture probes. EX2033 ¶¶77-80.

d) The Accuracy Program and the '394 patent claims

Mr. West’s Presentation memorializes much of the inventors’ work to conceive of the inventions that were ultimately claimed by the '394 patent. The inventors had formed a definite and permanent idea of the complete and operative invention described in each claim of the '394 patent by no later than May 8, 2012. A POSA would have been enabled to practice the invention without undue experimentation if they had been informed of the invention. EX2032 ¶209. Below is an explanation of conception of each of claims 1-19 with corroborating evidence.

(1) Claim 1 - Preamble

By no later than May 8, 2012, the Accuracy Program included methods for analyzing nucleic acid samples isolated from an individual. Conception is reflected by, e.g., Slide 5 of Mr. West’s Presentation, which is entitled an “Overview of Personalis Accuracy Program,” and reproduced below:

Overview of Personalis Accuracy Program

Characterize errors <u>Analysis</u> Rates by variant type & Q-score Underlying mechanisms Medical interpretation impact Regulatory impact <u>Methods</u> Comparison with literature Studies on limited regions <u>Whole genome analysis:</u> Single genome metrics Same person twice Family inheritance (MIE) Platform comparison Arrays ILMN / CGI / Ion T... Sanger capillary <u>Prioritize solutions</u> Bio-informatic approaches Laboratory approaches Content approaches	Informatic Solutions <u>Advances in 3rd party alg's</u> Aligner for > 200bp reads New versions, current alg's Other alg's (e.g. lobSTR) <u>Advances in our alg's:</u> SV's : Zygosity, accuracy Combine SV's & SNP's Broader use of Breakseq <u>New Personalis alg's</u> Alignment degeneracy Genome-aware alignment VNTR-specific <u>Advances in reference</u> Ethnic major-allele ref's Iterative Admixed InDel's / SV's <u>Flag or Filter Out</u> For problems not yet solved	Lab, Content Solutions <u>Combine technologies</u> WGS + exome Longer reads and/or inserts Multi-vendor Arrays (genotypes & SV's) Electrophoretic sizing Sanger validation <u>Content-based semi-custom</u> Array (genotypes & SV's) Pullout <u>Custom sample preps</u> Problematic motifs Degenerate regions Phasing <u>Content</u> Gold standard genomes Known healthy genomes
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Personalis Confidential May 8, 2012

5

EX2112 5 (highlighting added).

The Accuracy Program involved “analysis” of nucleic acid samples by “methods” that included “whole genome analysis” and further involved “combin[ing] technologies” of “WGS” (whole genome sequencing) with “content-based semi-custom” assays using capture probes to “pullout” genotypes and structural variants. The Program also involved nucleic acid samples that would be sequenced by “WGS,” supplemented by custom and/or semi-custom assays based on capture probe pullouts. *Id.*; EX2032 ¶¶211-216.

The Accuracy Program included “receiv[ing]” and “de-identify[ing] samples” from customers:

Personalis Laboratory Strategy

- Laboratory goals:
 - Direct relationship with the customer
 - Quality control, sample to results (important for research and later clinical)
 - Position as “Value-Added Genome”, not “a bio-informatics company”
 - Offer a superior genome, by combining technologies from multiple companies
 - Develop superior sample preps, esp based on Personalis content
- Outsourcing:
 - Whole genome sequencing service pricing now < reagents to do it yourself
 - Avoid infrastructure costs (instruments, initial computation, staffing)
 - Turn-around time is a disadvantage (quotes at 12-16 weeks)
 - Other assays we can outsource:
 - Arrays (standard & semi-custom)
 - Karyotyping
 - Exomes, RNAseq
- Personalis lab
 - Receive, de-identify samples
 - QC, sample tracking
 - Ship aliquots to multiple vendors
 - Validations following primary analysis
 - Develop custom sample preps

Personalis Confidential May 8, 2012

13

EX2112 13 (highlighting added).

(2) Limitations 1(a)-(b)⁴

Conception of limitations 1(a)-1(b) is reflected by, e.g., Slide 5 of Mr. West’s Presentation. The Accuracy Program involved “analysis” of nucleic acid samples by “methods” that included “whole genome analysis.” EX2112 5. Slide 13 shows that the Accuracy Program included “receiv[ing]” and “de-identify[ing] samples”

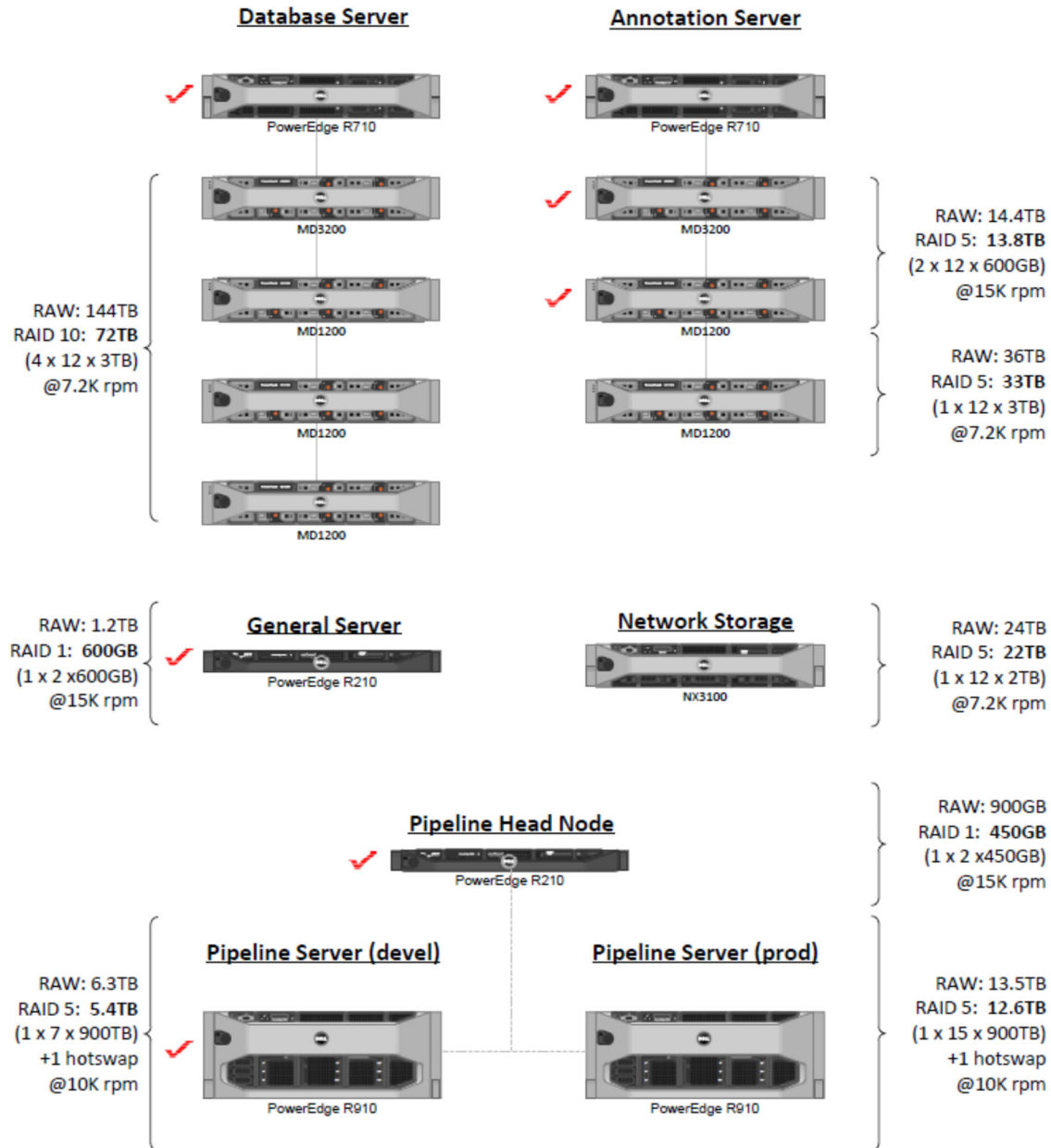
⁴ For ease of reference, the Challenged Claims are reproduced in Appendix A.

from customers. *Id.* 13. The WGS is a first sequencing assay conducted on a first sample from a customer, and that sample includes a first subset of nucleic acid molecules. The result of WGS is the sequence of the first nucleic acid sequence. EX2032 ¶¶217-222.

(3) Limitation 1(c)

Conception of limitation 1(c) is reflected by, for example, Slide 5 of Mr. West's Presentation. The Accuracy Program involved the use of "content-based semi-custom" capture probes to "pullout" genotypes and structural variants. "Pullout" refers to a panel of capture probes that would "pullout" target DNA via solution-phase hybridization and/or an array of capture probes. EX2112 5; EX2032 ¶¶223-227.

The capture probes were designed to hybridize to the "SV's", "SNP's", "allele", and "InDel's" polymorphisms that were identified by the "analysis" of the "whole genome analysis." EX2112 5. The genotypes and structural variants would be stored in databases on the Personalis servers (or elsewhere):



EX2044. The databases would include polymorphisms observed in a population of one or more samples from its customers. EX2112 5, 13; EX2032 ¶¶228-231.

An important business aspect of the Accuracy Program was to supplement the initial WGS data with additional sequencing of subsequently obtained biological

samples from the customer to provide “ongoing clinical use” of their genomic information rather than “just a genome once in your life”:

Publications & Upcoming Presentations

- Seminal paper by Mike Snyder & team published in Cell :
 - Ongoing clinical use of genome -scale sequencing
 - Not just a genome once in your life
- Multiple publications by Rong Chen
- JW invited to speak at CHI “The Clinical Genome” meeting
 - June 13, San Francisco
- JW invited to speak at Institute of Medicine meeting
 - Washington, DC, July

Personalis Confidential May 8, 2012

3

EX2112 3. The ongoing clinical use of the genome-scale sequencing would involve contacting the subsequently obtained biological sample of the customer with the “content-based semi-custom” capture probes to “pullout” the subset of the nucleic acid molecules having the genotypes and structural variants identified by the data generated from WGS. *Id.* 5; EX2032 ¶¶233-246.

(4) Limitation 1(d)

Conception of limitation 1(d) is reflected by, e.g., Slide 5 of Mr. West’s Presentation. The Accuracy Program involved supplementing a base whole genome

or exome with hybrid capture probe sets to generate additional DNA sequencing reads which:

Filled in some of the systematic gaps in sequencing coverage,

Included longer molecules to address alignment problems, and

Supplemented an exome (which focuses on the coding regions of genes) with additional content from outside the coding regions of the genes.

EX2109 2-3. These were the “content-based” “pullout” assay elements referred to in Slide 5 of the Presentation. The additional sequencing reads are obtained via a subsequent sequencing assay. EX2112 5; EX2032 ¶¶247-250.

(5) Limitations 1(e)-(f)

Conception of limitations 1(e)-(f) is reflected by, e.g., Slide 3 of Mr. West’s Presentation. As discussed for limitation 1(c), the Accuracy Program included using capture probes to generate an additional subset of nucleic acid molecules from an additional nucleic acid sample. The additional plasma sample would be obtained at a different (e.g., later) time point than the first sample to provide “ongoing clinical use of genome-scale sequencing.” EX2112 5. As discussed for limitation 1(d), the Accuracy Program involved supplementing a base whole genome or exome with hybrid capture probe sets to generate additional DNA sequencing reads which:

Filled in some of the systematic gaps in sequencing coverage,

Included longer molecules to address alignment problems, and

Supplemented an exome (which focuses on the coding regions of genes) with additional content from outside the coding regions of the genes.

EX2109 2-3. These were the “content-based” “pullout” assay elements referred to in Slide 5. The additional sequencing reads are a subsequent (e.g., third) sequencing assay conducted on a subsequent (e.g., third) subset of nucleic acid molecules that are pulled out by the capture probes in a subsequent (e.g., third) assay and the results of the subsequent sequencing assay is the sequence of the subsequent subset of nucleic acid molecules. EX2112 5; EX2032 ¶¶251-255.

(6) Limitation 1(g)

Conception is reflected by, e.g., Slide 5 of Mr. West’s Presentation, which includes identifying biomedical information regarding interpretable variants that were identified by the “analysis” of “WGS,” which included identifying “SV’s”, “SNP’s”, “allele[s]”, and “InDel’s” having “medical interpretation impact.” EX2112 5. For the “analysis” to have “medical interpretation impact,” the inventors intended to provide a report to the customer to interpret the medically impactful SV’s, SNP’s, alleles, and InDel’s identified by the Accuracy Program. Slide 13 provides additional details, which included “sample to results (important for research and later clinical” and “position as ‘value-added genome.’” The “results” that are “important for research and later clinical use” were to be identified in a report

for the customer so that Personalis would provide “value-added” biomedical information about the customer’s genome. EX2112 13; EX2032 ¶¶256-260.

e) Claim 2

Conception is reflected by, for example the above discussion of limitation 1(g). For example, Mr. West’s Presentation described identifying biomedical information regarding interpretable variants that were identified by the “analysis” of “WGS,” which included identifying “SV’s”, “SNP’s”, “allele[s]”, and “InDel’s” having “medical interpretation impact.” The inventors intended to provide a report to the customer to interpret the medically impactful variants identified by the Accuracy Program. The medically impactful variants include those that are predictive, prognostic, or diagnostic of one or more biomedical features such as a disease state, efficacy of a drug therapy, prediction of optimal drug dosage, recommendation of one or more therapies, and recommendation of a course of treatment of a disease. EX2112 5; EX2032 ¶¶261-263.

f) Claims 3-4

Conception is reflected by, for example the above discussion of claim 1. The Accuracy Program included identifying biomedically interpretable variants that were identified by the “analysis” of “WGS,” which included identifying polymorphisms of “SV’s”, “SNP’s”, “allele[s]”, and “InDel’s” having “medical interpretation impact” in genes. EX2112 5; EX2032 ¶¶264-271.

g) Claim 5

Conception is reflected by, e.g., Slide 4 of Mr. West's Presentation, which describes the use of a "cancer-gene pullout panel" of capture probes:

Market Developments

- Illumina / Roche
 - Financial pressure on Illumina may drive more aggressive approach to clinical potential
 - Illumina will be asked whether it is developing that opportunity as fast as Roche might
 - MiSeq moving to 510k; Cancer-gene pullout panel released
 - 2 x 250 reads now "summer" and only MiSeq
- Complete Genomics
 - Delivery times being quoted as 12-16 weeks
- Oxford Nanopore
 - No data seen yet, but tentative meeting in UK in July
- Life Ion Proton
 - Expect HapMap genome for analysis in the next month

Personalis Confidential May 8, 2012

4

EX2112 4. The "cancer-gene pullout panel" would include sequences encoding genes associated with cancer. Personalis also had licensed the PharmGKB, MendelDB, and Varimed databases, which include genes associated with cancer, EX2042 12, to include in reports to their customers. *Id.* 25; EX2032 ¶¶272-275.

h) Claim 6

Mr. West was aware of a paper authored by Dr. Snyder. EX2112 3. That paper reported on a 54-year-old man who was whole genome sequenced at an initial time point, and then assessed using blood samples (including analysis of plasma) at 20 time points over a 400-day period. EX2030 1294. The timing of blood samples from the man varied from as little as one day apart to as long as 95 days. *Id.* Figure 1(A). The inventors realized that the Accuracy Program would benefit from samples being taken at different intervals from customers, including a sample taken at least 1 week or more after the first sample. EX2032 ¶¶276-280.

i) Claim 7

As discussed for claim 6, the inventors realized that the Accuracy Program would benefit from samples being taken at different intervals, including at least 1 month or more after the first sample. EX2032 ¶¶281-283.

j) Claim 8

As discussed for claims 6-7, the inventors realized that the Accuracy Program would benefit from samples being taken at different intervals, including at least 1 week or more after the first sample. EX2032 ¶¶284-285.

k) Claim 9

As discussed for limitation 1(c), an important business aspect of the Accuracy Program was to supplement the initial WGS data with additional sequencing reads

for a subsequently obtained biological samples from the customer. The additional sequencing reads are a subsequent sequencing assay, and the results of the subsequent sequencing assay would be compared with the results from the previous sequencing assay(s). EX2032 ¶¶286-289.

l) Claim 10

Conception is reflected by, e.g., Slide 5 of Mr. West’s Presentation. The Accuracy Program included validation sequencing, such as “Sanger validation” sequencing, to verify that the capture probes effectively “pulled out” the targeted genotypes and structural variants of interest. The validation sequencing allowed the inventors to analyze the customer’s subsequent nucleic acid sample for the presence (or absence) of the targeted genotypes and structural variants (which are polymorphisms) of interest. EX2112 5; EX2042 10 (report listing variants detected); EX2032 ¶¶290-293.

m) Claim 11

Slide 11 of Mr. West’s Presentation included observing parental allele frequencies in children in the “CEPH1463 Pedigree Analysis:”

CEPH1463 Pedigree Analysis		Percent of the Genome Over Which We Can See, Across the Data From All of the Children Included:					
		All Inheritance states		All Parental Alleles		All Genotypes possible from parents	
		Once	Twice	Once	Twice	Once	Twice
All 11 Children		99.9%	99.9%	100.0%	96.8%	84.0%	32.0%
The combination of 5 children which maximizes % genome where all inheritance States are represented at least once (Children # 1,3,7,8,11)		91.0%	36.8%	94.7%	35.1%	22.0%	0.0%
As above, but at least twice (Children # 2,8,9,10,11)		87.4%	46.0%	89.1%	35.9%	20.6%	0.0%
All I.S. at least once, but meeting the criteria from X chromosome analysis (Children # 2,3,5,6,11)		89.5%	36.8%	92.9%	38.6%	26.4%	0.0%
As above, but using data from Son # 1 (recently sequenced by Illumina & submitted to the SRA) (Children 1,2,3,8,11)		88.3%	35.5%	92.6%	38.0%	24.9%	0.0%

All 11 children

Several optimal subsets with 5 of the 11 children

Mendelian Inheritance Error analysis can be confounded by genomic variation induced by the cell culture process. Being able to see each parental allele in two separate children should let us separate most of these errors from sequencing artifacts, letting us better identify them.

Personalis Confidential May 8, 2012

11

EX2112 11. The inventors had also focused on allele frequencies of individual genetic variants in data from individuals. EX2115 10, 12; EX2032 ¶¶294-297.

n) Claim 12

The Accuracy Program combined technologies to supplement WGS with “semi-custom” assays using “pullout” technologies. EX2112 5. It included “pulling out” desired content from a DNA sample by streptavidin-coated magnetic beads conjugated to biotin-labelled capture probes. At least Mr. West and Dr. Pratt were aware that custom and semi-custom capture probes could be designed and then manufactured under contract by Agilent that utilized biotinylated capture probes being conjugated to magnetic beads. EX2045 31; EX2033 ¶19; EX2032 ¶¶298-301.

o) Claim 13

At least Mr. West and Dr. Pratt were aware that it was possible to multiplex multiple samples by adding a DNA barcode to the end of each molecule of DNA to be sequenced. A sample-specific barcode in a ligated adaptor can be used in the library preparation of each sample. The barcode serves as an index which would become part of each sequence read, and in this way amortized the cost of sequencing over the pooled samples. Mr. West and Dr. Pratt were familiar with the use of DNA barcodes to multiplex samples for sequencing on the Illumina instruments based on their previous employment at Illumina. They were also aware that Agilent's customer-designed capture probe kits could be pooled for efficient sequencing by the use of barcoded libraries. EX2045 31, 33; EX2032 ¶¶302-306.

p) Claim 14

Slide 11 of Mr. West's January 5, 2012 slides is entitled "Examples of process variability," and the first line stated "[s]ample source (blood, saliva, tissue, cell culture)":

Examples of process variability

Many more likely to follow

- Sample source (blood, saliva, tissue, cell culture)
- Sample preservation, culturing & prep for sequencing
- DNA sequencing platform, lab & operator(s)
- Coverage
- Read length
- Paired-end insert length (a distribution)
- Cluster creation & Sequencing chemistry versions
- Cluster density
- Variation in data processing algorithms, input parameters, reference sequence
- DNA contamination or incomplete filtering of primer -related artifacts
- Availability of supplementary data from the same sample (e.g. genotyping)
- Inconsistent supplementary information from / about the individual sequenced

EX2046 12; EX2032 ¶¶307-309. The Accuracy Program therefore included sample sources obtained from the customer that included body fluid (e.g., blood, saliva), cell (e.g., culture cell), and tissues and organs.

q) Claim 15

Slide 3 of Mr. West’s Presentation described a “[s]eminal paper by Mike Snyder & team published in Cell” which supported his idea for the Accuracy Program to include “[o]ngoing clinical use of genome-scale sequencing” and “[n]ot just a genome once in your life.” EX2112 3.

The referenced paper reported on a 54-year-old man who was whole genome sequenced at an initial time point, and then assessed using blood samples (including

analysis of plasma) at 20 time points over a 400-day period. EX2030 1294. The inventors realized that the Accuracy Program could be more efficient than the untargeted RNAseq used in the Snyder paper on blood plasma samples by replacing it with a “content-based semi-custom” approach using “pullout.” EX2112 5. Thus, the Accuracy Program included the body fluid sample being a blood plasma sample. EX2032 ¶¶310-313.

r) Claim 16

The Accuracy Program included nucleic acid sample isolated from the individual being isolated from a tissue biopsy. Slide 11 of Mr. West’s January 5, 2012 slides is entitled “Examples of process variability,” and the first line stated “[s]ample source (blood, saliva, tissue, cell culture).” EX2046 12; EX2032 ¶¶314-315.

s) Claims 17-18

The Accuracy Program included whole genome sequencing producing at least 750,000,000 and 1,000,000,000 sequencing reads. The Accuracy Program included WGS of samples at 60x coverage. EX2112 12; EX2042 19; EX2032 ¶¶316-320.

t) Claim 19

By no later than May 8, 2012, the Accuracy Program included repeating said third sequencing assay one or more times on one or more subsequent samples to yield an additional result comprising a fourth nucleic acid sequence and generating

an additional biomedical report that includes biomedical information of said subject, which biomedical information identifies the presence or absence of said one or more polymorphisms identified by said additional result for the same reasons discussed above regarding limitations 1(e)-(g). EX2032 ¶¶321-322.

u) Conclusion

In conclusion, the inventors had conceived of the invention recited by claims 1-19 of the '394 patent by no later than May 8, 2012. The inventors recognized and appreciated that the Accuracy Program had the features that are now recited by claims 1-19. EX2032 ¶¶323-324.

2. Diligence

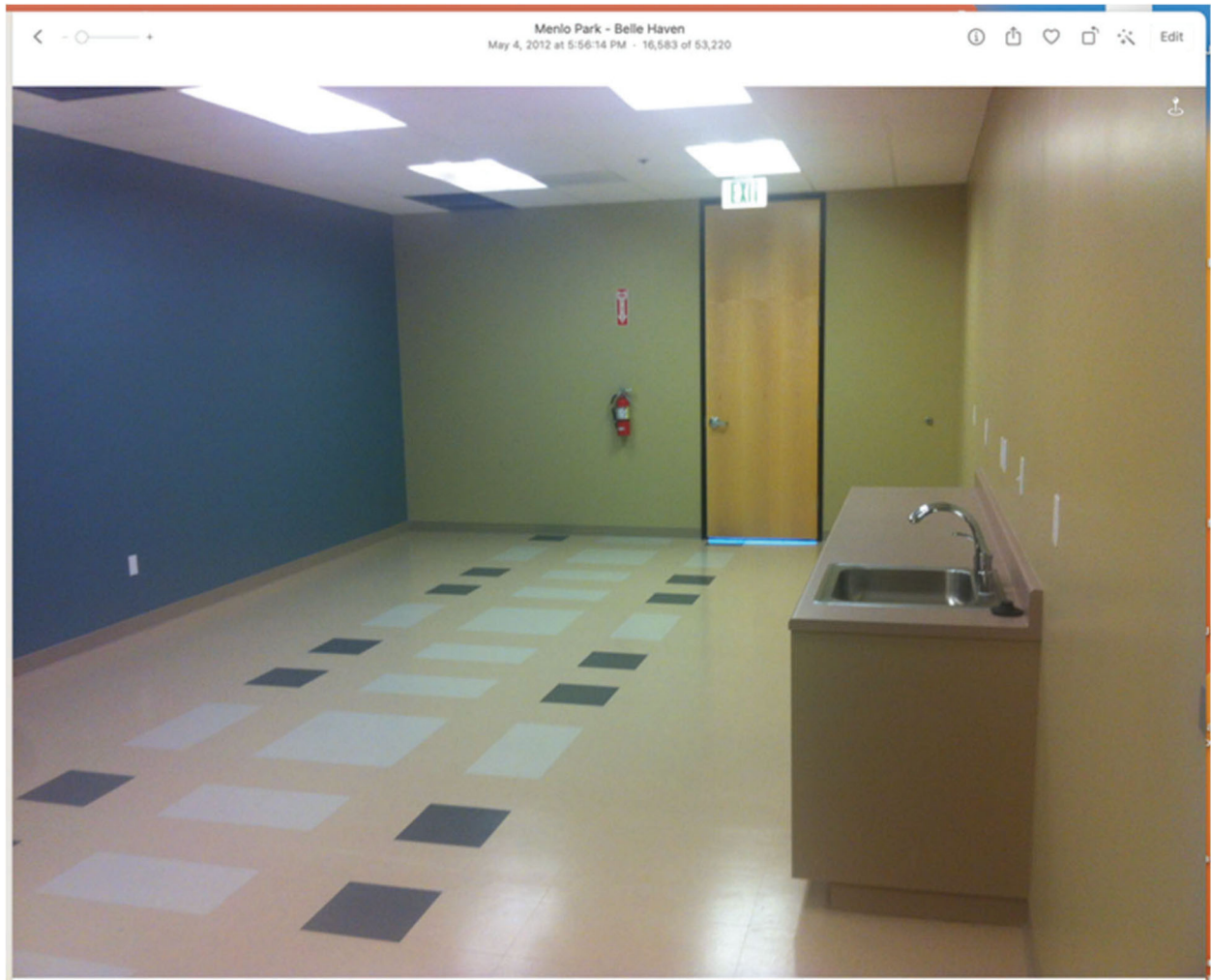
The inventors diligently pursued reducing the claimed invention to practice from May 8, 2012 through its constructive reduction to practice on January 17, 2013. During this time, Personalis constructed a relatively modest laboratory and preformed testing to diligently reduce the invention to practice. Below, each month of diligence is summarized.

a) May

The co-inventors were reasonably continuous and diligent from May 9-30, 2012.

In May 2012, Personalis was a small start-up company. It did not have laboratory space. During the May 8, 2012 Board Meeting (when Mr. West disclosed

the invention to the Board members), the Board approved leasing 12,000 square feet of space to build a laboratory and expend up to \$157,000 on genome sequencing to reduce the invention to practice. EX2043 2. The empty office space is shown below:



Over the coming months, the inventors turned the space into a small laboratory. EX2032 ¶¶325-330.

Further evidence of diligence exercised by the inventors include team meetings during which updates on the Accuracy Program were discussed on May 11, 21, and 25. EX2047; EX2048; EX2049; EX2050; EX2032 ¶¶332, 338, 342.

On May 14, 2012, Dr. Chen sent an email to Mr. West detailing the formation of “a Founder-led work group” to “meet weekly for 2-4 hrs and present updates every 4-6 weeks” to “keep making progress on” the various projects within the company. Mr. West was the Founder leader for the Accuracy Program and Dr. Pratt was the employee leader. EX2051; EX2032 ¶333.

On May 15, 2012, Dr. Pratt sent an email and attachment to Mr. West. Slide 1 of the attachment describes “facets” of the Accuracy Program including the use of “[c]omplementary assays and analytical methods for production use” including “[t]argeted pullout and tailored insert sequencing libraries.” EX2052; EX2032 ¶334.

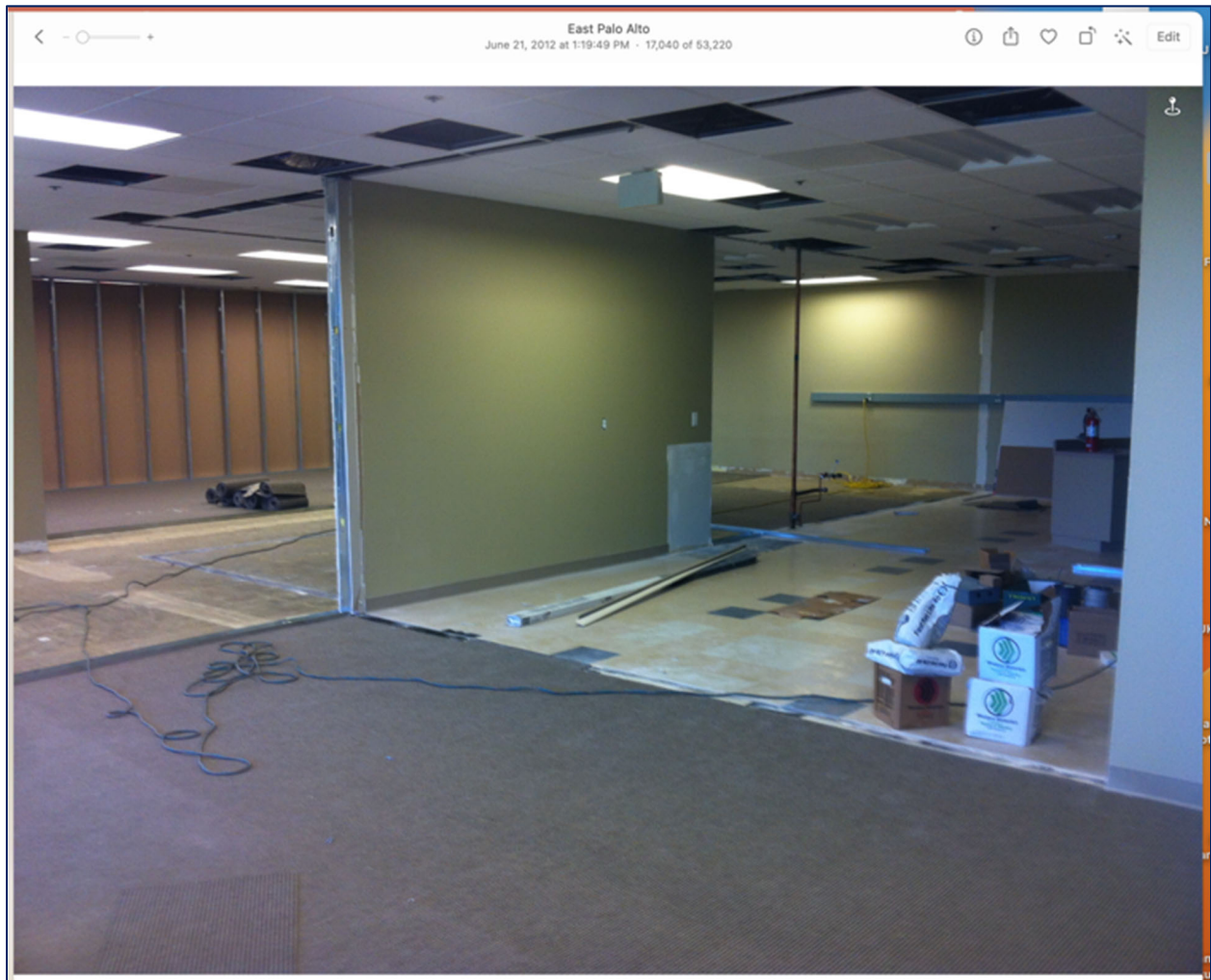
On May 15, 2012, Scott Kirk, a Personalis employee, sent an email to Mr. West and others containing notes referencing a “[m]eeting to define [a] path for how accuracy folds into the greater picture” of Personalis’ commercial business plan. EX2053; EX2032 ¶335.

On May 22, 2012, Mr. West sent emails and attachments on how to differentiate the Accuracy Program from existing technologies, EX2054, and an overview of the Accuracy Program. EX2055; EX2032 ¶¶339-340.

On May 29, 2012, Mr. West sent an email with several attachments to Personalis employees to explain progress on the Accuracy Program. EX2056; EX2032 ¶343.

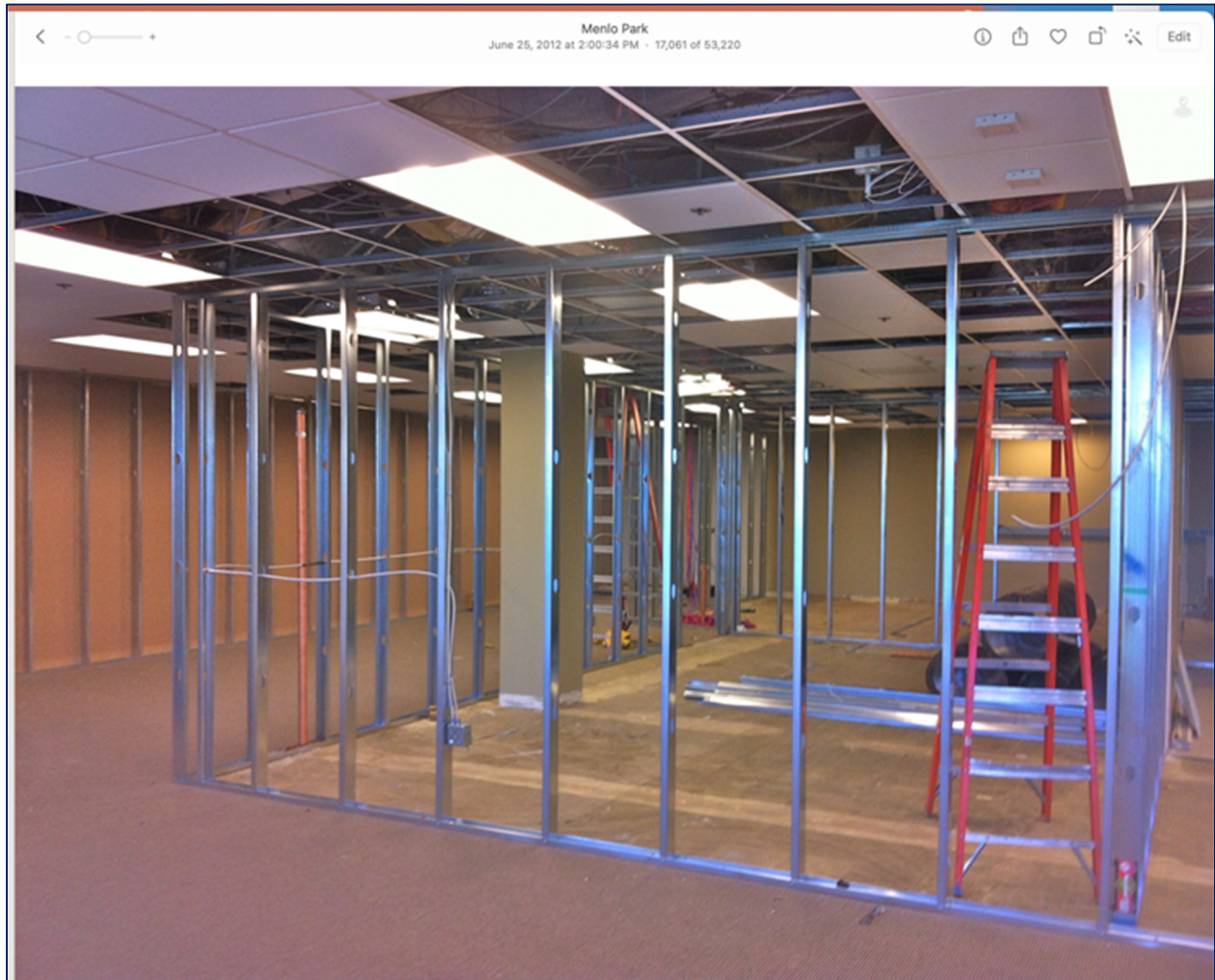
b) June

The co-inventors were reasonably continuous and diligent throughout June 2012. Evidence of diligence includes construction of Personalis' laboratory space. By June 21, 2012, walls had been torn down and laboratory construction was underway:



EX2032 ¶352.

By June 25, framing had been installed for the laboratory walls:



EX2032 ¶354.

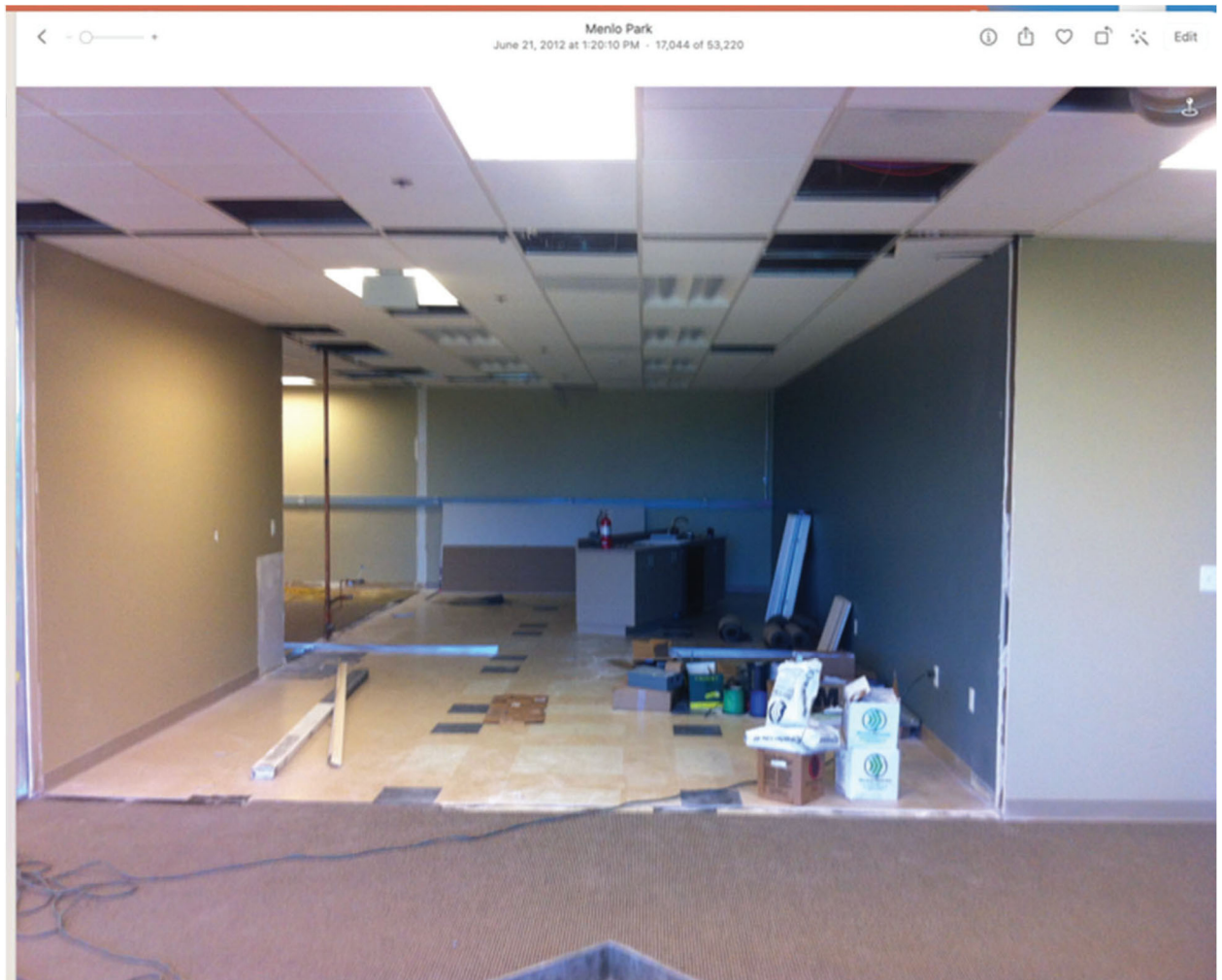
Further evidence of diligence includes team meetings during which updates on the Accuracy Program were discussed on June 1, 15, 22 and 29. EX2057; EX2058; EX2059; EX2060; EX2032 ¶¶344, 349, 353, 356.

On June 7, 2012, Mr. West sent an email and attachment to Dr. Chen explaining how the Accuracy Program can detect and eliminate various data error types. EX2061; EX2032 ¶345.

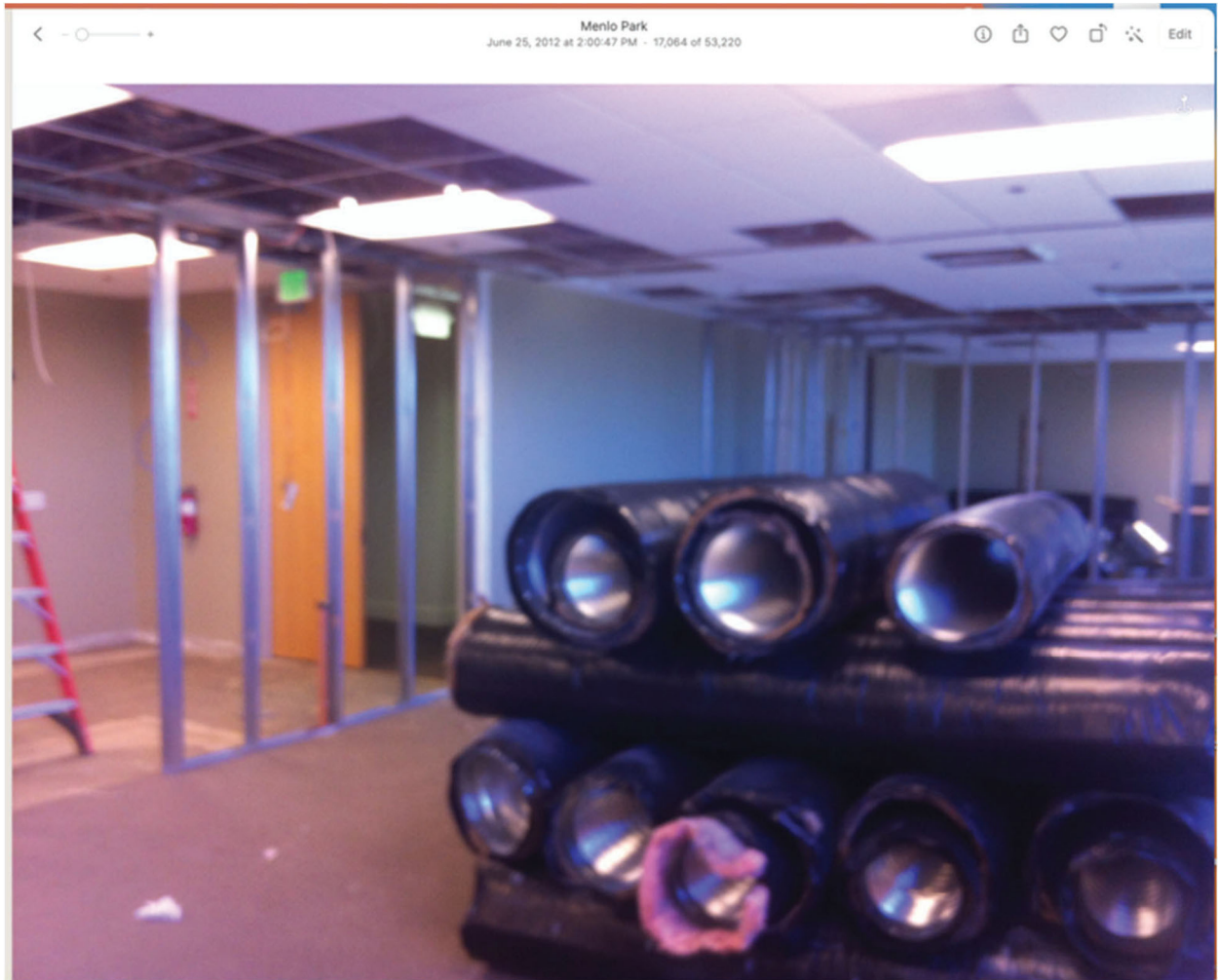
On June 12, 2012, Personalis held a Board of Directors meeting, during which Mr. West and Dr. Chen described progress on the Accuracy Program. EX2062; EX2063; EX2032 ¶¶346-348; EX2033 ¶¶27-31. The Board approved up to \$240,000 to purchase computing equipment and \$620,000 to purchase sequencing equipment. EX2064 2. HiSeq-2000 and MiSeq instruments were delivered on June 21, 2012. The HiSeq-2000 could not be installed until construction of the laboratory was completed. EX2032 ¶351.

On June 17, Mr. West sent an email to several Personalis employees describing his top three goals for pursuing the Accuracy Program. EX2065; EX2032 ¶350.

Construction of the laboratory had started by June 21, 2012:



EX2032 ¶¶352. Air ducts were installed:



EX2032 ¶¶354-355. The inventors ran their first sequencing run on the MiSeq instrument on June 29, 2012.

c) July

The co-inventors were reasonably continuous and diligent throughout July 2012. The inventors completed their first low coverage human genome sequencing experiment on July 19, 2012 and another on July 25. EX2032 ¶¶362, 365.

Further evidence of diligence includes team meetings during which updates on the Accuracy Program were discussed on July 6, 13, 20, and 27. EX2066; EX2067; EX2068; EX2069; EX2032 ¶¶357-358, 363, 366.

On July 18, 2012, Personalis held a Board of Directors meeting, during which Mr. West and Dr. Chen described progress on the Accuracy Program. EX2070; EX2071; EX2072; EX2032 ¶¶359-361; EX2033 ¶¶32-36.

On July 24, 2012, Dr. Pratt sent an email to Mr. West discussing progress on the Accuracy Program. EX2074; EX2032 ¶364.

d) August

The co-inventors were reasonably continuous and diligent throughout August 2012. Laboratory construction was complete by August 4, 2012, and the HiSeq-2000 was installed by August 13. The inventors continued to install instruments and purchase materials for use in the laboratory. EX2032 ¶¶368-370, 375; EX2075; EX2076; EX2077; EX2078.

Further evidence of diligence includes team meetings during which updates on the Accuracy Program were discussed on August 3, 10, and 17. EX2079; EX2080; EX2081; EX2032 ¶¶367, 371, 373.

On August 20, 2012 Mr. West sent an email and attachment describing “Accuracy at the laboratory level” and “Accuracy in medical interpretation.” EX2082; EX2032 ¶374.

e) September

The co-inventors were reasonably continuous and diligent throughout September 2012.

On September 5, 2012, Personalis held a Board of Directors meeting, during which Mr. West and Dr. Chen described progress on the Accuracy Program. EX2083; EX2084; EX2085; EX2086; EX2032 ¶¶376-379; EX2033 ¶¶37-41. The Board approved up to \$560,000 to purchase a second HiSeq-2000 sequencing instrument. EX2087 2.

On September 7, 2012, a team meeting was held during which updates on the Accuracy Program were discussed. EX2088; EX2032 ¶380.

On September 27, 2012, Personalis submitted a purchase order of \$29,444 for custom SureSelectXT capture probe libraries from Agilent Technologies for testing purposes to reduce the Accuracy Program to practice. EX2089; EX2032 ¶382.

f) October

The co-inventors were reasonably continuous and diligent throughout October 2012. Evidence of diligence includes team meetings during which updates on the Accuracy Program were discussed on October 5, 9, 10, and 24. EX2090; EX2091; EX2092; EX2093; EX2032 ¶¶384, 386, 388, 391.

On October 4 and 10, Mr. West received emails from Scott Kirk providing status updates on the Accuracy Program including data analysis performed by

Personalis to reduce the invention to practice. EX2094; EX2095; EX2032 ¶¶383, 387.

On October 9 and 12, Mr. West sent emails and attachments to Personalis employees summarizing the current status of the Accuracy Program, EX2096, and describing that the “[f]irst round pullout kits are due in about 3 weeks” from Agilent. EX2097; EX2032 ¶¶385, 389.

On October 19, 2012, Mr. West expressed interest in filing a patent application for the Accuracy Program. EX2098; EX2032 ¶390.

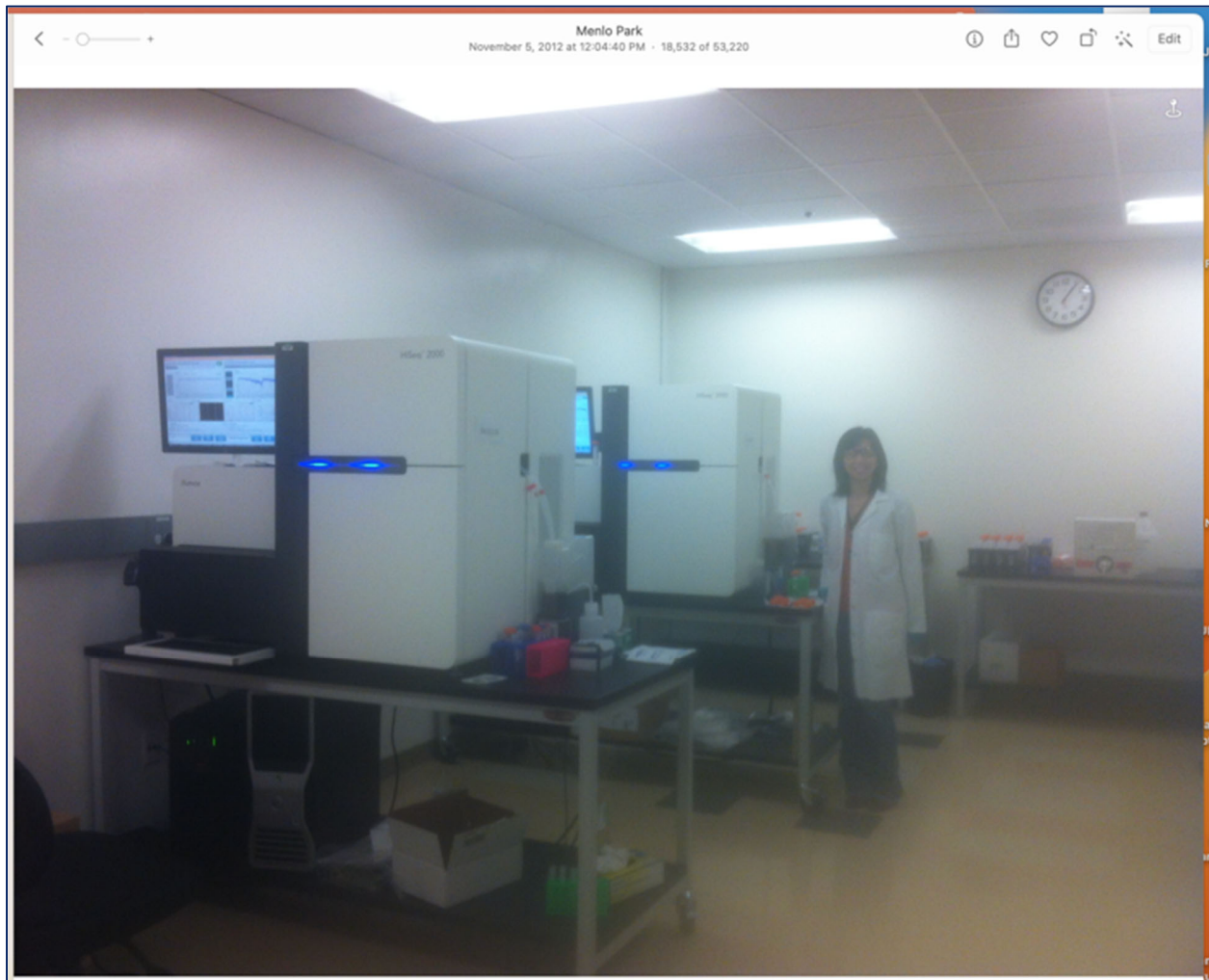
On October 31, 2012 the inventors received the first set of hybrid capture probes (which they had ordered on September 27). EX2032 ¶392.

g) November

The co-inventors were reasonably continuous and diligent throughout November 2012. By November 5, 2012, the laboratory space included Personalis’ cBot and MiSeq instruments, as shown with co-inventor Shujun Luo:



She is shown with the two HiSeq-2000 instruments:



She is shown with their molecular biology workbench:



EX2032 ¶399.

On November 1, 2012, Personalis held a Board of Directors meeting, during which Mr. West and Dr. Chen described progress on the Accuracy Program. EX2099; EX2100; EX2101; EX2032 ¶¶393-396; EX2033 ¶¶42-46. The Board approved up to \$110,000 to acquire an additional MiSeq instrument. EX2111 2.

On November 1, 2012, Mr. West received an email and attachment from Shujun Luo discussing laboratory updates for the Accuracy Program. EX2102; EX2032 ¶397.

Evidence of diligence includes team meetings during which updates on the Accuracy Program were discussed on November 1 and 21. EX2101; EX2103; EX2032 ¶¶398, 400.

h) December

The co-inventors were reasonably continuous and diligent throughout December 2012. Evidence of diligence includes a team meeting during which updates on the Accuracy Program were discussed on December 7. EX2104; EX2032 ¶401.

On December 14, 2012, Personalis held a Board of Directors meeting, during which Mr. West and Dr. Chen described progress on the Accuracy Program. EX2105; EX2106; EX2032 ¶¶402-403; EX2033 ¶¶47-51.

Privileged communications with patent counsel regarding the provisional application that was eventually filed in January occurred on December 18, 21, and 27. EX2032 ¶¶404.

i) January

The co-inventors were reasonably continuous and diligent from January 1, 2012 through the filing of the provisional application on January 17, 2012.

Privileged communications with patent counsel occurred on January 4, 10, 16, 17, and 18. EX2032 ¶408. Evidence of diligence further includes a team meeting during which updates on the Accuracy Program were discussed on January 16. EX2108; EX2032 ¶¶405-407.

Based on at least the foregoing, the inventors had conceived of the claimed invention by no later than May 8, 2012 and were reasonably continuously diligent in reducing the invention to practice from conception through January 17, 2013. Accordingly, Chan is not prior art to the '394 patent.

B. Chan and Liao do not cure the deficiencies of Leary

The combination of Leary, Chan, and Liao fail to disclose at least the following limitations of claim 1:

- the “whole genome sequencing” (WGS) required by limitation 1(b),
- the “second nucleic acid sample” required by limitation 1(c),
- the “capture probes” required by limitation 1(c),
- the “plurality of capture probes” required by limitation 1(e), and
- the “third sequencing assay” required by limitation 1(f).

As a result, Ground 3 fails to render obvious claim 1.

1. Limitation 1(b)

Leary fails to teach or suggest WGS. *Supra* Section III.A.3. Foresight asserts that Chan’s “shotgun sequencing of a plasma sample” constitutes the WGS required by limitation 1(b). Petition 63-64. Foresight is wrong.

The DNA circulating in plasma exists in a fragmented state with “an average length of 140 to 170 base pairs (bp) and is present in only a few thousand amplifiable copies per milliliter of blood, of which only a fraction may be diagnostically relevant.” EX1030 1. Nucleases digest DNA, and the DNA fragments that best survive nuclease digestion are bound to nucleosomes, whereas unbound DNA is almost completely degraded and lost. EX2031 ¶167. As a result, the portions of the genome that are not bound to nucleosomes are largely missing from the DNA circulating in plasma. *Id.*

Chan’s “shotgun sequencing of plasma DNA,” EX1008 223, does not constitute sequencing all or almost all of the patient’s genome because the fragmented DNA circulating in the plasma does not include the entire genome. EX2031 ¶¶168-169. Chan apparently recognizes this by describing its method as only performing “cancer genome *scanning*.” EX1008 223. Tellingly, Chan never characterizes its technique as “whole genome sequencing.”

Liao instructs a POSA that a target enrichment approach is a logical choice to use instead of WGS based on efficiency and expense. EX1009 92 (“Rather than

nonselectively sequencing the genome, target enrichment provides a logical approach for more efficient and cost-effective massively parallel sequencing because it increases the proportion of informative data from the targeted region(s).”). Thus, Liao teaches a POSA that WGS is undesirable. Accordingly, none of Foresight’s references teach or suggest the WGS required by limitation 1(b).

2. Limitation 1(c)

Foresight relies on a generalized statement in Chan about combining “targeted and shotgun approaches” in view of “solution-phase hybridization-based capture approaches hav[ing] already been successfully” used in the prior art to assert that a POSA would have modified Leary’s PCR primer approach to arrive at the “capture probes” recited by limitation 1(c). Petition 64-73. The Board described the specification of the ’394 patent as providing “no preference between PCR and solution-based hybridization enrichment strategies,” and would view them as “relatively interchangeable.” Decision 38.

A POSA was well aware that PCR primers and capture probes have a different “core reaction principle,” EX1006 375, and “[g]iven the operational characteristics of these different targeted enrichment methods, they naturally vary in their suitability for different fields of application,” *id.*, and provide “very divergent [] results” with “very different average coverage, evenness and specificity.” *Id.* 383; *supra* Section III.A.3.a. The generalized statement in Chan provides no reason why a POSA would

have modified Leary's specific PCR-based assay to use capture probes. For example, Foresight fails to explain how a POSA would have evaluated any of the seven parameters and seven metrics associated with the disadvantages of capture probes before abandoning the core reaction principle of Leary's PCR primers and replacing it with capture probes. *Supra* Section III.A.3.b. Foresight also fails to explain how capture probes could conceivably replace PCR *to serve as the detection method* for Leary's assay. EX2031 ¶¶172-174.

The claimed invention recites a specific method that first conducts WGS (which neither Leary, Chan, or Liao teach), and then uses capture probes *after* WGS sequencing on a second sample. Chan fails to teach using capture probes *after* WGS, and further fails to teach a second sample. Foresight asserts that Chan's supposed use of solution-phase hybridization capture is conducted *before* the sequencing—not after like claimed. Petition 69 (“The catch is then ‘pulled down’ or ‘fished out’ using beads that bind the biotin that was incorporated into the baits, and the catch can then be PCR amplified *before* analysis with Next-Generation Sequencing.”).

Foresight also asserts that a POSA would use solution-phase hybridization probes “in addition to the PCR primer capture probes” taught by Leary. However, Foresight's Mamanova exhibit teaches that PCR amplification has a “negative influence” on hybrid capture, that combining them should be “avoided,” and if used at all, only “after hybridization” as follows:

We noted a negative influence of PCR amplification on the uniformity of enrichment in both on-array and in-solution methods: performing 18 cycles of PCR amplification of libraries both before and after hybridization can introduce severe bias toward neutral G+C content in the resulting sequences (Fig. 5b). Avoiding the PCR step altogether before hybridization greatly improved the situation (Fig. 5c), so it is desirable to keep PCR amplification to a minimum and only perform it after hybridization.

EX1007 116. Foresight fails to address how a POSA would overcome the known incompatibilities of PCR primers and capture probes in its proposed combination of Leary, Chan, and Liao. This combination of references fails to teach or suggest the claimed invention.

3. Limitations 1(e) and 1(f)

Chan does not suggest “tun[ing] the capture technique to the types of mutations identified in the whole-genome sequencing step” as alleged by Foresight to meet limitation 1(e). Petition 74. Dr. Quackenbush merely parrots the petition on this issue, and his unsupported testimony is entitled to no weight. Foresight provides no citation to where Chan teaches this, which is not surprising because Chan has no such teaching.

Foresight relies on Leary for allegedly performing the “third sequencing assay” for limitation 1(f), and further asserts that a POSA would replace Leary’s PCR primers with capture probes based on Chan. As discussed above, a POSA

would not have been motivated modify Leary to include unnecessary re-verification sequencing, *supra* Section III.A.5, and a POSA would not have been motivated to replace Leary's PCR primers with capture probes based on Chan, *supra* Section V.B.2.

Based on at least the foregoing, Foresight failed to prove obviousness of independent claim 1 based on the combination of Leary, Chan, and Liao. It necessarily fails to prove obviousness of any of the dependent claims as well.

VI. OBJECTIVE INDICIA OF NONOBVIOUSNESS

Objective indicia "can be the most probative evidence of nonobviousness in the record." *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010).

A. Nexus

Personalis is entitled to a presumption of nexus because Personalis' NeXT Personal[®] assay embodies claim 1. EX2031 ¶178; *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018). Also, the evidence independently shows a nexus.

B. Industry Praise

Personalis' assay has received industry praise due in part to its sensitivity. *Arctic Cat Inc. v. Bombardier Recreational Prod. Inc.*, 876 F.3d 1350, 1364 (Fed.

Cir. 2017). *The Scientist* magazine ranked the patented approach disclosed in the '394 Patent as the top innovation of 2022. EX2001; EX2035 ¶11.

Three institutions “adopted Personalis’ NeXT Personal” for their TRACERx study due to its “highly sensitive [test].” EX2153; EX2035 ¶¶14-17. AstraZeneca extended its collaboration with Personalis regarding NeXT Personal for clinical research. EX2154; EX2156; EX2035 ¶¶18-20.

Personalis’ assay can detect tumor in DNA in blood plasma at levels of about one part per million (or 0.0001%). By comparison, the best sensitivity from plasma DNA in Leary was about 0.3%, which is several hundred times less sensitive than the claimed method. EX1002 4, Fig. 4B:

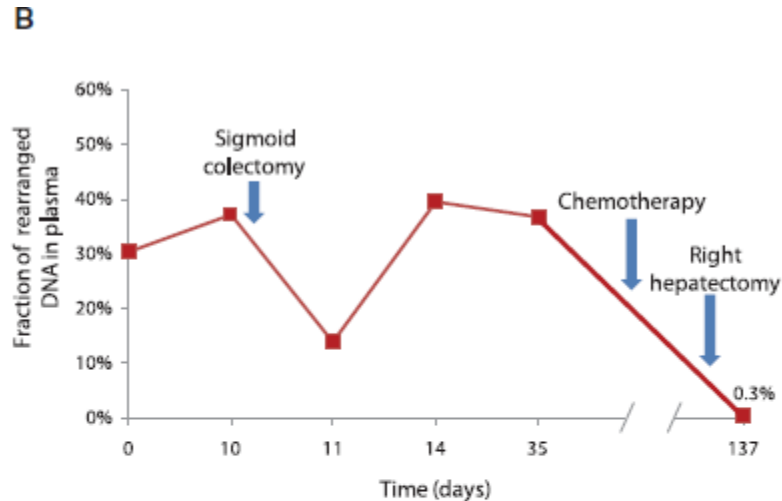


Fig. 4. Detection of tumor-specific rearrangements in plasma of cancer patients. (A) The identified chromosome 4:8 and 16 rearrangements were used to design PCR primers spanning breakpoints and to amplify rearranged DNA from tumor tissue and plasma from patients Hx402 and Hx403, respectively. A plasma sample from an unrelated healthy individual was used as a control for both rearrangements. (B) Plasma samples from patient Hx402 were analyzed at different time points using digital PCR to determine the fraction of genomic equivalents of plasma DNA containing the chromosome 4:8 rearrangement. The fraction of rearranged DNA at day 137 was 0.3%, consistent with residual metastatic lesions present in the remaining lobe of the liver.

EX1002 Fig. 4; 2031 ¶180. The patented technique has been lauded by independent judges as the top scientific innovation of 2022, and by research institutions and pharmaceutical companies.

C. Skepticism

The industry's experts held skepticism toward solving the challenges of conducting highly sensitive genome sequencing using capture probes. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335 (Fed. Cir. 2016). Forsheo explains that capture probes were “expensive” and “difficult to implement on a routine basis.” EX1030 10; EX1031 686. Other references outline industry-wide problems with next-

generation sequencing (NGS) at the time. Anderson emphasizes that “difficult engineering challenges must be overcome before these technologies could become commercially viable.” EX1004 48; EX2031 ¶¶181-182. Lo identifies difficulties regarding “how to handle the massive amount of sequencing data.” EX1017 3. This real-world evidence supports the nonobviousness of the '394 patent.

VII. CONCLUSION

The Board should confirm patentability of the '394 patent.

Respectfully submitted,

WEIL, GOTSHAL & MANGES LLP

Dated: October 6, 2023

/Derek C. Walter/

Derek C. Walter

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Counsel for Patent Owner Personalis, Inc.

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 13,961 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: October 6, 2023

/Derek C. Walter/
Derek C. Walter,
Lead Counsel for Personalis, Inc
Reg. No. 74,656

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 RESPONSE AND EXHIBITS 2016-2028, 2030-2123, 2151-2160, AND 2162** is being served electronically on October 6, 2023, to the e-mail addresses shown below:

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Dated: October 6, 2023

/Derek C. Walter/

Derek C. Walter,
Lead Counsel for Personalis, Inc
Reg. No. 74,656

APPENDIX A

Listing of Claims from U.S. 11,384,394	
Claim 1	
Preamble	1. A method for analyzing nucleic acid samples isolated from an individual, comprising:
1(a)	generating a first subset of nucleic acid molecules from a first nucleic acid sample obtained from said individual;
1(b)	conducting a first sequencing assay on said first subset of nucleic acid molecules to yield a first result comprising a first nucleic acid sequence wherein said first sequencing assay comprises whole genome sequencing;
1(c)	[i] ⁵ generating a second subset of nucleic acid molecules from a second nucleic acid sample of said individual by contacting said second nucleic acid sample with a plurality of capture probes, [ii] wherein said plurality of capture probes hybridize to one or more polymorphisms which are based on or extracted from one or more databases of polymorphisms, observed in a population of one or more samples, or a combination thereof, wherein said first sample or said second sample is obtained from said subject at a first time point;
1(d)	conducting a second sequencing assay on said second subset of nucleic acid molecules to yield a second result comprising a second nucleic acid sequence;
1(e)	using said plurality of capture probes to generate an additional subset of nucleic acid molecules from an additional nucleic acid sample isolated from an additional sample obtained from said subject at an additional time point different from said first time point;

⁵ Bracketed roman numerals, “[i]” and “[ii]”, have been added to limitation 1(c) for ease of references.

Listing of Claims from U.S. 11,384,394	
1(f)	conducting a third sequencing assay on said additional subset of nucleic acid molecules from said additional nucleic acid sample to yield a third result comprising a third nucleic acid sequence; and
1(g)	generating a biomedical report that includes biomedical information of said subject, which biomedical information identifies the presence or absence of said one or more polymorphisms identified by said second result or said third result.
Claim 2	
	2. The method of claim 1, wherein said biomedical information of said subject is predictive, prognostic, or diagnostic of one or more biomedical features selected from the group consisting of disease state, efficacy of a drug therapy, prediction of optimal drug dosage, recommendation of one or more therapies, and recommendation of a course of treatment of a disease.
Claim 3	
	3. The method of claim 1, wherein said one or more polymorphisms comprise one or more insertions, deletions, structural variant junctions, variable length tandem repeats, single nucleotide mutations, or a combination thereof.
Claim 4	
	4. The method of claim 1, wherein said one or more polymorphisms are in a set of genes with known biomedically interpretable variants.
Claim 5	
	5. The method of claim 4, wherein said set of genes with known biomedically interpretable variants comprise one or more genes or variants associated with cancer.

Listing of Claims from U.S. 11,384,394	
Claim 6	
	6. The method of claim 1, wherein said first time point and said additional time point are at least 1 week apart, or more.
Claim 7	
	7. The method of claim 1, wherein said first time point and said additional time point are at least 1 month apart, or more.
Claim 8	
	8. The method of claim 1, wherein said additional time point is later than said first time point.
Claim 9	
	9. The method of claim 1, further comprising comparing said first result and said second result.
Claim 10	
	10. The method of claim 1, further comprising identifying the presence or absence of said one or more polymorphisms in said second nucleic acid sample.
Claim 11	
	11. The method of claim 10, wherein said identifying comprises observing an allele frequency of said one or more polymorphisms.
Claim 12	
	12. The method of claim 1, wherein said plurality of capture probes are conjugated to beads.
Claim 13	
	13. The method of claim 1, wherein said plurality of capture probes further comprise barcodes.

Listing of Claims from U.S. 11,384,394	
Claim 14	
	14. The method of claim 1, wherein said samples isolated from said individual are isolated from a body fluid, cell, skin, tissue, organ, or combination thereof.
Claim 15	
	15. The method of claim 14, wherein said body fluid sample is a blood plasma sample.
Claim 16	
	16. The method of claim 14, wherein said tissue sample is a tissue biopsy sample.
Claim 17	
	17. The method of claim 1, wherein said whole genome sequencing produces at least 750,000,000 sequencing reads.
Claim 18	
	18. The method of claim 1, wherein said whole genome sequencing produces at least 1,000,000,000 sequencing reads.
Claim 19	
Preamble	19. The method of claim 1, further comprising:
19(i)	repeating said third sequencing assay one or more times on one or more subsequent samples to yield an additional result comprising a fourth nucleic acid sequence; and
19(ii)	generating an additional biomedical report that includes biomedical information of said subject, which biomedical information identifies the presence or absence of said one or more polymorphisms identified by said additional result.