

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS INC.,
Petitioner,

v.

PERSONALIS, INC.
Patent Owner.

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

PATENT OWNER RESPONSE

TABLE OF CONTENTS

	Page No.
I. INTRODUCTION	1
II. OVERVIEW OF THE '033 PATENT	4
III. FORSHEW AND CHAN ARE NOT PRIOR ART	5
A. Conception.....	7
1. Genesis of the Accuracy Program at Personalis	7
2. The Accuracy Program: November 2011 through May 8, 2012	10
3. Summary of Mr. West's May 5, 2012 Presentation	12
4. The Accuracy Program and the '033 patent claims	14
a) Claim 1 - Preamble	14
b) Limitation 1(a)(i)	17
c) Limitation 1(a)(ii)	18
d) Limitation 1(a)(iii)	19
e) Limitation 1(b).....	20
f) Limitation 1(c)	21
g) Limitation 1(d).....	22
5. Claim 2.....	24
6. Claim 3	25
7. Claim 4.....	26
8. Claim 5	26

TABLE OF CONTENTS
(*cont'd*)

	Page No.
9. Claim 6.....	28
10. Claim 7.....	28
11. Claim 8.....	29
12. Claim 9.....	30
13. Claim 10.....	30
14. Claim 11.....	31
15. Claim 12.....	32
16. Claim 13.....	33
17. Claim 14.....	34
18. Claim 15.....	34
19. Claim 16.....	35
20. Claim 17.....	35
21. Claim 18.....	36
22. Claim 19.....	36
23. Claim 20.....	36
24. Claim 21.....	36
25. Claim 22.....	37
26. Claim 23.....	38
27. Conclusion Regarding Conception	38

TABLE OF CONTENTS
(cont'd)

	Page No.
B. Diligence	39
1. May	39
2. June	42
3. July	46
4. August	47
5. September.....	48
6. October.....	48
7. November.....	49
8. December	53
9. January	53
IV. GROUND 1: FORSHEW DOES NOT ANTICIPATE THE CLAIMS	54
A. Forshew is not prior art	54
B. Forshew does not teach the “capture probes” recited by claim 1	54
1. Forshew does not teach the “capture probes” of limitation 1(a).....	55
a) Claim construction of “capture probes”	55
(1) The preliminary construction does not comply with the plain meaning of “capture probes”	57

TABLE OF CONTENTS
(*cont'd*)

	Page No.
(2) The specification does not contradict the plain meaning of “capture probe”	60
(3) Foresight incorrectly treats PCR primers as being interchangeable with capture probes.....	63
(4) Conclusion regarding claim construction	66
b) ForsheW does not teach “capture probes”	66
2. ForsheW does not teach the “plurality of capture probes” of limitation 1(b).....	67
3. ForsheW does not teach limitation 1(c).....	67
4. ForsheW does not teach limitation 1(d).....	68
V. GROUND 2: THE CLAIMS ARE NONOBVIOUS OVER FORSHEW AND WAGLE	68
A. ForsheW is not prior art	69
B. No motivation due to ForsheW’s miniscule amounts of DNA	69
C. No motivation to change the core reaction principle of ForsheW	72
D. No motivation to add capture probes to ForsheW	74
VI. GROUND 3: THE CLAIMS ARE NONOBVIOUS OVER WAGLE AND CHAN.....	76
A. Chan is not prior art.....	77

TABLE OF CONTENTS
(*cont'd*)

	Page No.
B. Wagle and Chan do not teach or suggest limitation 1(d).....	77
VII. OBJECTIVE INDICIA OF NONOBVIOUSNESS	79
A. Nexus.....	79
B. Industry Praise	80
C. Skepticism of Experts.....	82
VIII. CONCLUSION.....	83

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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<i>Crocs, Inc. v. Int’l Trade Comm’n</i> , 598 F.3d 1294 (Fed. Cir. 2010)	80
<i>Fox Factory, Inc. v. SRAM, LLC</i> , 944 F.3d 1366 (Fed. Cir. 2019)	81
<i>Henny Penny Corp. v. Frymaster LLC</i> , 938 F.3d 1324 (Fed. Cir. 2019)	81
<i>Hybritech Inc. v. Monoclonal Antibodies, Inc.</i> , 802 F.2d 1367 (Fed. Cir. 1986)	57
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<i>Luminara Worldwide, LLC v. Liown Elecs. Co.</i> , 814 F.3d 1343 (Fed. Cir. 2016)	56
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TABLE OF AUTHORITIES
(cont'd)

	Page No(s).
<i>Polaris Indus., Inc. v. Arctic Cat, Inc.</i> , 882 F.3d 1056 (Fed. Cir. 2018)	81
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<i>TIP Systems, LLC v. Phillips & Brooks/Gladwin Inc.</i> , 529 F.3d 1364 (Fed. Cir. 2008)	61
<i>Verdegaal Bros. Inc. v. Union Oil Co. of California</i> , 814 F.2d 628 (Fed. Cir. 1987)	56
<i>WBIP, LLC v. Kohler Co.</i> , 829 F.3d 1317 (Fed. Cir. 2016)	84

EXHIBIT LIST

Exhibit No.	Description
2001	The Scientist Staff, “2022 Top 10 Innovations,” Dec. 12, 2022, available at https://www.the-scientist.com/features/2022-top-10-innovations-70792
2002	Raphael, B., et al., “Identifying driver mutations in sequenced cancer genomes: computational approaches to enable precision medicine,” Genome Medicine 2014, 6:5
2003	Supplementary Figures 1-3 for Wagle, N., et al., “High-Throughput Detection of Actionable Genomic Alterations in Clinical Tumor Samples by Targeted, Massively Parallel Sequencing,” Cancer Discovery (2012) available at https://aacrjournals.org/cancerdiscovery/article/2/1/82/2910/High-Throughput-Detection-of-Actionable-Genomic
2004	Excerpt from U.S. Patent Appl. No. 14/810,337 prosecution history
2005	Excerpt from U.S. Patent Appl. No. 15/996,215 prosecution history
2006	Foresight Diagnostics Patent Issued for Minimal Residual Disease Detection Technology, dated Sept. 27, 2022 available at https://foresight-dx.com/news/foresight-diagnostics-patentissued-for-minimal-residual-disease-detection-technology-1
2007	Swanton, C., “Plasma-Derived Tumor DNA Analysis at Whole-Genome Resolution,” Clinical Chemistry 59:1 6-8 (2013)
2008	Embodying Product Claim Chart for U.S. Patent No. 11,403,033

Exhibit No.	Description
2009	Transcript of the deposition of John Quackenbush, Ph.D., taken on January 31, 2018 in Guardant Health, Inc. v. Foundation Medicine, Inc., Case IPR2017-01170, IPR2017-01447, IPR2017-01448
2010	<i>Curriculum Vitae</i> of Dr. Henry Morrice Furneaux
2011	Exhibit number not used
2012	Exhibit number not used
2013	Exhibit number not used
2014	Exhibit number not used
2015	Exhibit number not used
2016	Quackenbush hand-written genome sequencing calculations from September 21, 2023 deposition
2017	Berglund et al., Next-generation sequencing technologies and applications for human genetic history and forensics, <i>Investigative Genetics</i> , 2:23 (2011)
2018	Transcript of the deposition of John Quackenbush, Ph.D., taken on September 21, 2023
2019	RESERVED

Exhibit No.	Description
2020	RESERVED
2021	RESERVED
2022	RESERVED
2023	RESERVED
2024	Excerpt from File History of U.S. Patent No. 11,384,394
2025	Excerpt from File History of U.S. Patent No. 11,408,033
2026	Excerpt from Sambrook, et al., Molecular Cloning, Vol. 1, 2001
2027	Gellert, et al., Helix Formation by Guanylic Acid, Proc. N. A. S., Vol. 48, 1962
2028	Gerry, et al., Universal DNA Microarray Method for Multiplex Detection of Low Abundance Point Mutations, J. Mol. Biol (1999) 292, 251-262
2029	Exhibit number not used

Exhibit No.	Description
2030	Chen, et al., Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes, Cell 148, 1293-1307, March 16, 2012
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

Exhibit No.	Description
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

Exhibit No.	Description
2052	May 15, 2012 Email from Mark Pratt to John West re accuracy strategy notes with attachment
2053	May 15, 2012 Email from Scott Kirk to Richard Chen, et al., re Sprint 0 sprint backlog
2054	May 22, 2012 Email from John West to Richard Chen, et al., re Spreadsheet for 2pm discussion of Accuracy Differentiation with attachment
2055	May 22, 2012 Email from John West to Mark Pratt re My slides for meeting with Mike Snyder yesterday with attachments
2056	May 29, 2012 Email from John West to Scott Kirk re Accuracy documents to convert into project plan format with attachments
2057	June 1, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
2058	June 15, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
2059	June 22, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
2060	June 29, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
2061	June 7, 2012 Email from John West to Richard Chen re Accuracy next steps, spreadsheet to organize the discussion with attachment
2062	June 11, 2012 Email from Richard Chen to John West, et al. re updated board slides with attachment

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
2066	July 6, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
2067	July 13, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
2068	July 20, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
2069	July 27, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
2070	July 17, 2012 Email from Richard Chen to John West, et, al. re Final Board Slides with attachment
2071	July 18, 2012 Email from John West to Carol Tillis, et, al. re JW Board slides for printing with attachment
2072	July 18, 2012 Google calendar reminder re 2012 Personalis BOD Meeting
2073	July 18, 2012 Minutes of Meeting of The Board of Directors of Personalis, Inc

Exhibit No.	Description
2074	July 24, 2012 Quick Notes on Lab Sequencing From Discussion with JW
2075	August 6, 2012 Email from Mark Pratt to John West re Lab Projects with attachment
2076	August 6, 2012 Email from John West to Mark Pratt re Lab Projects
2077	August 10, 2012 Email from Richard Chen to John West re Sprint 4 pre planning =JW Questions & Input
2078	August 28, 2012 Email from Nan Leng to Hugo Lam re MiSeq 2x250 run completed over the weekend
2079	August 3, 2012 Google calendar reminder re Personalis Weekly Team Meeting
2080	August 10, 2012 Google calendar reminder re Personalis Weekly Team Meeting
2081	August 17, 2012 Google calendar reminder re Personalis Weekly Team Meeting
2082	August 20, 2012 Email from John West to Russ Altman re USE THIS ONE: my edits/slides v2 with attachment
2083	September 4, 2012 Email from Richard Chen to John West, et al. re Final Board Slides with attachment
2084	September 4, 2012 Email from John West to Carol Tillis re Personalis Board meeting preview

Exhibit No.	Description
2085	September 5, 2012 Google calendar reminder re 2012 Personalis BOD Meeting
2086	September 5, 2012 Email from John West to Carol Tillis and Eliane Sousa, et al. re John West's Board Slides with attachment
2087	September 5, 2012 Minutes of A Meeting of The Board of Directors of Personalis, Inc.
2088	September 7, 2012 Google calendar reminder re Personalis Monthly Team Meeting
2089	September 27, 2012 Purchase Order to Agilent
2090	October 5, 2012 Google Calendar reminder re Personalis Monthly Team Meeting
2091	October 9, 2012 Google Calendar reminder re accuracy requirements walk through
2092	October 10, 2012 Google Calendar reminder re Accuracy Bi-weekly
2093	October 24, 2012 Google Calendar reminder re Accuracy Bi-weekly
2094	October 4, 2012 Email from Scott Kirk to John West re Notes from the runs discussion
2095	October 10, 2012 Email from Scott Kirk to John West, et al., re PGS v1 Requirements draft (rev 1.10) with attachment

Exhibit No.	Description
2096	October 9, 2012 Email from John West to Richard Chen, et al., re Slide for accuracy requirements walkthrough meeting 3-5pm today with attachment
2097	October 12, 2012 Email from John West to Christian Haudenschild, et al., re Prioritization of Ops Sequencing projects with attachment
2098	October 19, 2012 Email from John West to Richard Chen, et al., re Applying for a patent on our idea of panels reflecting to exome / WGS
2099	November 1, 2012 Email from John West to Carol Tillis re Board slides from John West, ready to print with attachment
2100	October 31, 2012 Email from Richard Chen to John West, et al., re final board slides, ready to print with attachment
2101	November 1, 2012 Google Calendar reminder re Personalis BOD Meeting – Breakfast will be served between 8:15am and 9am
2102	November 1, 2012 Email from Shujun Luo to John West re Re: Can you please email me a copy of your slides from this afternoon? with attachment
2103	November 21, 2012 Google Calendar reminder re Accuracy Bi-weekly
2104	December 7, 2012 Google Calendar reminder re Accuracy Bi-weekly
2105	December 12, 2012 Email from Richard Chen to John West, et al., re Final board slides with attachment

Exhibit No.	Description
2106	December 13, 2012 Email from John West to Carol Tillis re CEO Update presentation for Board meeting with attachment
2107	December 14, 2012 Minutes of a Meeting of the Board of Directors of Personalis, Inc.
2108	January 16, 2013 Google Calendar reminder re Accuracy Bi-weekly
2109	January 13, 2012 Email from John West to Richard Chen re Draft of what we might offer as Laboratory Assays with attachment
2110	July 26, 2011 Minutes of a Meeting of the Board of Directors of Personalis, Inc.
2111	November 01, 2012 Minutes of a Meeting of the Board of Directors of Personalis, Inc.
2112	May 08, 2012 CEO Overview Board of Director Presentation by John West
2113	U.S. Provisional Patent Application No. 61/753,828
2114	January 19, 2010 Illumina Individual Genome Sequence Report
2115	January 18, 2011 Slides, “Incoming Data QC and our ability to detect commonly known genetic diseases”
2116	June 18, 2012 Email from John West to Mark Pratt, et al. re Shunjun getting started

Exhibit No.	Description
2117	January 11, 2013 Email from John West to Richard Chen re Name instead of “Exome+”
2118	August 14, 2012 Google calendar reminder re Personalis BOD Meeting
2119	January 14, 2013 Email from John West to Carol Tillis, et al. re Product naming decisions from staff meeting today
2120	May 17, 2012 Email from John West to Mark Pratt re Update Job Description for Shujun
2121	A Family Learns the Secrets of Its Genomes, MIT Technology Review, June 16, 2011
2122	Dewey, et al., Phased Whole-Genome Genetic Risk in a Family Quartet Using a Major Allele Reference Sequence, PLoS Genetics, September 2011, Vol. 7(9)
2123	November 2, 2012 Google calendar reminder re Personalis monthly team meeting
2124-2150	RESERVED
2151	Foresight Diagnostics, About, https://foresight-dx.com/about
2152	Newman, et al., An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage, HHS Public Access Author Manuscript

Exhibit No.	Description
2153	“Personalis MRD Assays to Support UK’s TRACERx ctDNA Monitoring Study,” Precision Medicine Online, April 5, 2023
2154	“Personalis, AstraZeneca Extend Collaboration Around Residual Cancer Detection Test,” GenomeWeb, March 7, 2023
2155	Blighe, Molecular analysis of circulating cell-free DNA in breast cancer patients, University of Leicester, 2012.
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
2159	Chilamakuri, “Performance comparison of four exome capture systems for deep sequencing,” BMC Genomics 15:449, 2014
2160	Excerpt from Sambrook, et al., Molecular Cloning, Vol. 1, 2001
2161	RESERVED
2162	Stephens et al., Complex landscapes of somatic rearrangement in human breast cancer genomes, Nature, 462:1005-1010 (2009) supplementary figures

Patent Owner Personalis Inc. (“Personalis”) submits this Response to the Petition filed by Foresight Diagnostic Inc. (“Foresight”) regarding U.S. 11,408,033 (“the ‘033 patent”). The instant case is related to IPR2023-00224, where Foresight challenges U.S. Patent No. 11,384,394 (“the ‘394 Patent”).

I. INTRODUCTION

Personalis is recognized as an undisputed leader in developing innovative personalized genomic assays. The ‘033 patent claims recite a novel and nonobvious process that starts with producing capture probes directed to polymorphisms that are associated with a disease or indication. By applying capture probes to a nucleic acid sample, one can collect nucleic acid molecules that are likely to include disease-causing mutations in, for instance, the tumor genome of a cancer patient. DNA sequencing is then used to analyze the sample, for example by identifying specific mutations present in the patient. Once the sample has been analyzed, the process of capturing DNA with capture probes and sequencing can be repeated over time, allowing one to monitor disease over time. Personalis’ NeXT Personal[®] detection and monitoring assay practices the ‘033 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 ¶¶58-63; EX1037. 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 based on three grounds: (1) alleged anticipation by the Forshew reference, (2) alleged obviousness based on Forshew and Wagle, and (3) alleged obviousness based on Wagle and Chan. Neither Forshew or Chan qualify as prior art to the '033 patent and each of grounds 1-3 necessarily fail.

The inventors of the '033 patent conceived of the claimed invention by no later than May 8, 2012 and diligently worked towards its constructive reduction to practice via filing of U.S. Provisional Appl. No. 61/753,828 on January 17, 2013. Forshew did not publish until several weeks later on May 30, 2012, and Chan did not publish until several months later in October 2012. Thus, Forshew and Chan are not prior art to the '033 patent.

Further, Forshew discloses a PCR primer-based assay that fails to teach the “capture probes” recited by claim limitations 1(a), 1(b), 1(c), and 1(d). Accordingly, Forshew fails to anticipate claim 1, which is the sole independent claim of the '033 patent.

Foresight asserts that it would have been obvious to redesign Forshew’s PCR primer-based assay to instead use capture probes based on Wagle. But its own

exhibits, statements by its own founders,¹ and its own expert witness (Dr. Quackenbush) provide numerous reasons why a person of ordinary skill in the art (POSA) would not have been motivated to abandon the core reaction principle of ForsheW's PCR primer-based assay in favor of capture probes.

Foresight asserts that it would have been obvious to repeat Wagle's assay on a second tumor sample or a plasma sample from the same patient. A POSA would have avoided subjecting the patient to a second invasive operation procedure to obtain a second tumor sample, and a POSA would not have been motivated to use Wagle's capture probes on the miniscule amounts of DNA circulating in a patient's plasma sample with a reasonable expectation of success because Wagle teaches that capture probes require orders of magnitude more DNA to operate than is present in a sample of a patient's plasma.

The patentability of Personalis' claims is further confirmed by objective indicia of nonobviousness including industry praise and skepticism in the field. The Board should reject Foresight's petition-inspired arguments that are overwhelmingly at odds with the rest of the record. After considering all of the relevant evidence,

¹ Foresight was founded by Ash Alizadeh, Maximilian Diehn, David Kurtz, and Jake Chabon. EX2016.

there is only one reasonable conclusion—Claims 1-23 of the '033 patent were not anticipated or obvious at the time of the invention.

II. OVERVIEW OF THE '033 PATENT

The '033 patent relates to systems and methods for sample processing and analysis to aid in the diagnosis, monitoring, treatment, and prevention of diseases.

EX1001 Abstract. Claim 1 is the only independent claim, and it recites:

1. A method for analyzing a nucleic acid sample obtained from an individual, comprising:
 - (a) producing, with the aid of a computer processor, a plurality of capture probes, wherein said plurality of capture probes hybridize to a plurality of polymorphisms, wherein said plurality of polymorphisms are in sequences encoding genes with known biomedically interpretable variants, and wherein said plurality of polymorphisms are based on or extracted from one or more databases of polymorphisms and are observed in a population of one or more samples;
 - (b) contacting said nucleic acid sample with said plurality of capture probes produced in (a);
 - (c) conducting a sequencing assay on a subset of nucleic acid molecules generated from said nucleic acid sample in step (b) to yield a result comprising a nucleic acid sequence, thereby analyzing said nucleic acid sample; and
 - (d) repeating steps (b)-(c) on a subsequently obtained biological sample from said individual.

The '033 Patent explains that prior art methods such as whole genome sequencing were not only costly, but could “fail to capture many biomedically important variants.” EX1001 1:23-34. Specifically, standard methods often “fail[ed] to target biomedically interesting non-exomic as well as exomic regions,” and would perform poorly in certain regions of the genome. *Id.*; *see id.* 69:49-70:19.

The inventors of the '033 Patent overcame these problems by using a personalized sequencing assay. Indeed, many of the issues and failures of prior art methods were due to problems that are difficult to address in bulk sequencing, but can “be more adequately addressed by specialized sequencing protocols and technologies.” *Id.* 70:20-24. The inventors of the '033 Patent developed an enrichment pulldown process and sequencing protocols to specifically improve performance over the prior art.

Personalis pioneered the use of such methods and other techniques for cancer detection and monitoring to overcome many of the problems and limitations with prior art methods.

III. FORSHEW AND CHAN ARE 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, the sufficiency of which is governed by a “rule of reason” analysis. *Id.*

Here, the inventors of the '033 patent conceived of the claimed invention by no later than May 8, 2012 and diligently worked towards its reduction to practice via filing of the provisional application on January 17, 2013. EX2113. Forshew did not publish until several weeks later on May 30, 2012, and Chan did not publish until several months later in October 2012. Thus, Forshew and Chan are not prior art to the '033 patent. Each of Grounds 1-3 necessarily fails because all of these grounds rely on either Forshew or Chan.

Personalis submits the following evidence showing prior invention before Forshew and Chan:

- Declaration of John West, EX2032. Mr. West is an inventor of the '033 patent. He co-founded Personalis and served as its founding CEO from August 2011 through December 2022. He is currently retired.
- 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 is not an inventor of the '033 patent. 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 is not an inventor of the '033 patent. 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.

A. Conception

The inventors conceived of the claimed invention no later than May 8, 2012, as demonstrated by a series of presentations, emails, and other documents discussed below.

1. Genesis of the Accuracy Program at Personalis

The invention claimed by the '033 patent was developed by the "Accuracy Program" at Personalis. The genesis for the Accuracy Program dates back to at least November 2009, when Mr. West paid \$160,000 to have his family of four's whole genomes sequenced. Mr. West received the data in 2010 and found that it had systematic gaps in the genomes, and it occurred to him that supplementing whole genome sequencing (WGS) data with additional assays could lead to more complete and accurate results. The sequencing of Mr. West's family generated publicity, which led to Mr. West working with four faculty members at Stanford University in June 2010. Mr. West and the four faculty members decided to found Personalis by

autumn of 2011 with the purpose of developing innovative products and methods to realize personalized medicines and diagnostic assays. Personalis was incorporated in February 2011, and closed its initial Series A financing for a moderate amount of \$20 million in August of 2011. EX2032 ¶¶20-28.

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

Dr. Richard Chen joined Personalis in the role of Chief Scientific Officer in November 2011. Dr. Chen earned his M.D. from Stanford University. EX2032 ¶30.

Dr. Hugo Lam joined Personalis in the role of Project Manager of Computational Biology in November 2011. Dr. Lam earned his Ph.D. from Yale University. EX2032 ¶31.

Dr. Mark Pratt joined Personalis in the role of Senior Director for the Accuracy Program in January 2012. Dr. Pratt earned his Ph.D. from the University of California, Santa Barbara. EX2032 ¶32.

Dr. Gemma Chandratillake joined Personalis in the role of Genomic Counselor in February 2012. Dr. Chandratillake earned her Ph.D. from The Open University in 2005. EX2032 ¶33.

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

Ms. Shujun Luo joined Personalis in the role of Senior Scientist on June 1, 2012. Ms. Luo earned her M.S. from Columbia University. EX2032 ¶35.

Based on at least the hirings of the co-inventors described above, Personalis had assembled a world-class team of scientists by mid-2012 that was well-positioned to innovate in the field of personalized genomics. A photo of the Personalis team as of May 4, 2012 is shown below, including co-inventors of the '033 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.

2. The Accuracy Program: November 2011 through May 8, 2012

The inventors of the '033 patent realized that prior art methods of genomic sequencing produced systematic gaps in the sequencing data. It occurred to them that supplementing whole genome data with data from additional hybrid capture technology using capture probes could lead to more complete and accurate results. 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 “interpretation of whole human genome sequences” for “maximal-accuracy analysis of a genome,” which included “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 pullout” to fill coverage gaps, resolve misalignments, and capture biomedically important portions of the genome from outside the exome. EX2032 ¶¶53-56; EX2109 2-3; EX2102 2.

On April 2, 2012, Mr. West describe Personalis’ laboratory plans, including “our NGS may include both whole genome and deeper sequencing of some regions selected by pullout. Mark Pratt is working on lists of regions we may want to pull out. Some of the pullout may be to sequence with a second paired-end insert length (likely quite long).” EX2036; EX2032 ¶61.

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

On May 8, 2012, Mr. West sent a copy of his “CEO Overview” presentation to non-inventor Carol Tillis. EX2041. On the same date, Dr. Chen sent a copy of his research and development presentation to Mr. West. EX2042. Both of these presentations were presented to the Personalis Board of Directors on May 8, 2012.

The meeting took place from 1:00pm to 3:30pm at the Personalis office located at 530 Lytton Avenue, Palo Alto, CA. 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 CEO Overview 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.

3. Summary of Mr. West's May 5, 2012 Presentation

Slide 5 of Mr. West's May 8, 2012 CEO 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	Informatic Solutions	Lab, Content Solutions
<u>Analysis</u> Rates by variant type & Q-score Underlying mechanisms Medical interpretation impact Regulatory impact	<u>Advances in 3rd party alg's</u> Aligner for > 200bp reads New versions, current alg's Other alg's (e.g. lobSTR)	<u>Combine technologies</u> WGS + exome Longer reads and/or inserts Multi-vendor Arrays (genotypes & SV's) Electrophoretic sizing Sanger validation
<u>Methods</u> Comparison with literature Studies on limited regions Whole genome analysis: Single genome metrics Same person twice Family inheritance (MIE) Platform comparison Arrays ILMN / CGI / Ion T... Sanger capillary	<u>Advances in our alg's:</u> SV's : Zygosity, accuracy Combine SV's & SNP's Broader use of Breakseq	<u>Content-based semi-custom</u> Array (genotypes & SV's) Pullout
<u>Prioritize solutions</u> Bio-informatic approaches Laboratory approaches Content approaches	<u>New Personalis alg's</u> Alignment degeneracy Genome-aware alignment VNTR-specific	<u>Custom sample preps</u> Problematic motifs Degenerate regions Phasing
	<u>Advances in reference</u> Ethnic major-allele ref's Iterative Admixed InDel's / SV's	<u>Content</u> Gold standard genomes Known healthy genomes
	<u>Flag or Filter Out</u> For problems not yet solved	

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, which is reflected in Slide 5 of Mr. West’s presentation. EX2033 ¶¶77-80.

4. The Accuracy Program and the '033 patent claims

Mr. West’s May 8, 2012 CEO Board Presentation (“Presentation”) memorializes much of the inventors’ work to conceive of the inventions that were ultimately claimed by the '033 patent. The inventors had formed a definite and permanent idea of the complete and operative invention described in each claim of the '033 patent by no later than May 8, 2012. Further, a person of ordinary skill in the art would have been enabled to practice the invention as of May 8, 2012 without undue experimentation if they had been informed of the invention. EX2032 ¶82. Below is an explanation of conception of each of the 23 claims of the '033 patent with corroborating evidence.

a) Claim 1 - Preamble

By no later than May 8, 2012, the Accuracy Program included methods for analyzing a nucleic acid sample obtained from an individual. Conception of the

preamble is reflected by, for example, 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).

As reflected by Slide 5, the Accuracy Program involved "analysis" of nucleic acid samples by "methods" that included "whole genome analysis." The Accuracy Program 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 Accuracy 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 ¶¶84-86.

Slide 13 provides additional details of the Accuracy Program, which 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).

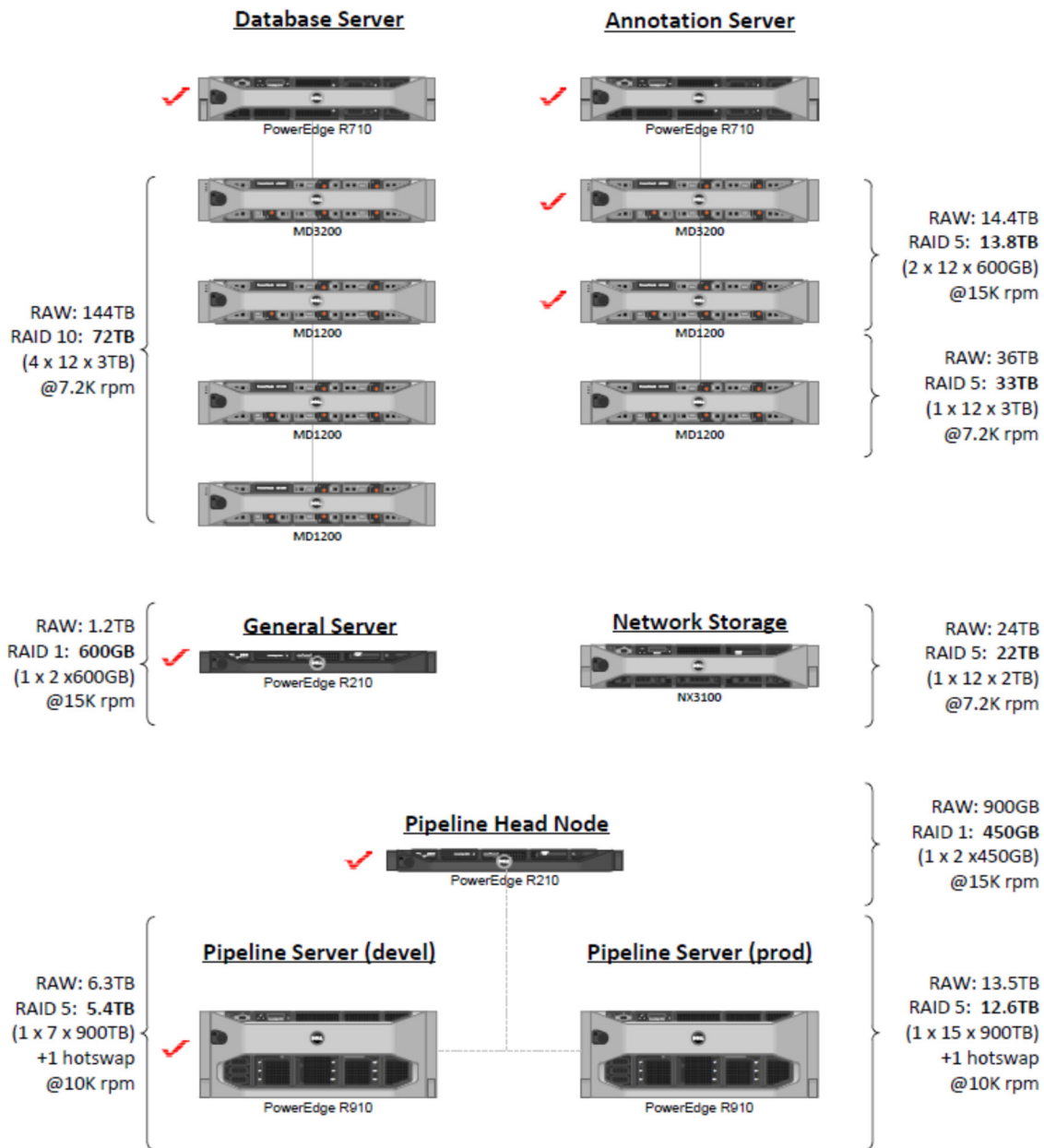
b) Limitation 1(a)(i)²

By no later than May 8, 2012, the Accuracy Program included producing, with the aid of a computer processor, a plurality of capture probes.

Conception of limitation 1(a)(i) 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 ¶¶91-93.

The design of the capture probes to "pullout" the genotypes and structural variants involved "informatic solutions" that included "alg's" (algorithms). EX2112 5. The algorithms used the aid of a computer processor. Personalis had computer servers and processors to handle the genomic data generated by WGS:

² For ease of reference, the Challenged Claims are reproduced in Appendix A.



EX2044; EX2032 ¶¶94-98.

c) Limitation 1(a)(ii)

By no later than May 8, 2012, the Accuracy Program included a plurality of capture probes that hybridize to a plurality of polymorphisms, wherein said plurality

of polymorphisms are in sequences encoding genes with known biomedically interpretable variants.

Conception of limitation 1(a)(ii) is reflected by, for example, Slide 5 of Mr. West's Presentation. The Accuracy program involved identifying biomedically interpretable variants that were identified by the "analysis" of "WGS," which included identifying "SV's", "SNP's", "allele[s]", and "InDel's" (which are each a type of polymorphism) having "medical interpretation impact." EX2112 5. For the "analysis" to have "medical interpretation impact," the inventors were aware that the identified polymorphisms would include polymorphisms encoding genes (because the polymorphisms encoding genes would have the most medical impact as opposed to polymorphisms in non-encoding regions of the genome). The capture probes were designed to "pullout" the polymorphisms encoding genes with known biomedically interpretable variants that were identified by the "analysis" of the "whole genome analysis." EX2032 ¶¶99-103.

d) Limitation 1(a)(iii)

By no later than May 8, 2012, the Accuracy Program included a plurality of capture probes that hybridize to a plurality of polymorphisms that are based on or extracted from one or more databases of polymorphisms and are observed in a population of one or more samples.

Conception of limitation 1(a)(iii) is reflected by, for example, Slide 5 of Mr. West's Presentation. As discussed above, the capture probes were designed to "pullout" "SV's", "SNP's", "allele[s]", and "InDel's" polymorphism encoding genes with known biomedically interpretable variants that were identified by the "analysis" of the "whole genome analysis." EX2112 5. The capture probes were designed based on the genotypes and structural variants involved in the "informatic solutions" that included algorithms ("alg's") to process the genomic data generated by WGS. The genotypes and structural variants would be stored in databases on the Personalis servers (e.g., EX2044) or elsewhere. Personalis had several genetic databases that included a plurality of polymorphisms in sequences encoding genes with known biomedically interpretable variants. EX2032 ¶¶104-106; EX2042 29-32. A database of polymorphisms stored on the Personalis servers could also include polymorphisms observed in a population of one or more samples. EX2112 5, 13; EX2043 2. At that time, the inventors had already been storing genotype and structural variant information in databases on the Personalis servers. EX2032 ¶¶107-109.

e) Limitation 1(b)

By no later than May 8, 2012, the Accuracy Program at Personalis included contacting the customer nucleic acid sample with said plurality of capture probes that were produced according to limitation 1(a).

Conception of limitation 1(b) is reflected by, for example, Slide 5 of Mr. West's Presentation. Slide 13 shows that the Accuracy Program included "receiv[ing]" and "de-identify[ing] samples" from customers. Slide 5 included "content-based semi-custom" capture probes to "pullout" genotypes and structural variants. The Accuracy Program involved contacting the customer sample with the panel of capture probes in order to "pullout" the genotypes and structural variants identified by the algorithms used to analyze the data generated by WGS. EX2112 5, 13; EX2032 ¶¶110-114.

f) Limitation 1(c)

By no later than May 8, 2012, the Accuracy Program at Personalis included conducting a sequencing assay on a subset of nucleic acid molecules generated from said nucleic acid sample in limitation 1(b) to yield a result comprising a nucleic acid sequence that analyzes the nucleic acid sample.

Conception of limitation 1(c) is reflected by, for example, 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 ¶¶115-118.

g) Limitation 1(d)

By no later than May 8, 2012, the Accuracy Program at Personalis included repeating the steps recited by limitations (b)-(c) on a subsequently obtained biological sample from said individual.

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,” as reflected by slide 3 of Mr. West’s Presentation:

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 ¶¶126-134. The inventors had described sequencing an individual “twice” or “multiple times,” EX2046 14, and they were familiar with applications for the Accuracy Program that would involve repeated blood testing of a genetic condition (such as a monthly blood draft in connection with a Factor V Leiden mutation). EX2032 ¶¶119-125.

5. Claim 2

By no later than May 8, 2012, the Accuracy Program at Personalis included subsequent to limitation 1(c), generating a biomedical report that includes biomedical information of said individual, which biomedical information is indicative of the result recited by limitation 1(c).

Conception of this claim is reflected by, for example, 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 of the Presentation provides additional details of the Accuracy Program, 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 ¶¶135-138.

6. Claim 3

By no later than May 8, 2012, the Accuracy Program at Personalis included generating a biomedical report that includes biomedical information of said individual that 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.

Conception of this claim is reflected by, for example the above discussion of claim 2. 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." 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. The medically impactful SV's, SNP's, alleles, and InDel's 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 ¶¶139-141.

7. Claim 4

By no later than May 8, 2012, the Accuracy Program at Personalis included a plurality of polymorphisms comprising one or more insertions, deletions, structural variant junctions, variable length tandem repeats, single nucleotide mutations, or a combination thereof.

Conception of this claim is reflected by, for example the above discussion of claim 1. For example, the Accuracy Program included identifying biomedically 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.” Each of the “SV’s”, “SNP’s”, “allele[s]”, and “InDel’s” are a type of polymorphism. EX2112 5; EX2032 ¶¶142-144.

8. Claim 5

By no later than May 8, 2012, the Accuracy Program at Personalis included sequences encoding genes with known biomedically interpretable variants that comprise a plurality of sequences encoding genes associated with cancer.

Conception of this claim is reflected by, for example, 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, and the inventors planned to include “Oncology/Neoplastic Disease” in reports to their customers. *Id.* 25; EX2032 ¶¶145-148.

9. Claim 6

By no later than May 8, 2012, the Accuracy Program at Personalis included identifying the presence or absence of said plurality of polymorphisms in said nucleic acid sample.

Conception of this claim is reflected by, for example, 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 ¶¶149-152.

10. Claim 7

By no later than May 8, 2012, the Accuracy Program at Personalis included observing an allele frequency of said plurality of polymorphisms.

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%	All 11 children
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%	Several optimal subsets with 5 of the 11 children
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%	

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 ¶¶153-156.

11. Claim 8

By no later than May 8, 2012, the Accuracy Program at Personalis included a plurality of capture probes in a hybridization array.

The Accuracy Program involved the use of “content-based semi-custom” capture probes in “array (genotypes & SV’s)” to capture genotypes and structural variants. The referenced “arrays” included capture probes arranged in a hybridization array where the capture probes are designed to hybridize to the “SV’s”, “SNP’s”, “allele[s]”, and “InDel’s” that were identified by the “analysis” of the

“whole genome analysis” within the Accuracy Program. EX2115 10; EX2032 ¶¶157-159.

12. Claim 9

By no later than May 8, 2012, using capture probes conjugated to beads was part of the Accuracy Program at Personalis.

The Accuracy Program combined technologies to supplement WGS with “semi-custom” assays using “pullout” technologies. EX2112 5. The Accuracy Program included “pulling out” desired content from a genomic 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 via the streptavidin coating on the beads. EX2045 31; EX2033 ¶19; EX2032 ¶¶160-163.

13. Claim 10

By no later than May 8, 2012, using capture probes that further comprise barcodes was part of the Accuracy Program at Personalis.

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. They were aware that this could be done by including a sample-specific barcode in a ligated adaptor used in the library preparation of each sample,

prior to pooling of the samples. The barcode served as an index which would become part of each sequence read, and in this way amortized the cost of sequencing over the pooled samples and lowered the sequencing cost per sample. Mr. West and Dr. Pratt were familiar with the use of DNA barcodes as sample identifiers 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 ¶¶164-168.

14. Claim 11

By no later than May 8, 2012, the Accuracy Program at Personalis included the nucleic acid sample obtained from the individual being obtained from a body fluid, cell, skin, tissue, organ, or combination thereof.

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 ¶¶169-171. 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.

15. Claim 12

By no later than May 8, 2012, the Accuracy Program at Personalis included nucleic acid sample obtained from blood plasma.

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 by Dr. Snyder 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. For at least these reasons, the Accuracy Program included the body fluid sample being a blood plasma sample. EX2032 ¶¶172-175.

16. Claim 13

By no later than May 8, 2012, the Accuracy Program at Personalis included using said capture probes to generate an additional subset of nucleic acid molecules from an additional nucleic acid sample isolated from an additional plasma sample obtained from said individual at an additional time point different from said first time point.

As discussed above for limitation 1(d), the Accuracy Program included using capture probes to generate an additional subset of nucleic acid molecules from an additional nucleic acid sample. As discussed for claim 12, the Accuracy Program further included additional nucleic acid samples that would be isolated from a plasma sample obtained from a customer. The additional plasma sample would be

obtained at a later time point than the first sample to provide “ongoing clinical use of genome-scale sequencing.” EX2112 3; EX2032 ¶¶176-178.

17. Claim 14

By no later than May 8, 2012, the Accuracy Program at Personalis included the first time point and the additional time point being at least 1 week apart or more.

Mr. West was aware of a paper authored by Dr. Snyder that published in Cell in March of 2012. 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 as his medical condition changed, from as little as one day apart during the period where he had viral infections, to as long as 95 days (from day “21” to day “116”) during a relatively healthy period. *Id.* Figure 1(A). Mr. West and his co-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 ¶¶179-181.

18. Claim 15

By no later than May 8, 2012, the Accuracy Program at Personalis included the first time point and the additional time point being at least 1 month apart or more.

As discussed for claim 14, 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 month or more after the first sample. EX2032 ¶¶182-184.

19. Claim 16

By no later than May 8, 2012, the Accuracy Program at Personalis included the additional time point being later than the first time point. For example, as discussed above with respect to claims 13-15, 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 ¶¶185-186.

20. Claim 17

By no later than May 8, 2012, the Accuracy Program at Personalis included the additional time point being earlier than the first time point. For example, as discussed above with respect to claims 13-15, the inventors realized that the Accuracy Program would benefit from samples being taken at different intervals from customers. This included a blood plasma sample being taken earlier than the sample used for WGS to permit verification that the capture probes effectively “pulled out” the targeted genotypes and structural variants of interest. EX2032 ¶¶189-190.

21. Claim 18

By no later than May 8, 2012, the Accuracy Program at Personalis included nucleic acid sample obtained from the individual being obtained 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 ¶¶189-190.

22. Claim 19

By no later than May 8, 2012, the Accuracy Program at Personalis included the subsequently obtained biological sample being a plasma sample for at least the reasons discussed above with respect to claim 12. EX2032 ¶¶191-192.

23. Claim 20

By no later than May 8, 2012, the Accuracy Program at Personalis included the subsequently obtained biological sample being a tissue biopsy sample for at least the reasons discussed above with respect to claim 18. EX2032 ¶¶193-194.

24. Claim 21

By no later than May 8, 2012, the Accuracy Program at Personalis one or more databases of polymorphisms that comprise a biomedical database.

Personalis exclusively licensed several databases, such as the MendelDB and PharmGKB databases that included genetic variants for various diseases. In addition, the Accuracy Program included capture probes designed to "pullout"

“SV’s”, “SNP’s”, “allele[s]”, and “InDel’s” polymorphism encoding genes with known biomedically interpretable variants that were identified by the “analysis” of the “whole genome analysis.” EX2112 5. The capture probes were designed based on the genotypes and structural variants involved in the “informatic solutions” that included algorithms (“alg’s”) to process the genomic data generated by WGS. The genotypes and structural variants would be stored in databases on the Personalis servers or elsewhere. EX2032 ¶¶195-197.

25. Claim 22

By no later than May 8, 2012, the Accuracy Program at Personalis included one or more polymorphisms that are observed in a population of a single sample.

As discussed above for claim 11, the sample obtained from Personalis’ customer could be obtained from a blood, saliva, tissue, or cell culture sample from the patient. EX2046 12. The first sample from a patient would be contacted with the capture probes that were designed to “pullout” “SV’s”, “SNP’s”, “allele[s]”, and “InDel’s” polymorphism encoding genes with known biomedically interpretable variants that were identified by the “analysis” of the first sample by “whole genome analysis.” EX2112 5. The capture probes were designed based on the genotypes and structural variants involved in the “informatic solutions” that included algorithms (“alg’s”) to process the genomic data generated by WGS. The genotypes and structural variants would be stored in a database on the Personalis or elsewhere.

The database of polymorphisms stored on the Personalis servers would include, e.g., polymorphisms observed in a population of the first (and single) sample from one of our customers. EX2112 5, 13. This database of polymorphisms would be observed in a population of the first (and single) sample. EX2032 ¶¶198-203.

26. Claim 23

By no later than May 8, 2012, the Accuracy Program at Personalis included a plurality of polymorphisms based on or extracted from the one or more databases of polymorphisms and observed in the population, wherein the population comprises a plurality of samples. For example, Mr. West was aware of a paper by Dr. Snyder describing whole genome sequencing of the primary subject of the study and also of his mother. EX2030 1294. The inventors realized that, by comparing the sequence of two samples (e.g., one sample being of the tumor and the other sample being a non-tumor tissue or blood from the same person), it was possible to determine which genetic variants seen in the tumor were part of the germline genome that the subject inherited from their parents, and which are new somatic variants unique to the tumor. EX2032 ¶¶204-205.

27. Conclusion

In conclusion, the inventors had conceived of the invention recited by claims 1-23 of the '033 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 1-23. EX2032 ¶¶206-207.

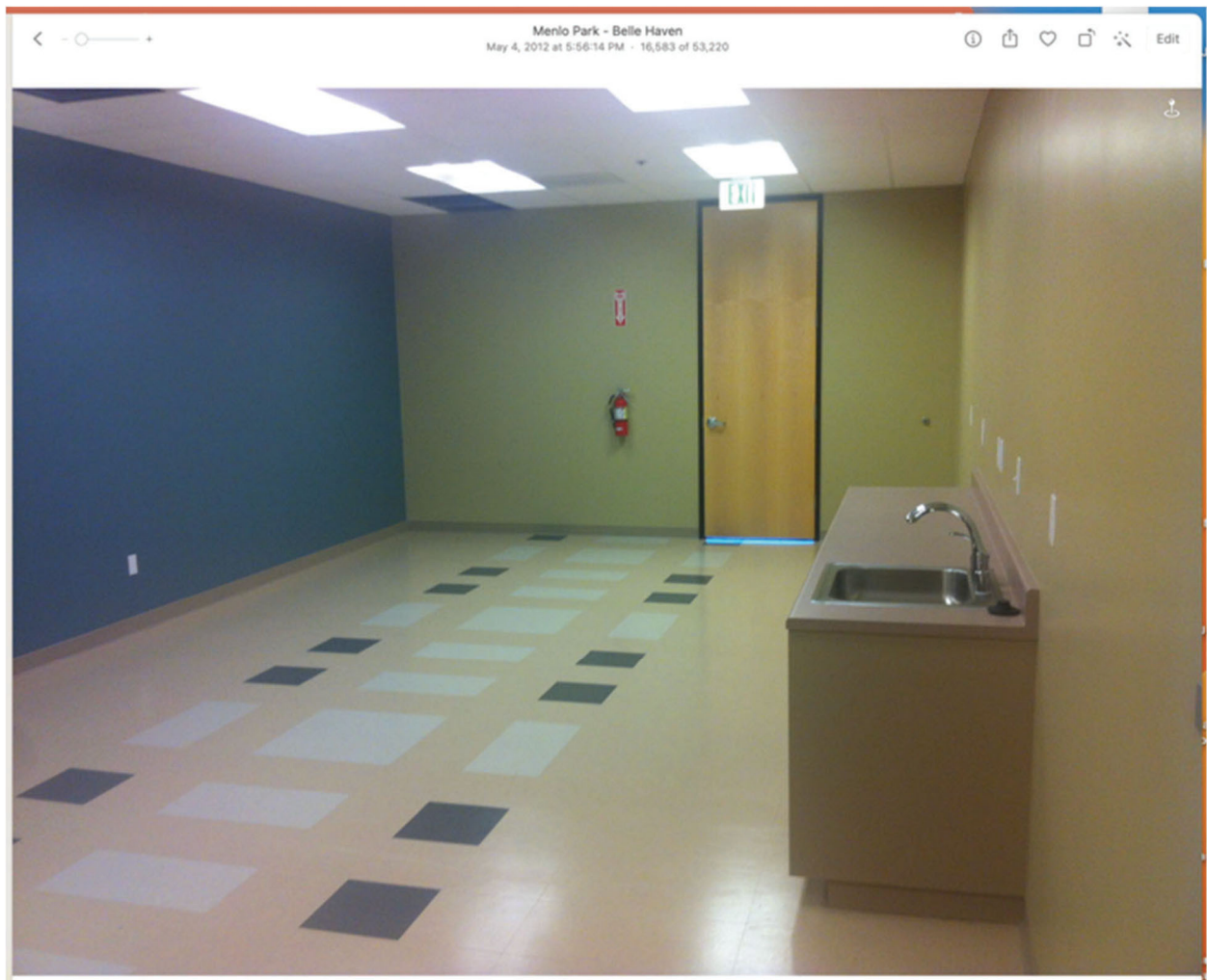
B. Diligence

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.

1. May

The co-inventors were reasonably continuous and diligent in pursuing the Accuracy Program and reducing it to practice 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, as described in the following subsections of this Response. EX2032 ¶¶325-330.

Further representative 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.

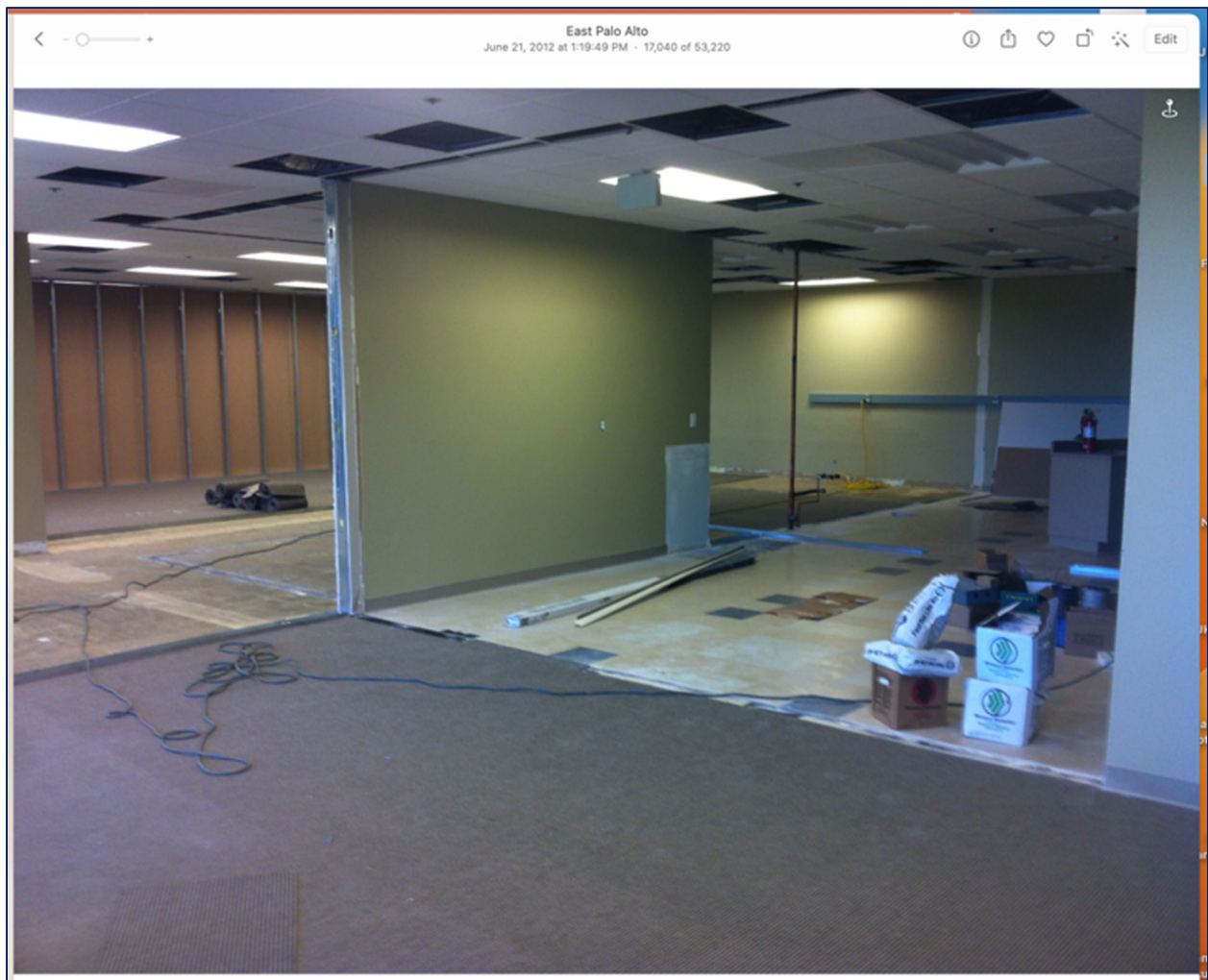
On May 15, 2012, Scott Kirk, a Personalis employee, sent an email to Mr. West and others containing notes referencing a “[m]eeting to define [a] path for how accuracy folds into the greater picture” of Personalis’ commercial business plan. EX2053; EX2032 ¶335.

On May 22, 2012, Mr. West sent emails and attachments on how to differentiate the Accuracy Program from existing technologies in the field, 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.

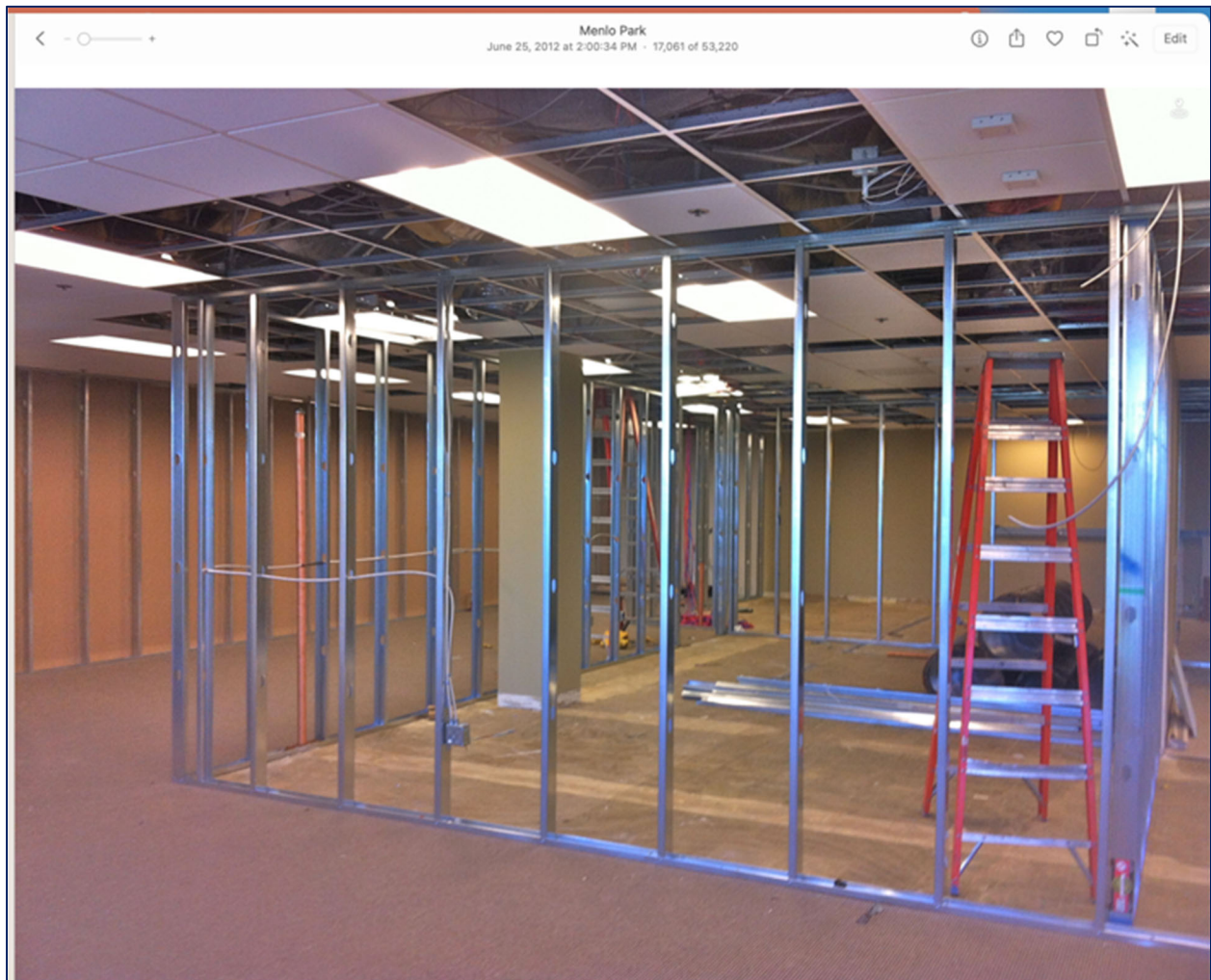
2. June

The co-inventors were reasonably continuous and diligent in pursuing the Accuracy Program and reducing it to practice 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.

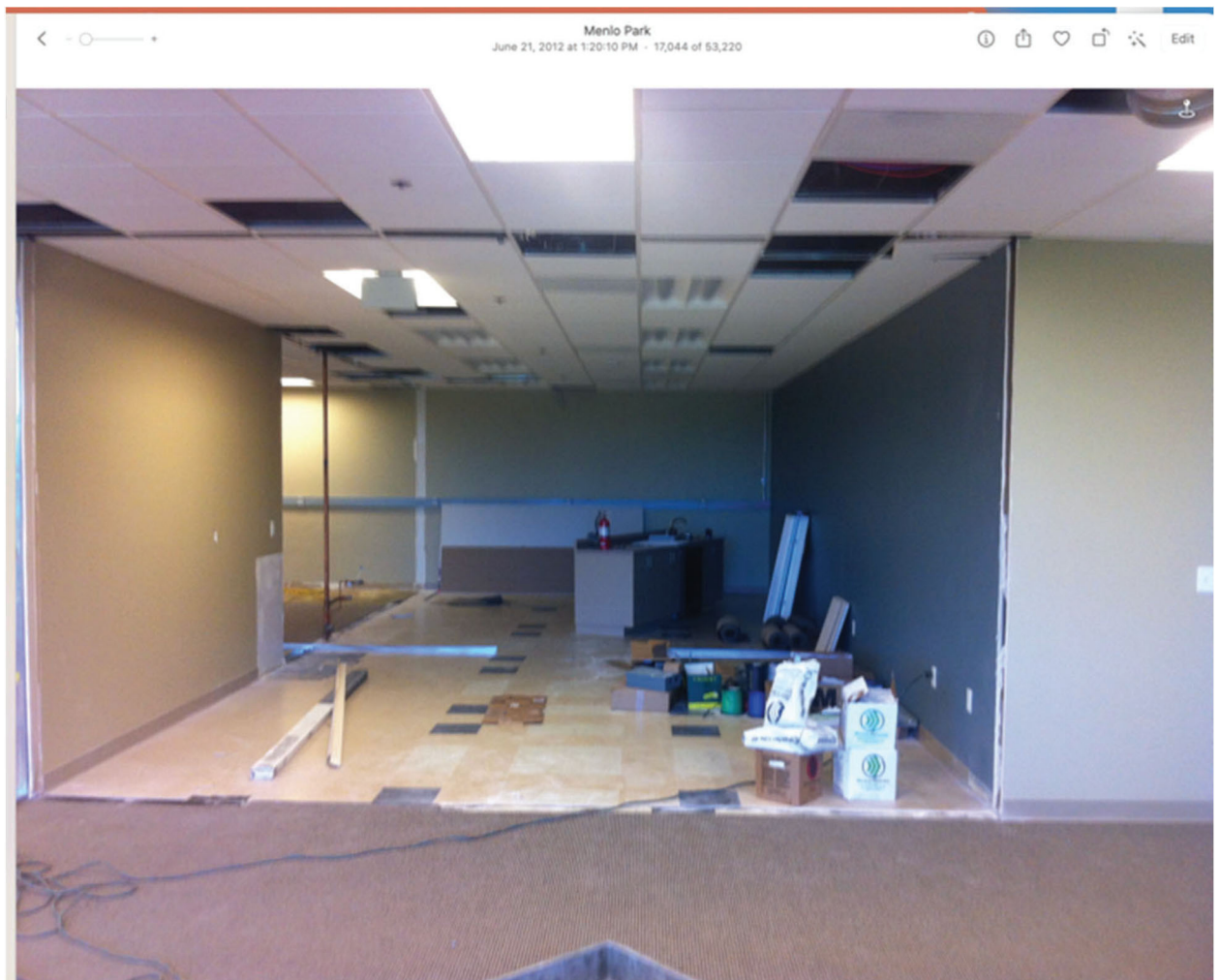
Further evidence of diligence includes team meetings during which updates on the Accuracy Program were discussed on June 1, 15, 22 and 29. EX2057; EX2058; EX2059; EX2060; EX2032 ¶¶344, 349, 353, 356.

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.

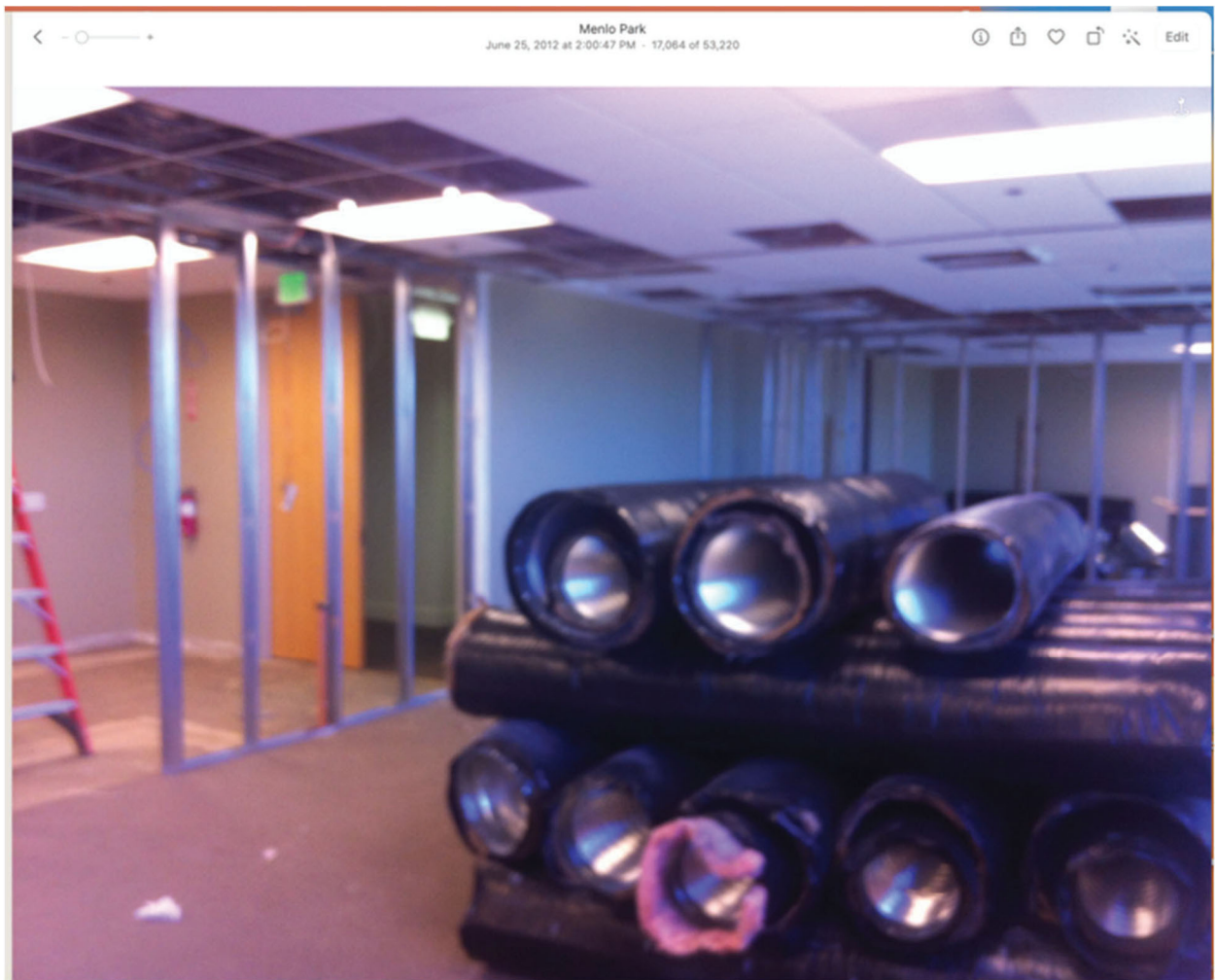
On June 12, 2012, Personalis held a Board of Directors meeting, during which Mr. West and Dr. Chen described progress on the Accuracy Program. EX2062; EX2063; EX2032 ¶¶346-348; EX2033 ¶¶27-31. The Board approved up to \$240,000 to purchase computing equipment and \$620,000 to purchase sequencing equipment. 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.

3. July

The co-inventors were reasonably continuous and diligent in pursuing the Accuracy Program and reducing it to practice 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.

4. August

The co-inventors were reasonably continuous and diligent in pursuing the Accuracy Program and reducing it to practice 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.

5. September

The co-inventors were reasonably continuous and diligent in pursuing the Accuracy Program and reducing it to practice 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.

6. October

The co-inventors were reasonably continuous and diligent in pursuing the Accuracy Program and reducing it to practice 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.

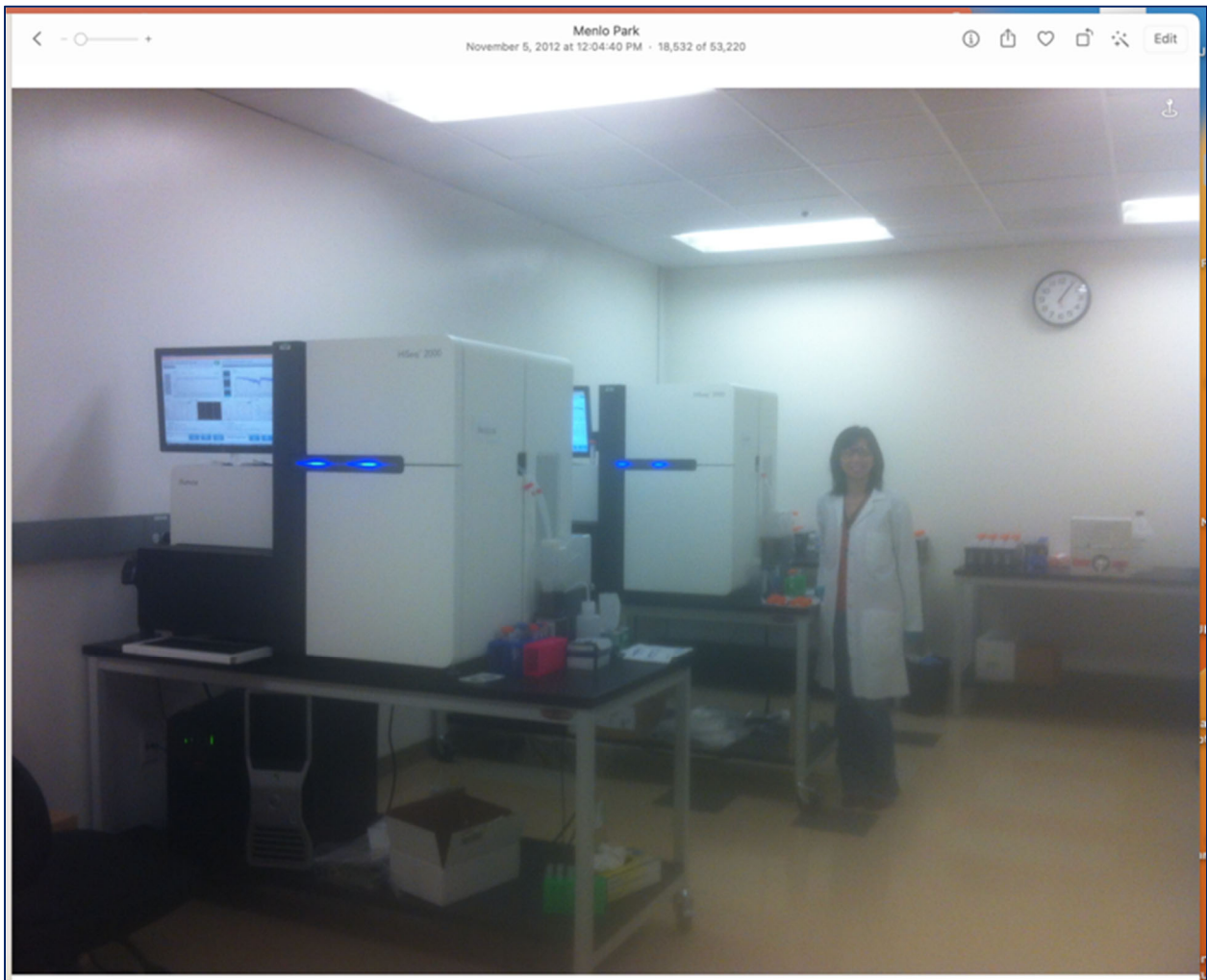
7. November

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



Foresight Diagnostics Inc. v. Personalis, Inc.
IPR2023-00317

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.

8. December

The co-inventors were reasonably continuous and diligent in pursuing the Accuracy Program and reducing it to practice 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 pursuit of the provisional patent application that was eventually filed on January 17, 2023 occurred on December 18, 21, and 27. EX2032 ¶¶404.

9. January

The co-inventors were reasonably continuous and diligent in pursuing the Accuracy Program and reducing it to practice from January 1, 2012 through the

filing of the provisional patent application on January 17, 2012. Privileged communications with patent counsel regarding the pursuit of the provisional patent application 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 continuous diligent in reducing the invention to practice from conception through its reduction to practice on January 17, 2013. EX2032 ¶¶409. Accordingly, Forshew and Chan are not prior art to the '033 patent.

IV. GROUND 1: FORSHEW DOES NOT ANTICIPATE THE CLAIMS

Forshew does not anticipate independent claim 1 at least because (1) Forshew is not prior art, and (2) Forshew fails to teach the “capture probes” recited by limitations 1(a), 1(b), 1(c), and 1(d).

A. Forshew is not prior art

Forshew is not prior art to the '033 patent. *Supra* Section III. Ground 1 necessarily fails.

B. Forshew does not teach the “capture probes” recited by claim 1

“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.”

Verdegaal Bros. Inc. v. Union Oil Co. of California, 814 F.2d 628, 631 (Fed. Cir. 1987). Forshew fails to anticipate claim 1 because it does not teach the “plurality of capture probes” recited by limitations 1(a), 1(b), 1(c), and 1(d). Also, because Forshew does not anticipate independent claim 1, it also fails to anticipate any of the dependent claims.

1. Forshew does not teach the “capture probes” of limitation 1(a)

Limitation 1(a) requires “a plurality of capture probes.” The Board’s preliminary construction of “capture probes” does not comply with how a POSA³ would have understood this term, and Forshew 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 18. 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).

³ For purposes of the trial phase of this proceeding only Personalis does not contest Foresight’s description of a POSA. Decision 14-18.

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 18-24. 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 (emphasis omitted). 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 375.⁴ 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 ¶¶53-57.

(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

⁴ All emphasis supplied unless otherwise noted.

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; EX2031 ¶58. “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 31:3-32:5, 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 23-24. 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 58; EX1020 ¶¶79, 206, 69 (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 ¶¶59-64.

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 '033 and '394 patents. EX2025 3-25 ("((enrich\$5 captur\$5 pull-down pulldown) with probe"); EX2024 3-8 (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 separated.” Decision 20 n.7 (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 20 (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 21-22, and that the specification “provides no indication as to whether the categories [of primers and capture probes] are overlapping, *id.* 21. 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 ¶¶74-77; EX2018 112:18-115:11. In contrast, only **one** capture probe is required to physically pulldown a target DNA strand. EX1020 ¶78 (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 ¶72, using “PCR ‘primers’ or ‘probes,’” *id.* ¶74, and “results in the **exponential amplification** of target DNA sequences,” *id.* ¶77. 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.* ¶¶73-77. 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 22 n.8, 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(a) 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 10’s recitation of “barcode” weighs moderately in favor of Foresight’s construction because barcodes are typically used on PCR primers. Decision 19-20. 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 10 does not expand “capture probe” 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,” “on-array hybrid capture,” and “in-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.

(4) 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) Forsheew does not teach “capture probes”

Foresight’s entire challenge to the ’033 patent hinges on a POSA conflating Forsheew’s PCR primers with the claimed “capture probes.” Petition 29-32. A POSA would not have considered Forsheew’s PCR primers to be “capture probes” because Forsheew’s PCR primers do not hybridize to target DNA so that one can physically capture the target DNA. Instead, Foresight asserts that Forsheew’s PCR primers meet the claimed capture probes simply because they “hybridize to’ the complementary sequences on the polymorphic gene comprising the point

mutations.” Petition 31. 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 Forshe’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 IV.B.1.a; EX2031 ¶¶193-194. Accordingly, Forshe fails to teach the “capture probes” required by limitation 1(a).

2. Forshe does not teach the “plurality of capture probes” of limitation 1(b)

Limitation 1(b) requires “a plurality of capture probes.” As discussed above, Forshe discloses PCR primers, and POSA would not have misapprehended Forshe’s PCR primers to be the claimed capture probes, and Forshe fails to anticipate limitation 1(b) for at least this reason. *Supra* Section VI.B.1.a; EX2031 ¶196.

3. Forshe does not teach limitation 1(c)

Limitation 1(c) requires “conducting a sequencing assay on a subset of nucleic acid molecules generated from said nucleic acid sample in step (b) to yield a result comprising a nucleic acid sequence[.]” Forshe does not anticipate this step because its sequencing assay is conducted on molecules that result from PCR

amplification—not on molecules captured by contacting the capture probes with the nucleic acid sample. *Supra* Section VI.B.1.a; EX2031 ¶198.

4. ForsheW does not teach limitation 1(d)

Limitation 1(d) requires “repeating steps (b)-(c) on a subsequently obtained biological sample from said individual.” ForsheW does not disclose this step because it never conducts steps (b) and (c) to begin with, let alone repeat them. EX2031 ¶200.

V. GROUND 2: THE CLAIMS ARE NONOBVIOUS OVER

FORSHEW AND WAGLE

A petition based on “obviousness requires a suggestion of all limitations in a claim.” *CFMT, Inc. v. YieldUp Int’l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003). ForsheW and Wagle do not render obvious independent claim 1 for at least four reasons that are detailed below.⁵

⁵ The Board stated that “Petitioner provides an element-by-element comparison of the claims to the cited art” for Ground 2. Decision 29. However, the Petition lacks an element-by-element comparison for claims 1-7 and 10-23 for Ground 2. Petition 46-49.

A. ForsheW is not prior art

ForsheW is not prior art to the '033 patent. *Supra* Section III. Ground 2 necessarily fails.

B. No motivation due to ForsheW's miniscule amounts of DNA

Foresight asserts that a POSA would have been motivated and “reasonably expected to succeed in using Wagle’s hybridization-based probes in place of ForsheW’s PCR-based capture step.” Petition 47. In reality, however, this ground only serves to highlight why a POSA would not conflate PCR primers and capture probes, and also why a POSA would not have been motivated to replace ForsheW’s PCR primers with Wagle’s capture probes.

ForsheW’s TAM-Seq PCR-based assay is designed to operate on “minute,” EX1030 8, amounts of DNA *ranging from just 0.9-19.7 nanograms of DNA*. *Id.* 6, Table 2; EX2031 ¶¶204-206. ForsheW repeatedly explains that its assay is designed to operate on the amount of DNA present in just microliters of blood plasma as follows:

- “[u]sing the equivalent amount of DNA present in 30 to 120 µl of plasma,” EX1030 4;
- “using DNA present in ~0.15 ml of plasma per reaction,” *id.* 4, which is approximately 150 µl of plasma, EX2031 ¶206;

- using between 30 to 120 μ l of “[p]lasma per amplification reaction,” EX1030 5, Table 1;
- using between 70 to 170 μ l of “[p]lasma volume per amplification reaction,” EX1030 6, Table 2.

Forsheew explains that 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.” *Id.* 1; EX2031 ¶207.

Forsheew teaches that PCR is ***required*** to “amplify” the small amount of circulating DNA to generate enough DNA to use in its TAM-Seq assay. EX1030 2; *id.* 9 (“this method effectively amplifies even small amounts of fragmented DNA such as are present in circulating DNA.”). In fact, the amount of DNA used in Forsheew’s TAM-Seq assay is so tiny that ***three rounds*** of PCR amplification are required to generate sufficient amounts of DNA to use in its assay. The first round consists of 15 cycles of “preamplification” PCR, which is followed by a second round of 35 cycles of “single-plex PCR,” and a third round of 15 cycles of “barcoding PCR.” *Id.* 2-3, Fig. 1(B); EX1032 2-3; EX2031 ¶207.

A POSA would not have been motivated to replace Forsheew’s PCR-based amplification with capture probes with a reasonable expectation of success because capture probes do not amplify DNA. Because capture probes do not amplify DNA,

they can only capture the incredibly small amounts of DNA that are already present in the microliters of plasma used in Forshew's TAm-Seq samples. Foresight's Mamanova exhibit teaches that approximately 3 micrograms of DNA are required for capture probes to operate effectively. EX1007 114, Table 1. Similarly, Wagle teaches that its capture probe assay requires "3,600 nanograms" of DNA (i.e., 3.6 micrograms). EX1033 91. The 3.6 *microgram* amounts of DNA required for Wagle's capture probes is at least 100 times more—and in many cases over 3,000 times more—than the 0.9-19.7 *nanogram* amounts of DNA present in Forshew's plasma samples. EX2031 ¶208.

Forshew itself recommends *not* using Wagle's capture probes for plasma samples because they have "not been applied to analysis of circulating tumor nucleic acids" as follows:

The intermediate scale of sequencing is most likely to have immediate impact on clinical genomics. Targeted sequencing has been applied for tumor DNA (34, 35) and cyst fluid (33) to detect mutations down to 5% AF, *but has not been applied for analysis of circulating tumor nucleic acids*.

EX1030 9. Reference 35 in Forshew is Wagle. *Id.* 11. Forshew further criticizes capture probes for being "expensive." *Id.* 10 ("Previously proposed methods for personalized monitoring of tumor dynamics relied on expensive custom-designed probes."); EX2031 ¶¶209-210.

Dr. Quackenbush admitted that he did not consider the amount of DNA present in plasma samples when generating his report. EX2018 100:14-103:1. Dr. Quackenbush and Foresight fail to provide any reason why a POSA would have been motivated to use Wagle's capture probes in Forshew's assay in view of the vast discrepancy between the microgram amounts of DNA required to use Wagle's capture probes and the nanogram amounts of DNA in Forshew's plasma samples. Foresight also fails to provide any reason why a POSA would have reasonably expected to succeed in using Wagle's capture probes in Forshew's assay in view of the vastly different amounts of DNA required by the two assays.

C. No motivation to change the core reaction principle of Forshew

Foresight provides no convincing reason why a POSA would have been motivated to abandon Forshew's PCR primer-based assay to instead use Wagle's capture probes. As discussed above, Foresight's Mamanova exhibit teaches that "[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 teaches that a POSA would have needed to evaluate seven parameters associated with the disadvantages of capture probes before discarding the core reaction principle of Forshew's PCR primer-based assay and replacing it with capture probes.

The vast majority of these parameters would have counseled a POSA to avoid attempting to redesign Forshew'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 of MIPs." *Id.* Further, Mamanova teaches that PCR has higher *reproducibility* of "up to 100%" than capture probes. *Id.* Table 1. Forshew 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 ¶¶211-213. The *sensitivity* and *amount of DNA required* are parameters that would, at best, be considered neutral; but the risks associated with modifying Forshew's already-working assay could very well cause the assay to lose sensitivity or even worse, not work at all.

Similarly, Foresight's Mertes exhibit explains that PCR primers and capture probes have different "operational characteristics" that "naturally vary in their suitability for different fields of application." EX1006 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." *Id.* 383. Mertes teaches that a POSA would have needed to evaluate seven metrics associated with the disadvantages of capture probes before forsaking the already-working core reaction principle of Forshew's PCR primers for Wagle's capture

probes. Foresight fails to grapple with the teachings of its own references on this issue. A POSA would not have been motivated to make such a drastic change to Forshew's core reaction principle.

D. No motivation to add capture probes to Forshew

Foresight asserts that a POSA would have been motivated and “reasonably expected to succeed in using Wagle’s hybridization-based probes *in addition to* Forshew’s PCR-based capture step.” Petition 48. This assertion fails to prove obviousness for several reasons.

First, Foresight is hopelessly vague regarding this proposed combination. Foresight generically states “a POSA would have been motivated to use hybridization followed by PCR, or vice-versa, in some scenarios.” Petition 48. Foresight leaves the Board and Patent Owner guessing at how Forshew’s workflow would be modified to include both PCR-based amplification and hybridization-based capture with capture probes. Forshew’s TAM-Seq assay requires “[a]n initial preamplification step” for 15 cycles “using a pool of the target-specific primer pairs to preserve representation of all alleles in the template material,” followed by a “single-plex PCR” where “[r]egions of interest in the preamplified material were then selectively amplified in individual (single-plex) PCR, thus excluding nonspecific products,” followed by “sequencing adaptors and sample-specific barcodes [being] attached to the harvested amplicons in a further PCR,” EX1030 2,

Fig. 1(B), followed by performing “100-base single-end sequencing (GAIIx sequencer, Illumina), with an additional 10 cycles using the barcode sequencing primer,” *id.* 3. Foresight provides no explanation as to which step within Forshew’s workflow it believes would benefit from the addition of Wagle’s capture probes. Foresight further fails to explain which steps in Forshew’s workflow would need to be removed, rearranged, or further supplemented to accommodate such a combination of two different core reaction principles with a reasonable expectation of success. Foresight’s failure to identify with particularity its proposed combination is insufficient to prove obviousness. *See 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.”); EX2031 ¶¶216-217.

Second, Forshew disparages capture probes as being “expensive” and “difficult to implement on a routine basis.” EX1030 10. Forshew goes out of its way to call out Wagle’s capture probes as having “not been applied to analysis of circulating tumor nucleic acids.” *Id.* 9. A POSA would not have been motivated to further complicate Forshew’s already-working and already-complicated process with unnecessary and admittedly “expensive,” “difficult to implement,” and untested steps.

Third, 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; EX2031 ¶218. Foresight fails to address how a POSA would overcome the known incompatibilities of PCR primers and capture probes in its proposed combination of Forsheew and Wagle. This combination of references fails to render obvious the claimed invention.

VI. GROUND 3: THE CLAIMS ARE NONOBVIOUS OVER

WAGLE AND CHAN

Wagle and Chan do not render obvious independent claim 1 for several reasons. First, Chan is not prior art to the '033 patent. Second, Wagle in view of Chan does not teach or suggest limitation 1(d).

A. Chan is not prior art

Chan is not prior art to the '033 patent. *Supra* Section III. Ground 3 necessarily fails.

B. Wagle and Chan do not teach or suggest limitation 1(d)

Wagle in view of Chan does not teach or suggest limitation 1(d), which requires “repeating steps (b)-(c) on a subsequently obtained biological sample from said individual.”

Wagle discloses a “massively parallel sequencing approach to detect tumor genomic alterations in formalin-fixed, paraffin-embedded (FFPE) tumor samples,” EX1033 83, using “a solution-based exon capture/massively parallel sequencing approach in which a pool of long oligonucleotides complimentary to these exons of interest were used to reduce the complexity of tumor genomic DNA for clinically oriented sequencing,” *id.* 84. Foresight admits that “Wagle did not repeat steps (b)-(c) because of the sample type and also because it was an interrogation of tumor tissue to personalize cancer treatment (as opposed to tumor monitoring over time) and did not require repeating.” Petition 67.

Foresight asserts that a POSA would have been motivated to repeat Wagle’s solution-based exon capture and massively parallel sequencing approach on (i) “subsequently obtained tumor samples,” or (ii) “plasma samples that included cell-free tumor DNA.” Petition 67. Foresight is wrong on both accounts.

First, a POSA would not have been motivated to repeat Wagle’s assay on a subsequently obtained tumor sample from the same patient because obtaining a second tumor sample from Wagle’s patient would require an undesirable invasive procedure to be performed on the patient. For example, Forshew explains that “[b]iopsies are invasive and costly.” EX1030 1. Foresight’s founders admit that tumors “cannot be repeatedly sampled without invasive procedures.” EX2111 2. Chan does not cure this deficiency with Wagle because Chan does not teach or suggest obtaining a first tumor sample, let alone a second tumor sample from a patient. EX2031 ¶¶222-225. Wagle further explains that cost remained “a limiting barrier” of his current approach, EX1033 90, and that his approach had a long turnaround time of 2 weeks. *Id.* (“the potential turnaround time for the current approach is ~2 weeks”). In view of the invasiveness, expense, and length of Wagle’s original assay, a POSA would not have been motivated to repeat the assay on a subsequently obtained tumor.

Second, a POSA would not have been motivated to repeat Wagle’s assay on a plasma sample that included cell-free tumor DNA. As discussed above, cell-free tumor DNA is not present in sufficient quantities to have motivated a POSA to use Wagle’s capture probes on a plasma sample containing nanogram amounts of DNA with a reasonable expectation of success. *Supra* Section V.B. Forshew itself expressly calls out Wagle’s capture probes as having “not been applied to analysis

of circulating tumor nucleic acids.”. EX1030 9; EX2031 ¶226; *supra* Section V.B. Foresight provides no explanation how a POSA would have been motivated to modify Wagle’s workflow to analyze the tiny amounts of DNA in Chan’s cell-free tumor DNA plasma samples with a reasonable expectation of success.

Wagle in view of Chan fails to render the challenged claims obvious for at least these reasons.

VII. OBJECTIVE INDICIA OF NONOBVIOUSNESS

As explained above, Foresight failed to make a prima facie showing obviousness under the asserted combinations of references. Even if Foresight had made such a showing, however, objective indicia of nonobviousness must be carefully evaluated to avoid hindsight bias. *See Crocs, Inc. v. Int’l Trade Comm’n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010). Indeed, such objective indicia “can be the most probative evidence of nonobviousness in the record,” and “may often establish that an invention appearing to have been obvious in light of the prior art was not.” *Id.*

A. Nexus

To receive “substantial weight in the obviousness analysis, the evidence of secondary considerations must have a ‘nexus’ to the claims.” *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019). Nexus can be shown in two ways. First, a nexus is presumed when the patentee shows that the objective evidence is tied to a specific product and that product “embodies the claimed

features, and is coextensive with them.” *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018). Once the patentee has established a presumed nexus, it falls to the challenger to rebut that presumption with evidence that the objective indicia of nonobviousness were caused by “extraneous factors other than the patented invention.” *Id.* Here, Personalis is entitled to a presumption of nexus because, as detailed by Dr. Furneaux, Personalis’ NeXT Personal[®] assay embodies claim 1 of the ’033 Patent. EX2031 ¶228.

Second, even if a presumption of nexus does not apply, “the patent owner is still afforded an opportunity to prove nexus.” *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019). The evidence discussed below independently shows the existence of a nexus. Therefore, Personalis has carried its burden.

B. Industry Praise

Personalis’ assay has received widespread industry attention and praise due in part to its sensitivity relative to other methods. *Arctic Cat Inc. v. Bombardier Recreational Prod. Inc.*, 876 F.3d 1350, 1364 (Fed. Cir. 2017) (“Evidence that the industry praised a claimed invention or a product that embodies the patent claims weighs against an assertion that the same claimed invention would have been obvious.”). For example, last December, *The Scientist* magazine published its list of the Top 10 Innovations of 2022. The patented approach disclosed in the ’033 Patent earned the #1 ranking. *See* EX2001; EX2035 ¶11.

Additional evidence of industry praise comes from an article reporting that three institutions “adopted Personalis’ NeXT Personal” for their TRACERx study due to its “highly sensitive test.” EX2153; EX2035 ¶¶14-17. Yet another article highlights the extended collaboration between Personalis and AstraZeneca regarding NeXT Personal in clinical research and drug development. EX2154; EX2156; EX2035 ¶¶18-20.

Indeed, the differences between the prior art method used in Leary EX1002 (the primary reference asserted by Foresight in related IPR20230-00224) and the method claimed in the '033 patent yield radically different results. 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 the Leary reference was about 0.3%, which is several hundred times less sensitive than the claimed method. EX1002 4 (“However, the fraction of mutant tumor DNA did not reach zero (remaining at 0.3% at day 137), consistent with the fact that this patient had residual metastatic lesions in the remaining left lobe of the liver”). This is shown below by the right most end of the graph in Fig. 4B of Leary:

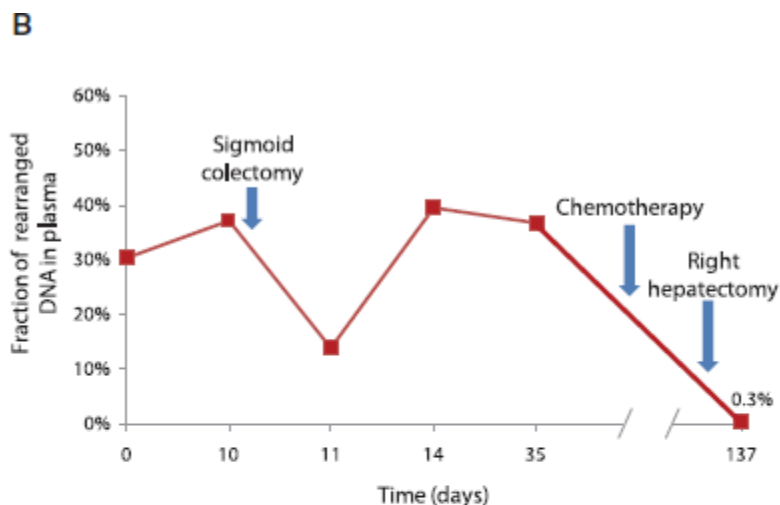


Fig. 4. Detection of tumor-specific rearrangements in plasma of cancer patients. (A) The identified chromosome 4:8 and 16 rearrangements were used to design PCR primers spanning breakpoints and to amplify rearranged DNA from tumor tissue and plasma from patients Hx402 and Hx403, respectively. A plasma 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; EX2031 ¶230. If it were true that others had conceived of and disclosed the patented techniques “long before” the inventors of the '033 patent, as Foresight alleges, then this patented technique would not be lauded by independent judges as the top scientific innovation of 2022, and by research institutions and pharmaceutical companies.

C. Skepticism of Experts

Art cited by Foresight demonstrates that the industry’s experts held skepticism toward solving the difficult challenges of conducting highly sensitive genome sequencing using capture probes. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335

(Fed. Cir. 2016) (“Evidence of industry skepticism is a question of fact that weighs in favor of non-obviousness.”). Forshew acknowledges that using capture probes for cancer monitoring was “expensive” and that achieving sensitive monitoring for mutations across entire genes has been “more challenging.” EX1030 10; *id.* 1; *see also* EX1031 (discussing “the key challenges in cancer genome sequencing”). Experts in the field were clearly skeptical of the capture probes Forshew described as “difficult to implement on a routine basis.” EX1030 10.

Other references outline clear industry-wide problems with next-generation sequencing (NGS) at the time, which were unexpectedly solved by the methods in the '033 Patent. For example, Anderson emphasizes that “difficult engineering challenges must be overcome before these technologies could become commercially viable.” EX1004 48. Further, Lo identifies difficulties facing experts regarding “how to handle the massive amount of sequencing data” when utilizing NGS for profiling cancer genomes. EX1017 3; EX2031 ¶¶231-232.

This objective real-world evidence supports a finding that the claims of the '033 patent are nonobvious and, consequently, Foresight’s attempt to demonstrate that the claims of the '033 patent are unpatentable fails.

VIII. CONCLUSION

For the foregoing reasons, the Board should confirm patentability of all challenged claims of the '033 patent.

Respectfully submitted,
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Dated: October 6, 2023

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), Counsel for Patent Owner Personalis, Inc. hereby certifies that this document complies with the type-volume limitation of 37 C.F.R. § 42.24(b). This document contains approximately 13,956 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

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CERTIFICATE OF SERVICE

I hereby certify that, pursuant to 37 C.F.R. § 42.6(e) and with the agreement of counsel for Petitioner, a true and correct copy of **PATENT OWNER RESPONSE AND EXHIBITS 2016-2018, 2024-2028, 2030-2123, 2151-2160, 2162** are being served electronically on October 6, 2023, to the e-mail addresses shown below:

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APPENDIX A

Listing of Claims from U.S. 11,408,033	
Claim 1	
Preamble	1. A method for analyzing a nucleic acid sample obtained from an individual, comprising:
1(a)	[i] ⁶ producing, with the aid of a computer processor, a plurality of capture probes, wherein said plurality of capture probes hybridize to a plurality of polymorphisms, [ii] wherein said plurality of polymorphisms are in sequences encoding genes with known biomedically interpretable variants, and [iii] wherein said plurality of polymorphisms are based on or extracted from one or more databases of polymorphisms and are observed in a population of one or more samples;
1(b)	contacting said nucleic acid sample with said plurality of capture probes produced in (a);
1(c)	conducting a sequencing assay on a subset of nucleic acid molecules generated from said nucleic acid sample in step (b) to yield a result comprising a nucleic acid sequence, thereby analyzing said nucleic acid sample; and
1(d)	repeating steps (b)-(c) on a subsequently obtained biological sample from said individual.
Claim 2	
	2. The method of claim 1, further comprising, subsequent to (c), generating a biomedical report that includes biomedical information of said individual, which biomedical information is indicative of said result.

⁶ Bracketed roman numerals, e.g., “[i]” and “[ii]”, have been added to limitation 1(a) for ease of references.

Listing of Claims from U.S. 11,408,033	
Claim 3	
	3. The method of claim 2, wherein said biomedical information of said individual 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 4	
	4. The method of claim 1, wherein said plurality of polymorphisms comprise one or more insertions, deletions, structural variant junctions, variable length tandem repeats, single nucleotide mutations, or a combination thereof.
Claim 5	
	5. The method of claim 1, wherein said sequences encoding genes with known biomedically interpretable variants comprise a plurality of sequences encoding genes associated with cancer.
Claim 6	
	6. The method of claim 1, further comprising identifying the presence or absence of said plurality of polymorphisms in said nucleic acid sample.
Claim 7	
	7. The method of claim 2, wherein said identifying comprises observing an allele frequency of said plurality of polymorphisms.
Claim 8	
	8. The method of claim 1, wherein said plurality of capture probes are in a hybridization array.

Listing of Claims from U.S. 11,408,033	
Claim 9	
	9. The method of claim 1, wherein said plurality of capture probes are conjugated to beads.
Claim 10	
	10. The method of claim 1, wherein said plurality of capture probes further comprises barcodes.
Claim 11	
	11. The method of claim 1, wherein said nucleic acid sample obtained from said individual is from a body fluid, cell, skin, tissue, organ, or combination thereof.
Claim 12	
	12. The method of claim 11, wherein said body fluid is blood plasma.
Claim 13	
	13. The method of claim 12, wherein said plasma sample is obtained from said individual at a first time point, and further comprising, subsequent to (c), using said capture probes to generate an additional subset of nucleic acid molecules from an additional nucleic acid sample isolated from an additional plasma sample obtained from said individual at an additional time point different from said first time point.
Claim 14	
	14. The method of claim 13, wherein said first time point and said additional time point are at least 1 week apart, or more.
Claim 15	
	15. The method of claim 13, wherein said first time point and said additional time point are at least 1 month apart, or more.

Listing of Claims from U.S. 11,408,033	
Claim 16	
	16. The method of claim 13, wherein said additional time point is later than said first time point.
Claim 17	
	17. The method of claim 13, wherein said additional time point is earlier than said first time point.
Claim 18	
	18. The method of claim 11, wherein said tissue is a tissue biopsy.
Claim 19	
	19. The method of claim 1, wherein said subsequently obtained biological sample is a plasma sample.
Claim 20	
	20. The method of claim 1, wherein said subsequently obtained biological sample is a tissue biopsy sample.
Claim 21	
	21. The method of claim 1, wherein said one or more databases of polymorphisms comprises a biomedical database.
Claim 22	
	22. The method of claim 1, wherein said one or more polymorphisms are observed in a population of a single sample.
Claim 23	
	23. The method of claim 1, wherein said plurality of polymorphisms are based on or extracted from said one or more databases of polymorphisms and observed in said population, wherein said population comprises a plurality of samples.