

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS INC.,
Petitioner,

v.

PERSONALIS, INC.,
Patent Owner.

Case Nos. IPR2023-00224 and IPR2023-00317
U.S. Patent Nos. 11,384,394 and 11,408,033

DECLARATION OF JOHN WEST

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2030	Chen, et al., Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes, Cell 148, 1293-1307, March 16, 2012
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
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.

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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
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2047	May 11, 2012 Google Calendar reminder, Personalis Weekly Team Meeting
2048	Google Calendar reminder re Accuracy review / brainstorm on May 5, 2012
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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
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

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2054	May 22, 2012 Email from John West to Richard Chen, et al., re Spreadsheet for 2pm discussion of Accuracy Differentiation with attachment
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2063	June 11, 2012 Email from John West to Richard Chen, et al. re Draft Board slides for your comments with attachment

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2065	June 17, 2012 Email from John West to Scott Kirk re Sprint 2 overview
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2068	July 20, 2012 Google Calendar reminder re Personalis Weekly Team Meeting
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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
2074	July 24, 2012 Quick Notes on Lab Sequencing From Discussion with JW

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

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

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

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2106	December 13, 2012 Email from John West to Carol Tillis re CEO Update presentation for Board meeting with attachment
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
2112	May 08, 2012 CEO Overview Board of Director Presentation by John West
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 Shujun getting started
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

Exhibit No.	Description
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

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1. I, John West, make this Declaration in connection with the Patent Owner Responses filed in IPR2023-00224 regarding U.S. Patent No. 11,384,394 (“the ’394 patent”) and IPR2023-00317 regarding U.S. Patent No. 11,408,033 (“the ’033 patent”). I am a named inventor on the ’394 and ’033 patents.

I. BACKGROUND AND QUALIFICATIONS

2. Summary: I studied engineering as an undergraduate and graduate student at MIT and later completed an MBA in Finance at the University of Pennsylvania. I began work on automating DNA sequencing in 1982, when it was a completely manual process. I launched one of the first commercial automated DNA sequencing instruments in 1987 and by 2001 was Vice President at Applied Biosystems, the market leader with DNA sequencing revenue approaching \$1 billion / year. By then the technology had improved by a factor of about 1,000-fold. I then left to be CEO of a small startup company in England named Solexa. We were able to make the Solexa technology work and with further improvements achieved approximately another factor of one million-fold improvement in DNA sequencing performance. In the process, the technology was acquired by Illumina and largely due to that, their market capitalization reached as high as \$80 billion. This technology made it possible to sequence the genomes of individual people and in 2009 I had my genome, and those of my family sequenced. We did this in part to pioneer a new field but discovered that there was room to improve both the DNA

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sequencing assays and the clinical interpretation of the data. I founded Personalis in 2011 with four Stanford professors to take on that challenge. I was able to raise over \$550 million for Personalis, including a \$150 million 2019 Nasdaq IPO. At Personalis, we have always sought to progress the field with more advanced technology and new approaches, which we filed for patent protection. Because we started early, had a track record, and had financing, we were able to attract some of the first experts in this field to be part of the company. I retired at the end of 2022 after over 40 years in DNA sequencing, but Personalis is continuing to push forward. The following paragraphs provide more detailed information on this history.

3. I incorporated Personalis in February 2011 with four faculty members from Stanford University as co-founders:

- Michael Snyder, Ph.D. (Chairman of the Stanford Genetics Department);
- Russ Altman, M.D., Ph.D. (Chairman of the Stanford Bioengineering Department);
- Euan Ashley, M.B., FRCP, D.Phil. (founder of the Clinical Genomics Program and the Center for Inherited Cardiovascular Disease at Stanford);
- Atul Butte, M.D., Ph.D. (Chief of the Division of Systems Medicine at Stanford University School of Medicine).

I served as the founding Chief Executive Officer of Personalis from August 2011 through December 2022. We focused on the development of new assay technologies

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which could be more comprehensive, more accurate and more sensitive than the straightforward use of Illumina DNA sequencing systems. This is described further below. Our first customer revenue was recognized in January 2013 and we achieved peak annual revenue, so far, of \$85 million, in 2021. I took the company public on the Nasdaq in 2019 and raised a total of over \$550 million to finance the company over the years. I retired from Personalis at the end of 2022. I provided consulting services to Personalis from January 2022 until May 2023. I am currently retired, informally advising a number of startup companies in their development and commercialization of new technologies. Over my career, I have been the sole or co-inventor on at least 30 issued US patents.

4. Prior to founding Personalis, I spent the period from February 2008 to April 2009, exploring opportunities to advance DNA sequencing technology. I focused in particular on an optical advance known as “super-resolution microscopy”, for which the Nobel prize was later awarded (in 2014). By early 2009, a serious recession had begun in the United States, and it became clear that it could be difficult to finance a new startup company. I also received an offer to be Chief Executive Officer of ViaCyte (a venture capital financed company, previously known as NovoCell) which was developing a treatment for type 1 diabetes based on human embryonic stem cells. While ViaCyte’s goal was inspiring in its own right, I was aware that DNA sequencing technology at Illumina was continuing to advance and

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there would be an opportunity to be an early adopter and build new levels of technology using it as a foundation (I had been Illumina's 1st VP of DNA sequencing, as described below). I negotiated a contract with ViaCyte under which I would be their CEO starting in May 2009, but could also separately explore ideas in the non-competitive area of DNA sequencing, in parallel. By two months later, Illumina had announced a Personal Genome Sequencing service. In October 2009 they presented it to me in detail and in November I committed to have my whole family sequenced by Illumina, for \$160,000. As described below, this led to the formation of Personalis. I stayed as CEO of ViaCyte through May of 2011, but in parallel began to work on concepts for the new company. ViaCyte's technology is a breakthrough in its own area and will be transformational for diabetics if it is eventually successful, but the time scale of clinical trials can be very long. After I left it, ViaCyte continued to pursue its technology, entered human clinical trials, and was eventually acquired by Vertex Pharmaceuticals, Inc. in July of 2022.

5. I was the Senior Vice President of DNA Sequencing at Illumina, Inc. from January 2007 until January 2008. Illumina became the world leader in DNA sequencing systems during that year based on its acquisition of my prior company, Solexa, Inc. Illumina's annual revenue rose from \$160M the year before it acquired Solexa, to over \$4 billion in 2022, primarily because of their DNA sequencing business built on the Solexa foundation. Although Solexa had begun shipping a few

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systems to customers in mid-2006, prior to its combination with Illumina, it had not recognized any revenue on them. During my first year at Illumina (2007) we began to recognize revenue, growing from zero to almost \$100 million in revenue in one year. My involvement with Solexa is briefly described in the next paragraph.

6. Solexa, Ltd. was a venture backed 1998 spin-out company from Cambridge University (United Kingdom) that developed a new DNA sequencing-by-synthesis technology. I was recruited to be CEO of Solexa, starting in August 2004, based on my prior role as VP of DNA sequencing at the prior market leader, Applied Biosystems (described below). At the time, Solexa Ltd. had about 45 employees, no product, and was entirely located in a small research park in the countryside south of Cambridge, England. I realized that Solexa would need to become US-based and negotiated, in my first week on the job, the acquisition of US-based Lynx Therapeutics. Lynx had its own advanced DNA sequencing technology (MPSS), had 90 employees based in the San Francisco area, was Nasdaq listed, and was within a few months of running out of money. We completed the combination in March 2005 and I became the CEO of the combined company, then called Solexa, Inc. With the potential created by the combination, I was able to raise about \$95M in financing in 2005, complete the development of the initial Solexa DNA sequencing system, and ship the first systems to customers by mid-2006. This attracted interest from Illumina, Inc, which wanted to acquire a DNA sequencing

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platform. Following a negotiation, we announced in November 2006 that Illumina would acquire Solexa for 30 million Illumina shares. That would eventually value the acquisition at over \$15 billion. The acquisition was completed in January 2007.

7. I was the Vice President of Genetic Analysis (DNA Sequencing) at Applied Biosystems, Inc. (ABI, a unit of Applied Biosystems Corp.) from January 2001 to June 2001. I then became Vice President for all of ABI's DNA Platforms, a business with total revenue over \$1 billion / year. This included DNA sequencing, real-time PCR, preparative PCR, DNA synthesis and DNA arrays, and continued in that role through November 2003. I was the Vice President of Business Development at Applied Biosystems from December 2003 through July 2004. DNA sequencing was Applied Biosystems largest revenue component during my tenure, with a peak quarterly revenue of approximately \$200,000,000. I repositioned the Applied Biosystems sequencing business from de novo sequencing of new species to the search for rare variants by "re-sequencing" (by sequencing a portion of a species' genome which was already known) to find individual-to-individual genetic variants. One of my key themes was the importance of individually-rare variants, which are often more functionally significant than common variants. Although these genetic variants are individually rare, there are so many of them collectively that they actually represent a major fraction of human genetic variation. Rare variants are even more important

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in cancer, and I highlighted that in my presentations both to customers but also to investors.

8. I was the Vice President of Marketing for Microfluidics at Coventor, Inc. (a venture capital-backed startup company spun out of MIT) from January 1999 to January 2001. Coventor (which was previously named Microcosm), developed and sold computer aided design software for non-electronic devices fabricated using semiconductor manufacturing technologies. In this position I leveraged experience gained in my prior company, Princeton Instruments, where we designed custom silicon integrated circuits for scientific imaging and spectroscopy. At Coventor, I focused on developing business in the new field of microfluidic lab-on-a-chip devices for biotechnology applications, including DNA sequencing. Applied Biosystems was then the world leader in DNA sequencing instrumentation, and became a major customer of Coventor. I moved from Coventor to be VP of DNA sequencing (formally VP, Genetic Analysis) in January 2001. Long after I left, in 2017, Coventor was acquired by Lam Research.

9. I was the General Manager of privately held Princeton Instruments (“PI”) from June 1990 until it’s May 1997 acquisition by Roper Industries, which I helped to negotiate. Following that acquisition, Princeton Instruments operated as a stand-alone division of Roper and I was President through June 1998. At PI, I was responsible for developing cooled charge-coupled device (CCD) cameras for

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scientific applications, including fluorescence microscopy of live cells, single molecule imaging, and DNA sequencing. This included developing a number of large custom silicon integrated circuits for optical detection. Long after I left, in 2019, Princeton Instruments was further sold to Teledyne.

10. I was the Chief Executive Officer of BioAutomation from August 1988 until June 1990. I founded BioAutomation as a start-up company and hired about half a dozen R&D staff. The company developed a prototype automated DNA sequencing instrument. To improve performance over earlier systems, we implemented a number of the pattern recognition algorithms in a new type of integrated circuit called a field-programmable gate array. The company was awarded Phase 1 and Phase 2 SBIR grants for this by the Human Genome Project, starting in 1988, its first year. At that time, venture capital was very limited in the Philadelphia area and we closed the company in mid-1990.

11. I was a Business Unit Manager at Bio-Rad Laboratories from August 1982 until June 1988. At Bio-Rad, I recruited and led a team which developed one of the first commercial automated DNA sequencing instruments, launched commercially under the name “GeneMaster” in 1987. It was described in an article that I authored “Automated sequence reading and analysis”, in Nucleic Acids Research, Volume 16 No 5, pg 1847-1856, January 1988.

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12. I earned my Master of Business Administration in Finance from the Wharton School of Business of the University of Pennsylvania in 1988. This was an executive MBA program concurrent with my work at Bio-Rad, described above.

13. I earned my Masters of Science in Mechanical Engineering from the Massachusetts Institute of Technology (MIT) in 1980. In addition to topics in Mechanical Engineering, I took classes in electrical engineering and computer science. The core of my Masters thesis was a new solution to a set of equations describing a manufacturing process, but I implemented them in real-time on a microprocessor controlling a 90-ton machine. The company who sponsored the research, licensed the technology from MIT, commercialized it, and paid royalties to the end of the 20-year patent life.

14. I earned my Bachelors of Science degree in Nuclear Engineering from the Massachusetts Institute of Technology (MIT) in 1978. During all four years and summers that I was an undergraduate at MIT, I worked on a major controlled nuclear fusion experiment named Alcator. I designed and operated a custom laser diagnostic instrument, and wrote associated data analysis software, to measure the temperature and density of the magnetically confined hydrogen plasma. My work at Alcator helped me become comfortable pioneering in areas which had never been developed before. I took a wide range of subjects at MIT, in both science and engineering.

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This gave me a multidisciplinary base that held me in good stead throughout my career.

15. I have authored or co-authored over 10 publications in peer-reviewed journals, including Nature, Nature Communications, Nature Biotechnology, PNAS, PLoS Genetics, Cancer Research, Genome Medicine, Nucleic Acids Research and Molecular & Cellular Proteomics. I have also made oral and poster presentations, myself or with collaborators, at numerous scientific and technical conferences including American Association for Cancer Research (AACR), Advances in Genome Biology and Technology (AGBT), International Cancer Genome Consortium (ICCG), American College of Medical Genetics (ACMG), American Society of Human Genetics (ASHG), Society for Immunotherapy of Cancer (SITC), and Cold Spring Harbor Laboratory's (CSHL's) Personal Genomes.

16. I have been an invited presenter at biotechnology and genomics-focused investor conferences throughout the United States and abroad. When I joined Solexa as CEO in 2004, the company had about 45 employees, no product and no revenue. It's most recent financing had been at a valuation of about \$36 million. By the time I left in 2008, when Solexa was a part of Illumina, revenue had increased from zero to almost \$100 million in the first year. Since that time, Illumina's total revenue, almost entirely derived from that DNA sequencing business, has totaled over \$34 billion. In early 2021, Illumina's market

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capitalization had increased to over \$80 billion (146 million shares outstanding Jan 3, 2021 and peak stock price shortly after that over \$550.). This was not only a financial success. It transformed the world of DNA sequencing, including cancer sequencing and, more recently, Covid sequencing.

17. I am sole or joint inventor on at least 30 issued US patents, assigned to MIT, Princeton Instruments, Illumina and Personalis. I filed for my first US patent in 1980 (US 4,408,471 which was licensed, commercialized and paid royalties through its expiration 20 years later). The subject matter for these patents has ranged from silicon semiconductor chip design (e.g. US 5,432,335 “Charge Coupled Device for Spectroscopic Detection”), to DNA sequencing technology (e.g. US 10,036,063, “Method for sequencing a polynucleotide template”, provisional filed in 2009 and assigned to Illumina), to cancer diagnostics (e.g. US 10,450,611 “Personalized Genetic Testing”). In addition, many of these US patents have also been issued in other countries, including in Europe and China.

18. As CEO, I have raised over \$650 million from investors to finance my companies, an indication of their confidence in the technologies we have developed, and still expected to develop.

19. When I first began to work on automated DNA sequencing in 1982, the idea of sequencing “the” human genome (just one !) seemed a distant dream. By

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the time I retired, my company Personalis had sequenced over 150,000 whole human genomes, more than any other for-profit US company.

II. BRIEF HISTORY OF PERSONALIS

20. As mentioned above, I incorporated Personalis in February 2011 with four faculty members from Stanford University: Michael Snyder, Ph.D.; Russ Altman, M.D., Ph.D.; Euan Ashley, M.B., FRCP, D.Phil.; and Atul Butte, M.D., Ph.D. Our purpose in founding Personalis was to develop innovative products and methods to realize personalized medicines and diagnostic assays.

21. My interest in personalized medicines and diagnostic assays dates back to at least December 8th, 2003. Although I was generally healthy, I woke up that morning with a completely unexpected and rather extensive pain in my back. By the end of the day I was in our local hospital, where I stayed for four days. Testing revealed that I had experienced a pulmonary embolism and that the pain I felt was from my lungs, not my back. Testing further showed that I had a fairly common genetic variant called Factor V Leiden, which causes excessive blood clotting, typically in the lower extremities of the legs. If such a blood clot breaks free, it can move to the tiny blood vessels of the lungs, where it can block further blood flow and cause tissue death. I was started on a “blood thinning” medicine named warfarin, which would counteract the clotting effect of the Factor V mutation. The

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correct dose of warfarin is challenging to set, can vary over time, and needed to be checked, and sometimes adjusted, based on a blood test once a month. By the time we filed the provisional patent application for the '033 and '394 patents in January 2013, I had personally been undergoing monthly blood testing for a genetic condition for over nine years.

22. At the time of my pulmonary embolism, I was Vice President of the largest DNA sequencing business in the world, and the Factor V Leiden mutation had been discovered scientifically over ten years earlier, yet I had not been tested for it and had to discover that I had it by suffering an embolism. I was determined that if I ever got the chance, I would test my genome and those of my family, to make sure we did not have any more unnecessary surprises. Unfortunately, in December 2003, the cost of sequencing a human genome was about \$1 billion, so there was nothing I could do. One month later, I received a telephone call, asking if I would be interested in becoming CEO of Solexa, Ltd.

23. I took the CEO position at Solexa Ltd. even though it involved commuting 5,000 miles and eight time zones each way on a monthly basis. As described above, we did make the technology work, shipped the first systems to customers in mid-2006, and sold the company to Illumina in early 2007. I left to explore other career opportunities a year later, but the technology continued to

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improve. In mid-2009, Illumina announced that they would begin to offer personal genome sequencing, at a price of \$48,000 per person. I called them and signed up.

24. In November of 2009, I personally paid Illumina \$160,000 to have my family of four whole genome sequenced. I received the genome data in early 2010, and conducted considerable analysis of it. In particular, I found that the data had systematic gaps in the genome where there was little or no data. In view of the systematic gaps I saw in the genomic data, it occurred to me that there was a need for improvement in the field of genomic assays. Because Illumina provided no medical interpretation of our data, I reached out to experts I knew at MIT, Harvard and elsewhere. The sequencing of our family generated a fair amount of publicity, including television coverage and articles in the Wall Street Journal, Technology Review and the Times of London. One of these connections alerted me to a group at Stanford who, on May 1st 2010, had published in The Lancet, a truly clinical interpretation of the genome of Stanford professor Steve Quake, centered on a serious cardiac disease in his family, but also exploring what else might be determined medically from his genome. In June 2010, I began to meet with and work with the four faculty members from Stanford University and by the autumn we had decided to found Personalis. We secured an \$18M Series-A financing commitment by January 2011 and incorporated the company the following month.

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25. In July of 2011, I presided over the first Personalis Board of Directors meeting. All of my co-founders were present (except Dr. Butte, who was absent due to travel). Also present were three investors: Jonathan MacQuitty of Abingworth, Sue Siegel of Mohr Davidow, and Andrew Chung of Lightspeed. Also present was counsel Robin Bennet, who was present in-person, and Lisa Kenkel, who was present by phone for a portion of the meeting. During the meeting, we discussed licensing certain intellectual property from Stanford University. We also discussed developing innovative products for realizing personalized medicines and diagnostic assays, as well as scientific updates regarding pilot academic research for clinical implementation, research regarding the Snyder family personal genomes, and topics regarding Mendelian diseases and cardiology. We also discussed operational planning, such as hiring personnel, obtaining office and laboratory space, and budgetary planning.

26. In August of 2011, Personalis closed the initial tranche of its \$20,000,000 Series A financing (it had grown a little from the initial \$18M commitment and been delayed while we completed a license agreement with Stanford University). Also in August of 2011, we purchased the rights to the personalis.com domain. In September of 2011, we launched the company's first website.

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27. On September 15th 2011, with the Stanford co-founders of Personalis and a team from Harvard, I co-authored a peer-reviewed research article in the PLOS Genetics Journal describing the whole-genome sequencing results for my family quartet. Exhibit 2122 is a true and correct copy of that article, titled “Phased Whole-Genome Genetic Risk in a Family Quartet Using a Major Allele Reference Sequence.”

28. The following day, the MIT Technology Review published an article about my family of four’s decision to sequence our genomes and the results which we had just published in PLoS Genetics. Exhibit 2121 is a true and correct copy of that article, titled “A Family Learns the Secrets of Its Genomes.” This added to the recognition of our plans for Personalis and helped with our recruitment of a strong initial team of employees.

29. In November of 2011, Sarah Garcia, Ph.D., joined Personalis in the role of Senior Genomic Counselor. Dr. Garcia earned her Bachelor of Science in Microbiology, Immunology, and Molecular Genetics from the University of California, Los Angeles in 2003, and her Ph.D. in Genetics from the Stanford University School of Medicine in 2010. Following her Ph.D., Dr. Garcia completed a further MS degree at Stanford, in Genetic Counseling. In this program, she completed clinical rotations at Kaiser, at the Stanford Genome Technology Center focused on cancer, and at Illumina. During her rotation at Illumina, Dr. Garcia

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worked on clinical interpretation of variants identified through whole genome sequencing, including a family quartet genome data set that Illumina had generated. Only about 3% of genetic counselors in the United States also hold Ph.D. degrees. Dr. Garcia did, and she became the first employee of Personalis after me.

30. In November of 2011, Richard Chen, M.D., joined Personalis as its Chief Scientific Officer. Dr. Chen earned his Bachelor of Science in Computer Science in 1992, his Masters of Science in Biomedical Informatics in 1998, and his M.D. in 2007, all from Stanford University. From the completion of his MD in 2008, to 2011, Dr. Chen worked as a resident at the Stanford Medical School. During that time, Dr. Chen collaborated with other Stanford researchers to use high throughput RNA sequencing to identify new biomarkers and mechanisms of disease for cutaneous lymphoma and autoimmune skin disease. After he joined Personalis, Dr. Chen continued to see patients at Stanford one day per week. In addition to his medical education and work experience, Dr. Chen was an experienced and successful genomics-focused entrepreneur. In 1998, he won first place in the Stanford business plan competition and based on that co-founded Ingenuity Systems. They raised venture capital, curated a leading database of gene pathways and developed software leveraging that database. The company grew to 120 employees, \$30 million / year in revenue, and was sold for \$105M to Qiagen in April 2013. At Ingenuity, Dr. Chen was co-inventor on two issued US patents (6,741,986 and

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6,772,160 both in 2004). Prior to joining Personalis, Dr. Chen had co-authored ten peer reviewed scientific papers and a book chapter. Through his time at Stanford, Dr. Chen worked closely with Dr. Russ Altman, Chairman of the Bioengineering Department. When Dr. Altman co-founded Personalis in 2011, he recommended Dr. Chen as a possible key employee. From the time he joined Personalis through to the January 2013 filing of Personalis first provisional patent application, Dr. Chen was responsible for recruiting and managing its R&D team. Beginning in February 2012, Dr. Chen regularly provided R&D updates at meetings of the Personalis Board of Directors. In July 2021, Dr. Chen was promoted to the dual role of Chief Medical Officer (CMO) and Senior Vice President R&D. On March 2nd, 2023, Personalis announced that Dr. Chen had been promoted to Executive Vice President, R&D, in addition to his role as Chief Medical Officer.

31. In November of 2011, Hugo Lam, Ph.D., joined Personalis as Project Manager of Computational Biology. Dr. Lam earned his Bachelor of Science in Biology from the Hong Kong University of Science and Technology in 1999, his Master of Science in Computer Science from the Imperial College of London in 2000, and his Ph.D. in Computational Biology and Bioinformatics from Yale University in 2010. His PhD thesis title was “Computational Analysis on Genomic Variation: Detecting and Characterizing Structural Variants in the Human Genome”. This included development and 2010 publication of an algorithm called “BreakSeq”

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to identify structural variation by identifying “junction sequences”. Dr. Lam’s Ph.D. thesis advisor at Yale was Dr. Mark Gerstein. Dr. Gerstein had been a long term collaborator of Dr. Michael Snyder, who also spent over 20 years at Yale. In 2009, Dr. Snyder was recruited to be the new head of the Genetics Department at Stanford. Dr. Snyder asked Dr. Lam to join him in the move to Stanford and in 2010 Dr. Lam moved to a post-doc position under Dr. Snyder at Stanford. At Stanford, Dr. Lam developed a comprehensive and computationally parallel software system for identifying SNPs, InDels and Structural Variants from human whole genome DNA sequencing data. It was called HugeSeq, because it was designed to support much larger numbers of genomes than prior systems. In 2011, Dr. Lam moved to Personalis. Prior to joining Personalis, Dr. Lam had authored, or co-authored, 15 peer reviewed scientific publications, including in Nature, Nature Biotechnology, PLoS Genetics, Nucleic Acids Research, and Genome Research. Dr. Lam published an article describing HugeSeq with Dr. Snyder in March 2012.

32. In January of 2012, Mark Pratt, Ph.D., joined Personalis as Senior Director for the Accuracy Program. Dr. Pratt earned his Bachelors of Science degree in Physics from Walla Walla University in 1990, and his Ph.D. in Physics from the University of California, Santa Barbra in 1997. I met Mark Pratt in 2003 when we were both at Applied Biosystems and he was on an R&D team developing a multiplexed genotyping product called SNPlex. I was impressed by Mark’s rigorous

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and constructively analytical approach to this development. After I moved to Solexa and we had established a US presence by acquiring Lynx Therapeutics, I recruited him to join us to be our system engineering lead. In this role he led development of the original Solexa Genome Analyzer system and the subsequent Solexa Genome Analyzer IIx system. Mark stayed with the company after the acquisition by Illumina and was also system engineering lead on development of the Illumina HiSeq-2000 instrument. In late 2011, after Personalis began operations, Mark was one of the first people I contacted and he moved from Illumina to become one of our first employees. In addition to Mark's experience developing state of the art DNA sequencing systems, he was also an experienced and successful entrepreneur. Earlier in his career, in the year 2000, Mark founded nLight Photonics Corporation. The company developed advanced semiconductor-driven fiber-optic lasers. It reached over \$100M in revenue in 2016, went public (Nasdaq : LASR) in 2018, and achieved a market cap over \$1 billion. Before joining Personalis, Mark was a named inventor on US patents and patent applications assigned to nLight, Applied Biosystems, Solexa, and Illumina.

33. In February of 2011, Gemma Chandratillake, Ph.D., joined Personalis in the role of Genomic Counselor. Dr. Chandratillake earned her Master of Arts in Genetics from the University of Cambridge (UK) in 2000, her Master of Philosophy in Molecular Genetics from the University of Cambridge in 2001, her Ph.D. in

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Molecular Genetics from The Open University in 2005, and her Master of Science in Genetic Counseling from Stanford in 2011. At Stanford's Genetic Counseling program, Gemma was unusual in already having a Ph.D. in Genetics. Sarah Garcia, mentioned above, was in the same class and was also building on a Ph.D. When Sarah joined Personalis, we came to appreciate the deep understanding of a Ph.D. educated genetic counsellor and asked if she knew anyone else with those rare credentials that we could recruit. She led us to Gemma, who joined Personalis shortly thereafter.

34. On May 1, 2012, Gabor Bartha, Ph.D., joined Personalis in the role of Senior Bioinformatics Scientist and he was immediately tasked with working on the Accuracy Program under Mark Pratt. Dr. Bartha earned his Bachelors of Art in Physics from Harvard University, and his Ph.D. in Biology from the University of Southern California. Before joining Personalis, Gabor already had almost seven years of commercial experience analyzing DNA sequencing data, at InCyte. In October 2015, at Personalis, he was promoted to Principal Scientist and in August 2021 he was promoted to Distinguished Scientist. He was the only employee to be recognized with that title.

35. On June 18th, 2012, Shujun Luo joined Personalis in the role of Senior Scientist, Accuracy R&D. In October 2014 she was promoted to Director, Laboratory R&D. In September 2015, she was promoted further to Director of

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Laboratory Operations. Ms. Luo earned her Masters of Science in Cellular and Molecular Biology from Columbia University, and her Bachelor of Science in Cellular and Molecular Biology from the University of Science and Technology of China. From 1997 through 2012, she worked on the development of next generation DNA sequencing technologies and applications of them, initially at Lynx Therapeutics, then at Solexa after it acquired Lynx, and then at Illumina after it acquired Solexa. In these roles she overlapped with me (while I was CEO of Solexa and then SVP of DNA sequencing at Illumina) and Mark Pratt (system engineering lead at Solexa and then Illumina). Before joining Personalis, Shujun had authored, or co-authored, over 30 peer reviewed scientific publications, including in Science, Nature and Cell. From her work before joining Personalis, Shujun was a named co-inventor on at least five US patents, assigned to Illumina.

36. Based on at least the personnel hirings 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 and fulfill the vision that I shared with my co-founders when we founded Personalis. Indeed, the world-class team of scientists at Personalis have diligently sought to transform the development of next-generation therapies through the development of some of the world's most advanced personalized genetic tests for cancer and provided more comprehensive molecular data about each of our patient's cancer and immune response.

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37. Today, Personalis has over 270 employees, and an estimated annual revenue of \$70,000,000 to \$72,000,000. Personalis' tests, including methods developed by the inventors of the '033 and '394 patents, are routinely used by many of the largest oncology-focused pharmaceutical companies for analysis of patient samples from their clinical trials and, more recently, by a growing number of leading cancer centers. The results of Personalis' innovation include several commercial products on the market today, which include: NeXT Personal®, ImmunoID NeXT®, NeXT Liquid Biopsy®, NeXT Dx®, and NeXT Personal Dx® (which will become available in the marketplace soon). These products are genetic testing services that are provided to clinicians or pharmaceutical companies. A brief summary of the Personalis commercial products are provided below.

A. NeXT Personal®

38. Personalis launched NeXT Personal in December 2021 as a biopharmaceutical product. NeXT Personal is a next generation, tumor-informed liquid biopsy assay designed to detect and quantify minimal (or molecular) residual disease ("MRD") and recurrence in patients previously diagnosed with cancer.

39. NeXT Personal is designed to deliver industry-leading MRD sensitivity down to the 1 part-per-million range, which represents an approximately 10- to 100-fold improvement over other available technologies, through the use of whole genome sequencing of a patient's tumor to identify up to 1,800 specially-selected

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somatic variants that are used to create a personalized liquid biopsy panel for each patient. In addition to its proprietary error suppression techniques, NeXT Personal has a $\geq 99.99\%$ specificity that minimizes the rate of false positives.

40. NeXT Personal is unique in that it is also designed to simultaneously detect and quantify clinically known, targetable cancer mutations, drug resistance mutations, and new variants which can emerge over time and in response to therapeutic pressure. NeXT Personal also permits monitoring circulating tumor DNA to track responses to therapies, and promotes precision therapy for individualized treatment recommendations.

41. In December of 2022, Personalis' NeXT Personal was ranked Number One on The Scientist's Top 10 Innovations of 2022. *See* EX2001 at pages 1-2. This award was issued to Personalis by an independent panel of judges.

B. ImmunoID NeXT[®]

42. Personalis launched ImmunoID NeXT in November 2018 as a biopharmaceutical platform. Personalis began offering ImmunoID NeXT through its Early Access Program in January 2019, with the clinical diagnostic test release occurring later in 2019.

43. ImmunoID NeXT is a universal cancer immunogenomics platform that provides comprehensive analytics of tumors and tumor microenvironments. As a single platform, ImmunoID NeXT enables users to evaluate and characterize

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complex interactions between tumor cells and immune cells. ImmunoID NeXT also provides a multidimensional view of cancer biology that other industry competitors are lacking. For example, ImmunoID NeXT leverages analytical algorithms that allow users to understand various tumor and immune-related information, including immunocellular profiles within a tumor microenvironment, T-cell and B-cell receptor repertoire, neoantigen prediction with SHERPA[®], tumor mutational burden, microsatellite instability characterization, and oncoviral detection.

44. ImmunoID NeXT is designed to deliver deep sequencing capabilities with approximately 300X mean coverage across the entire footprint of more than 20,000 genes of both the exome and transcriptome. ImmunoID NeXT provides clinical-grade coverage across 247 cancer-related genes, as well as specific targeting of HLA genes, MSI-related loci, T-cell and B-cell repertoire, and oncoviral genes. These capabilities contribute to ImmunoID NeXT's innovative design that enables accurate characterization of investigational and predictive precision oncology biomarkers.

C. NeXT Liquid Biopsy[®]

45. Personalis launched NeXT Liquid Biopsy in August 2020 as a biopharmaceutical product. NeXT Liquid Biopsy is a revolutionary platform in the genomic industry, offering exome-scale tumor-profiling capabilities. NeXT Liquid

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Biopsy is a liquid biopsy assay designed to evaluate blood samples for early cancer detection, treatment, and management.

46. NeXT Liquid Biopsy offers multiple applications that would otherwise be unachievable using competing technologies. Such applications include assessing tumor heterogeneity, monitoring clonal evolution and tumor dynamics, interrogating mechanisms of intrinsic and acquired resistance, and accessing tumor biology insights that are inaccessible with panel-based approaches. Each application benefits from Personalis' deep sequencing approach. NeXT Liquid Biopsy is capable of producing approximately 2,000X mean coverage across the entire exome of approximately 20,000 genes. In addition, NeXT Liquid Biopsy offers approximately 5,000 mean coverage across 247 cancer-related genes, which delivers enhanced sensitivity.

47. NeXT Liquid Biopsy can also work in conjunction with ImmunoID NeXT. When these two platforms are paired, users benefit from an even more comprehensive immune-genomics view of tumors based on tissue and plasma samples. Further, pairing NeXT Liquid Biopsy and ImmunoID NeXT enables users to monitor tumors over time based on blood samples, particularly for late-stage tumors.

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D. NeXT Dx[®]

48. Personalis launched NeXT Dx in January 2020 as a clinician-focused testing product. NeXT Dx is a cutting-edge laboratory developed test designed to aid oncologists in identifying potential therapies and clinical trial options for cancer patients. NeXT Dx provides a personalized approach to genomic profiling that is capable of identifying cancer-related germline variants.

49. Unlike competitor products that can only focus on a few hundred genes, NeXT Dx is capable of profiling approximately 20,000 genes in both tumor exomes and transcriptomes.

50. NeXT Dx provides clinicians with diagnostic reports based on advanced analytics. NeXT Dx relies on ImmunoID NeXT's clinical-grade sequencing and analysis platform to deliver reports identifying DNA base substitutions, insertions/deletions, gene fusions, and copy number alterations in cancer driver genes. NeXT Dx processes these complex datapoints to provide clinicians with test reports that are precisely tailored to each individual patient, including treatment recommendations.

E. NeXT Personal[®] Dx

51. NeXT Personal Dx is Personalis' newest innovative product in the pipeline. Though not yet released, NeXT Personal Dx will leverage Personalis' technology for early cancer detection.

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52. NeXT Personal Dx is the LDT version of NeXT Personal.

III. CONCEPTION OF THE '033 AND '394 INVENTIONS

53. As mentioned above, my interest in personalized medicines and diagnostic assays dates back to at least November of 2009, which is when I paid \$160,000 to have my family of four whole genomes sequenced. I conducted considerable analysis of the genomic data when I received it in 2010. I found that the data had systematic gaps in the genome where there was little or no data. It occurred to me that supplementing whole genome data with data from additional assays, such as hybrid capture technology using capture probes, could lead to more complete and more accurate results. Gaps in DNA sequencing coverage were not the only accuracy challenges I identified in our family genome data. By phasing variants which occurred on the same sequence read, I found regions which exhibited three haplotypes. I also identified variants with solid evidence of three alleles at the same position. Humans are a diploid species, meaning that there should be at most two haplotypes in any one region and at most two alleles at each specific genomic position. Further experimental data showed that a human genome, sequenced twice, could result in over 400,000 discrepancies. At each discrepancy, one answer or the other had to be an error. Although there was a lot of excitement in the field at that time about the possible clinical diagnostic use of the new DNA sequencing

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technologies, I felt there was a significant business opportunity in being first to thoroughly characterize, understand, and then solve these accuracy problems. This concept was the genesis of what became known as the “Accuracy Program” at Personalis and the products we developed were to implement our solutions to these problems.

54. Below is a brief summary of the development of the Accuracy Program at Personalis leading up to my May 8, 2012 CEO Board of Directors Presentation. I note that over time the Accuracy Program became included a few products in development, which came to be called “Whole genome Plus”, “Exome plus,” “exome+,” and “ACE exome.” I will use the term “Accuracy Program” throughout this declaration for simplicity. The “plus” in these names referred to my idea, mentioned above, of supplementing whole genome data with data from additional assays, such as hybrid capture technology using capture probes. Slide 2 of my January 13, 2012 “Laboratory Assays” powerpoint described this:

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Laboratory assays – Whole genome Plus

- Illumina or CGI whole genome sequence with short-insert paired-end reads (may be provided by customer). Coverage & read length recommendations TBD
- Targeted re-sequencing using array or oligo-based pullout:
 - Additional coverage to fill in systematic gaps due to bias of biochemistry / molecular biology used for whole genome
 - Long-fragment pullout to resolve repeats, particularly in approx 3,000 genes with alignment problems due to gene-family homologies
- Whole genome and/or exome-focused genotyping to provide:
 - Technologically orthogonal validation of numerous specific medically interpretable alleles
 - Calibration of the sequencing error model
 - Independent assessment of Copy Number Variation
- Electrophoretic assay of certain VNTR's which are difficult to assess with NGS
- FISH assay of chromosomal translocations, difficult to assess with NGS
- RNA-seq from same sample, for expression, allelic bias, genetic variant-driven splice variation, partial phasing of individual genomes

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EX2109 “Laboratory Assays JW 13Jan2012.PPT” at Slide 2 (highlighting added). Specifically this slide showed our plan to begin with conventional whole genome sequencing and then to supplement that using hybrid capture “oligo-based pullout”. It identified two types of supplement, one to fill in the systematic coverage gaps of the genome and the other to use longer molecules “fragments” to resolve misalignment problems which can occur due to repeats or families of genes which are very similar (“homologies”).

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55. The following slide of that presentation (slide 3) went on to extend the idea to an exome, to create what we called “Exome plus:”

Laboratory assays – “Exome plus”

- Exon re-sequencing by pullout from customer sample (may be provided by customer)
- Additional re-sequencing by pullout, to capture regions outside the exons which are in VariMed, Regulome, lincRNA catalog & possibly others
- Other elements from the list of assays which supplement the Whole Genome product. Selection likely to be based on customer’s specific goals and pricing

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3

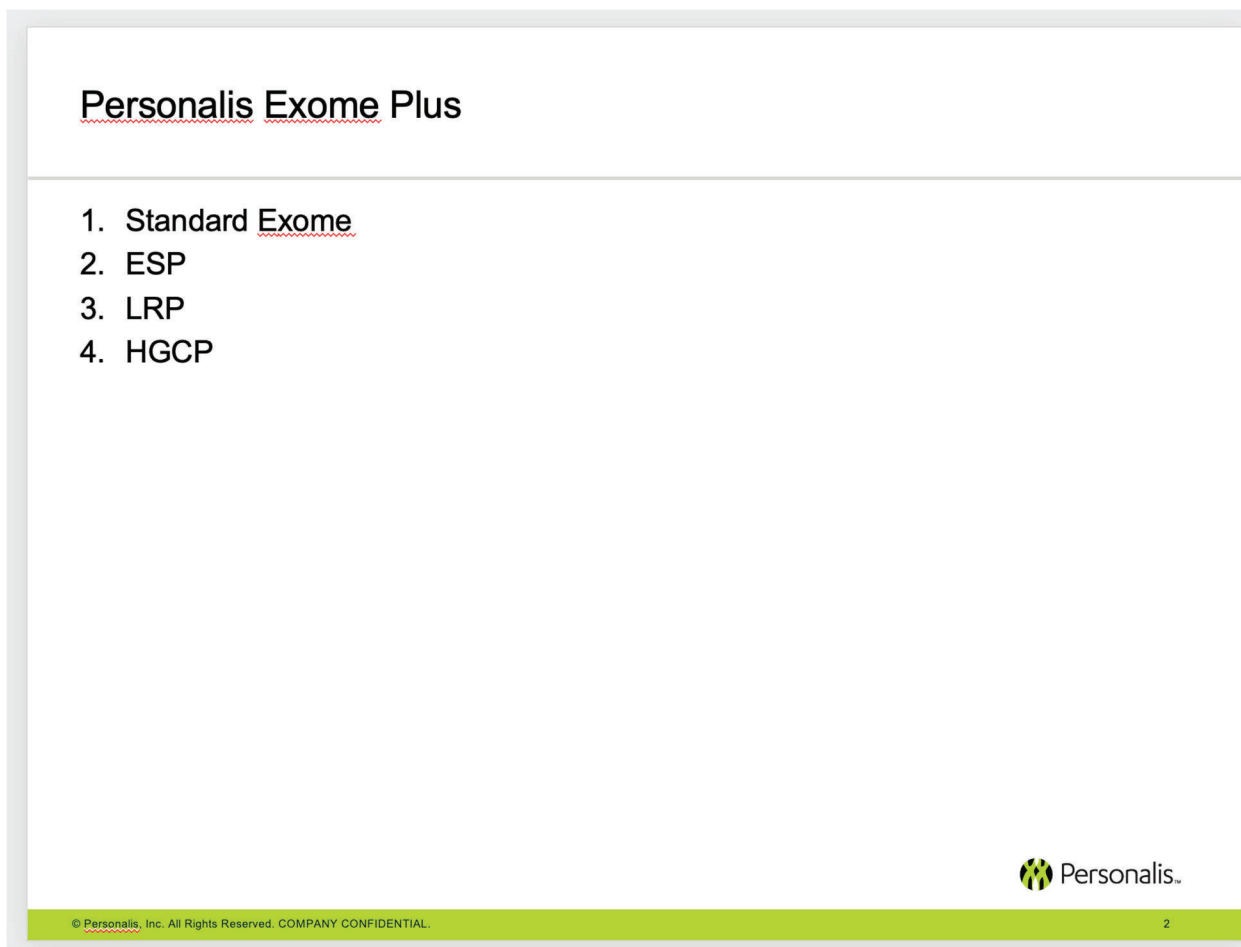
EX2109 “Laboratory Assays JW 13Jan2012.PPT” at Slide 3 (highlighting added). In this case the base assay being supplemented (the “plus”) was an exome (“exon re-sequencing by pullout”). The third bullet says that the supplementation could use the elements already described on the prior slide for supplementing a whole genome, i.e. filling in coverage gaps and using long fragment pullout to resolve alignment problems. In the second bullet, I proposed a third type of hybrid capture based

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supplement (“pullout”), which would be specific to an exome base assay. This third type of supplement was to capture DNA from parts of a genome which are biomedically important, but outside the exons targeted in an exome. It listed three databases from which we could select this genomic content : VariMed, Regulome and lincRNA. Regulome was a database Personalis licensed from Stanford University in August 2011. VariMed was also a database Personalis licensed from Stanford in August 2011 and it was still growing by benefit of a contract Personalis funded for ongoing curation by a third-party company.

56. These three supplement concepts (filling in coverage gaps, selectively adding longer molecules to resolve alignment problems, and biomedically important genomic content outside the coding regions of genes) became core parts of our first product development. They were the three separate sets of Personalis-designed capture probes that we first ordered from Agilent on 9/27/2012 and which we referred to on the order as ELID numbers 0432371, 0432391 and 0432422. *See* EX2089. They were also listed on Slide 2 of EX2102 which was a lab update November 2nd from Shujun Luo, copied here:

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EX2102 at Slide 2. This showed that our planned product, “Exome Plus” consisted of a standard exome with three pullouts (hybrid capture probe sets) to supplement it. The three pullouts listed on the slide were:

ESP : Exome Supplement Pullout, generally content outside the coding regions of genes

LRP : Long Read Pullout, longer molecules and sequences to resolve alignment problems

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HGCP : High %GC Pullout, to capture DNA sequences with a high percentage of “G” and “C” bases. These were known to cause many of the systematic coverage gaps and we used this pullout to fill those in.

57. My co-inventors and I met many times between November 2011 and May 8, 2012 to discuss ideas for the Accuracy Program. For example, EX2046 is a true and correct copy of an email and attachment that I sent to Mark Pratt, Richard Chen, Hugo Lam, Sarah Garcia, and Rong Chen on January 6, 2012. The subject of the email is “draft framework or Personalis accuracy-related product development,” and the body of the email states, in part, “I am attaching some thoughts in PowerPoint about our accuracy-related product development.” Slide 2, which is reproduced below, indicates that we were working on “interpretation of whole human genome sequences” for “maximal-accuracy analysis of a genome,” which included “Personalis : Specifies the combination of next-gen sequencing performed,” (either a whole genome “plus” or an exome “plus”) and “conduct[ing] follow-up genetic ... testing to validate results”.

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Research Market Products

- Comprehensive medically-focused interpretation of whole human genome sequences
 - Huge # of potential results
 - Even a low % error can swamp customer & waste time trying to track down invalid hypotheses
 - If research is in a clinical setting, particularly with return of results to patients, IRB's may want "FDA-like" quality systems in place
 - Standard quality approaches
 - Standard quality terminology & reporting
 - Accuracy / quality to "near-FDA" standards can be a sales advantage in the research market
- Maximal-accuracy analysis of a genome. Personalis :
 - Takes responsibility for the sample
 - Specifies the combination of next-gen sequencing performed
 - Augments NGS with other technologies to determine key variants
 - Conducts genotyping & assesses concordance
 - Conducts follow-up genetic & non-genetic testing to validate results

EX2046, attachment to email sent on January 6, 2012 at Slide 2 (highlighting added).

The reference to "follow-up" testing was further described on slide 13, copied in below:

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

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

EX2046, attachment to email sent on January 6, 2012 at Slide 13 (highlighting added). It specifically called for sequencing twice, or even “multiple times”.

58. Slide 9 of the same presentation includes several “genetic variant types to include” in our Accuracy Program, including “SNP’s” (single nucleotide polymorphisms), “InDel’s” (insertions and deletions), “Larger deletions,” “STR / VNTR’s” (short tandem repeats / variable number tandem repeats), “Structural variants,” “Copy Number Variation,” and “Trisomies”:

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Genetic variant types to include in model

- SNP's
- InDel's
- Larger deletions
- STR / VNTR's
- Structural variants
- Copy Number Variation
- Trisomies
- Combinations:
 - Any of these can be heterozygous
 - Compound heterozygosity
 - Small variants within larger het deletions or other CNV's
 - Clusters of closely spaced variants, which might interfere with each others' detection

EX2046, attachment to email sent on January 6, 2012 at Slide 9.

59. Slide 9 also pointed out that any of these variant types can combine to form what is known as “Compound heterozygosity”. This is when two genetic variants are close to each other on a chromosome and by phasing them we determine whether they both affect the same copy of that chromosome (leaving the other copy unaffected and thus healthy) or if they occur on the two different copies of the chromosome, potentially leaving no healthy copy. Compound heterozygosity was important to me personally. The Factor V Leiden (rs6025) SNP in my genome,

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which had caused me to have a pulmonary embolism in December 2003, was heterozygous, meaning that it only affected one copy of my chromosome 1 (where the Factor V gene is located). Analyzing my genome, and those of my family members, I found additional SNP variants in that same gene. If they were “in phase” they would affect just one copy of my chromosome 1, leaving the other copy healthy. If they were “out of phase”, they could potentially damage both copies, leaving me with no healthy copy. I was able to resolve this using the data of our family quartet, but I realized that many future diagnostic patients would not be able to have their families sequenced along with them. I also expected that compound heterozygosity was more common than generally appreciated, so if Personalis could develop a technology to phase nearby variants, we could lead in that type of analysis. The work I did using our family genomes showed that closely spaced genetic variants could be phased using the read lengths of whole genome sequencing (e.g. 100-base reads using the Illumina technology of that time) but that longer reads would be needed for many, such as those in our family’s Factor V genes. Reads that long were too expensive for whole genome sequencing, but if we could use “long fragment pullout” as described above, we would be able to phase variants which were further apart. Because the pairs of variants which may form compound-heterozygosity are different for each person, this “long fragment pullout” would need to target genomic regions specific to each person, identified by having sequenced them. By my CEO

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Update to the Personalis Board of Directors on May 5th 2023, this was listed as an element of our Accuracy Program. Slide 5 from that presentation, copied below with highlighting, showed that we planned custom sample preparations for phasing, leveraging hybrid capture probes “pullout”. They were custom because the variants each person would need to have phased would be different, and they would be identified based on their genome sequence, as my Factor V genetic variants had been.

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>Methods</u> Comparison with literature Studies on limited regions Whole genome analysis: Single genome metrics Same person twice Family inheritance (MIE) Platform comparison Arrays ILMN / CGI / Ion T... Sanger capillary <u>Prioritize solutions</u> Bio-informatic approaches Laboratory approaches Content approaches	<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	<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 Custom sample preps Problematic motifs Degenerate regions Phasing <u>Content</u> Gold standard genomes Known healthy genomes

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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (highlighting added).

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60. EX2109 is a true and correct copy of an email and attachment I sent to Richard Chen on January 13, 2012. The body of the email states “I have put together an outline of the Laboratory Assays we might offer” and “some of this should be the subject of patent filings, so we should not circulate it outside the company until we do that.” The PowerPoint slides attached to this email include an overview of laboratory assays we planned to offer, including “genome-scale assays which can be applied to any sample without prior knowledge of the sample – whole genome plus – exome plus – genotyping plus”:

Laboratory Assays - Overview

- Generic genome-scale assays which can be applied to any sample without prior knowledge of the sample
 - Whole genome Plus
 - Exome Plus
 - Genotyping Plus
- Custom validation of key results from specific genomes
- “Virtual genomes” directly inferred from sequence data of others (e.g. children from parents)

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EX2109, attachment to email sent on January 13, 2012 at Slide 1. Additional details of these laboratory assays are included on Slides 2-6. Slides 2 and 3 in particular

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were discussed above, in the introduction to our terminology “Whole genome Plus” and “Exome Plus”. I sent the same set of PowerPoint slides to Mark Pratt on January 13, 2012. *See* EX2109 email and attachment from John West to Mark Pratt on January 13, 2012.

61. EX2036 is a true and correct copy of an email that I sent to Christian Haudenschild and Carol Tillis (who are not inventors of the ‘033 and ‘394 patents) as well as Mark Pratt and Richard Chen on April 2, 2012. The subject of the email is “Confidential: Personalis Laboratory Plans” and the body of the email states “our NGS [next-generation sequencing] 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).” This demonstrates that several of the co-inventors of the ‘033 and ‘394 patents had contemplated combining whole genome sequencing with additional sequencing of selected targeted regions by at least April of 2012.

62. EX2037 is a true and correct copy of an email and attachment I sent to Mark Pratt on May 3, 2012. In this email, I explained that the Accuracy Program should be prioritized “by quantitation of errors by type & underlying mechanism.”

63. EX2038 is a true and correct copy of a Google Calendar invitation for the Personalis Development Group Weekly Team Meeting that was attended by

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several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. The meeting took place on Thursday, May 3, 2012, from 2-4:30pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

64. EX2040 is a true and correct copy of a Google Calendar invitation for the Personalis Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. The meeting took place on Friday, May 4, 2012, from 4-6pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

65. EX2039 is a true and correct copy of a Google Calendar invitation for the Personalis Pipeline Timeline Walk Through Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, and myself, among others. The meeting took place on Friday, May 4, 2012, from 1-2pm. During the weekly team meeting, we discussed timeline goals for the Accuracy Program.

66. EX2041 is a true and correct copy of an email and attached PowerPoint presentation I sent to Carol Tillis on May 8, 2012. The PowerPoint presentation is my “CEO Overview” that was presented to the Personalis Board of Directors during the May 8, 2012 Board of Directors Meeting. My “CEO Overview” presentation

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includes an overview of the Accuracy Program, and is discussed in more detail below.

67. EX2042 is a true and correct copy of an email and attached PowerPoint presentation from Richard Chen to me dated May 8, 2012. The PowerPoint presentation contained Dr. Chen's research and development update that was presented to the Board of Directors during the May 8, 2012 Board of Directors Meeting.

68. EX2043 is a true and correct copy of the Meeting Minutes from the May 8, 2012 Personalis Board of Directors Meeting. 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 myself.

69. In summary, the period from November 2011 and May 8, 2012 was a very fruitful and collaborative time where my co-inventors and I worked to develop and conceive the details of the Personalis Accuracy Program. My May 8, 2012 CEO Board presentation memorializes much of our work to conceive of the inventions that were ultimately claimed by the '033 and '394 patents. The next section provides

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a detailed description of our conception of each claim of the '033 and '394 patents with reference to documents that corroborate the conception of our inventions.

A. Summary of Slides 3 and 5 of My May 8, 2012 CEO Presentation

70. In developing Personalis, I sought to build a technology platform company, not just a single product. Our platform was built primarily on our innovative combined use of two core technologies: Next-Generation DNA Sequencing (NGS) and hybrid capture, based on the massively parallel chemical synthesis of DNA sequences. At the time, both were quite new and I was intimately familiar with both. As the CEO of Solexa and subsequently as the first SVP of DNA sequencing at Illumina (after Illumina acquired Solexa) I had led development of the most successful Next-Generation DNA Sequencing system to that time. During that time, I had also worked personally with the leaders at Agilent and the MIT/Harvard Broad Institute in their development of massively parallel hybrid capture.

71. Our Personalis method of combining the two technologies was the centerpiece of my description of our platform, in my CEO Update presentation at the May 8th 2012 meeting of the Personalis Board. Slides 3 & 5 of that presentation had the key points, several of which were expressed using acronyms or short-hand names that were understood by our Board members because a number of them also had prior experience in our genetic analysis technology field and because many of the concepts and terms were also presented at earlier Personalis Board meetings and

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in presentations by others, particularly our CSO Dr. Richard Chen and the Stanford faculty who co-founded the company with me.

Overview of Personalis Accuracy Program

Characterize errors

Analysis

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

Methods

Comparison with literature
Studies on limited regions

Whole genome analysis:

Single genome metrics
Same person twice
Family inheritance (MIE)
Platform comparison
Arrays
ILMN / CGI / Ion T...
Sanger capillary

Prioritize solutions

Bio-informatic approaches
Laboratory approaches
Content approaches

Informatic Solutions

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

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

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

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

Flag or Filter Out
For problems not yet solved

Lab, Content Solutions

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

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

Custom sample preps
Problematic motifs
Degenerate regions
Phasing

Content
Gold standard genomes
Known healthy genomes

EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5.

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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

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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 3.

72. Slide 5 of my presentation outlined our use of the two technologies, and slide 3 emphasized their use at many time points over the life of a patient. The market potential created by analysis of the same person at many time points made practical the most advanced concept of our technology – the use of hybrid capture assays (which we and others in the field referred to as “pullout”) in a custom, or semi-custom format for each patient. These assays would be customized to the individual patient by the patient’s own genetic “content”, i.e., their personal genetic information. We were very attuned to the idea of using a person’s individual genetic information because the company was founded based on my family’s, and the

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Stanford professors' experience with some of the very first personal genome sequences in 2010.

73. Slide 5 of my presentation described the plan of our company in three panels, under the heading of our Accuracy Program. We knew that a human genome sequence determined using NGS could have hundreds of thousands of errors, because sequencing the same person twice had resulted in hundreds of thousands of discrepancies. We saw it as a business opportunity to develop products which overcame these errors and which could deliver much more accurate results. We felt that was key to medical adoption of NGS, which we saw as a large market opportunity. We knew from our experience that many different types of errors could occur in DNA sequencing and so to prioritize our development of technological solutions, we began with careful analysis. We felt that if we understood the mechanisms which led to the errors, it would help us devise solutions to them. We also felt it would be important to prioritize developing technological solutions for the types of errors which would have the largest impact on medical interpretation of a genome sequence, or which regulators of genetic tests (in the USA we felt this could be the FDA) would consider most important.

74. We had devised several methods for identifying which genetic results were errors. Based on use of my family's four genome sequences (the raw data, not their medical interpretation) we had already demonstrated a mechanism in which a

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“Mendelian Inheritance Error” (MIE) occurs. These are genetic sequences which may be plausible on their own, but are very unlikely to be correct if we know the family relationships of the people involved. We proposed on later slides of this presentation to conduct this type of MIE analysis on an even larger family of 17 people spread over three generations and our Board approved the budget for that.

75. At the bottom of the 1st panel on slide 5, we listed three different technological approaches we planned for reducing errors. These were:

- Bio-informatic approaches: Improved algorithms implemented in computer software.
- Laboratory approaches: Specific combinations of assays which together could provide more accurate results than either assay alone.
- Content approaches: This included
 - Our idea of using content (genetic data) from just one or a few related individuals, to create “custom” or “semi-custom” assays.
 - Gold standard genomes, analyzed at greater expense than could be commercially normal, but to serve as a known high-quality standard.

The center panel of Slide 5 addressed primarily bioinformatic solutions we were working on. The large number of algorithms involved mainly reflected the variety of genetic variant types in a human genome, including SNPs, InDels, VNTRs (variable number (or length) tandem repeats, and SVs (structural variants). Not all of the algorithms were our innovations, but to support them, it meant that our assays (Lab Content Solutions – the third panel on this slide) had to cover all of these variant types.

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76. The third panel of Slide 5 described our proposed Lab (assay) and Content solutions to the accuracy problem. This embodied our two foundational technologies, used together in an innovative way. Our Board members were already familiar with our plans for “supplemented either genome sequencing or exome sequencing with additional data created using hybrid capture panels. We had already described internally, in January 2012, three specific goals of that supplementation (as shown above in the descriptions of the “Whole Genome Plus” and “Exome Plus”):

- Filling in systematic coverage gaps caused by the biases of NGS technology.
- Use of longer molecules and sequence reads for just specific parts of the genome to address regions of alignment degeneracy. We realized that longer read sequencing might involve a different vendor from that used for whole genome or exome sequencing, in particular because a prominent long-read DNA sequencing company, Pacific Biosciences, was right next door to Personalis.
- Adding content, from outside the coding regions of the genes, to an exome. This could include, for example, regulatory regions of genes documented in the Regulome database we had licensed from Stanford.

The key addition of this presentation was the idea that the content for supplementation could be either custom (i.e., specific to the particular patient), or semi-custom (some custom and some standard).

77. Because our technological approach was novel, we knew that for regulatory purposes we might need to validate some of our results using older, more

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established technologies, until it became more accepted. The validation technologies we listed were:

- (Genotyping) arrays, which could validate specific SNP genotypes and structural variants. We had previously shown our Board data on the concordance between whole genome sequence data and that from use of genotyping arrays on the same individual, so they were familiar with this.
- Sanger sequencing (the old type of DNA sequencing, used before “Next-Generation” sequencing was invented, and which used electrophoresis). Sanger sequencing was more appropriate for validating rare SNPs that did not appear on genotyping arrays, and for validating short InDels.
- Electrophoretic sizing, which used the electrophoretic capability of the old Sanger sequencing instruments and was the established standard for measuring VNTRs, such as in Fragile X and Huntington’s disease, and long insertions and deletions)

78. We planned to provide those validation technologies as additional options for customers who felt they needed the validation of our results.

We selected the two core technologies we used (NGS, and massively parallel hybrid capture) from a broad field of other genetic analysis technologies available at the time. We believed that these technologies offered the ability to multiplex (combine) many separate genetic assays into one. Most of them could perform hundreds of measurements in a single instrument “run” and some could achieve thousands. We selected massively parallel hybrid capture, even though it was newer and less well established, because we could obtain oligos (synthetic DNA molecules with user-specified sequences) up to 50,000 at a time, which we could combine to achieve multiplexing of hundreds of thousands of genetic variants. We believed NGS was a

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good match for hybrid capture because it could produce hundreds of millions, or even billions of DNA sequence reads from the targeted genetic variant positions, in a single instrument “run”. This combination moved against what many others in the field were pursuing at least because creating “custom” or “semi-custom” assays was quite expensive, particularly relative to all of the other technologies we considered, but did not choose, for our multiplexed genetic analysis.

79. Technologies we considered but did not choose included:

- Microfluidic, highly parallel PCR systems, commercialized by Cepheid (now part of Danaher Corporation)
- Real-time PCR, although we knew it was used in the:
 - OncoType Dx test for risk of breast cancer reoccurrence (commercialized by Genomic Health, Inc. in 2004)
 - AlloMap test for heart transplant rejection, commercialized by XDx, Inc. (now CareDx, Inc.) and FDA approved in 2006.

I was familiar with real-time PCR because I was responsible for the Applied Biosystems commercialization of it when I worked there 2001 – 2004. By that time, we could conduct up to 384 different genetic assays in parallel and had implemented substantial laboratory robotic automation to enable hands-free analysis of many thousands of genetic targets in a single instrument “run”.

- Luminex bead-based xMAP technology for multiplexing up to 500 molecular assays in as little as a single drop of fluid. Each bead group had a different mixture of fluorescent labels, letting the instrument multiplex them.
- NanoString Technologies system for multiplexed DNA and RNA assays, even though I purchased one of these systems for ViaCyte (which was acquired by Vertex Pharmaceuticals), the company where I was CEO 2009 – 2011, and it could multiplex up to at least 768 assays from a single sample.

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- Digital droplet PCR, based on 2003 work by Kinzler and Vogelstein and commercialized by QuantaLife (which was acquired by Bio-Rad) and other companies. It would partition a small liquid sample into tens of thousands of microscopic water droplets suspended as an emulsion in oil, for highly parallel analysis of many genetic features.
- Fluidigm (founded 1999 and IPO'd in February 2011; now named Standard BioTools Inc.), which commercialized microfluidic Lab-on-a-Chip devices under the brand name BioMark, to conduct hundreds and eventually thousands of assays in parallel. We did not select this even though I had spent two years earlier in my career (1999-2000) focused on microfluidic technologies when I worked at Coventor, Inc
- Mass spectrometry, even though it was used in the March 2012 paper we considered “seminal”. Mass spectrometry had been commercialized for multiplexed measurement of genetic variants such as SNPs, by Sequenom, Inc. (now part of Laboratory Corporation of America Holdings (LabCorp)).

We rejected all of these well-known technology options even though, particularly for “custom” or “semi-custom” assay development, any of them would likely have been less expensive to begin with. We believed that there would be more potential eventually from the higher multiplexing capacity of the new technologies we picked. We projected, based on our unique experience and expertise, that the costs would become manageable for use in “custom” and “semi-custom” assays, particularly as the number of time points at which each patient would be assayed over their lifetime increased. The paper from March 2012, which we cited as “seminal” (even though it did not use our approach) showed that 20 time points over 400 days was in fact medically useful for the patient involved, and we felt that would become the future.

80. My CEO update presentation to the Personalis Board on May 8th 2012, particularly slides 3 & 5, showed that we had focused on a specific combination of

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advanced technologies to create products in which whole genome or exome sequencing would be supplemented by content, including custom or semi-custom hybrid capture sequencing assays, and used at many time points over a patient's lifetime. We specifically chose to use capture probes, which are nucleic acid sequences that hybridize to target DNA, either in solution or on a solid support, so that one can physically capture and isolate the target DNA. Capture probes are not PCR primers. PCR primers are used to make copies of DNA via a polymerase chain reaction. Two PCR primers are required for the polymerase chain reaction. In contrast, a single capture probe can pulldown a single target DNA molecule.

B. Conception of the '033 patent

81. U.S. Patent Application No. 17/078,857 ("the '857 application") was filed on October 23, 2020 and issued as U.S. Patent No. 11,408,033 ("the '033 patent") on August 9, 2022. The '857 application is a continuation application of U.S. Patent Application No. 16/816,135, filed on March. 11, 2020, which application is a continuation application of U.S. Patent Application No. 16/526,928, filed July 30, 2019, which application is a continuation application of U.S. Patent Application No. 15/996,215, filed June 1, 2018, now U.S. Patent No. 10,415,091, which application is a continuation application of U.S. Patent Application No. 14/810,337, filed July 27, 2015, now U.S. Pat. No. 10,266,890, which application is a divisional application of U.S. Patent Application No. 14/141,990, filed December 27, 2013,

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now U.S. Pat. No. 9,128,861, which claims priority to U.S. Provisional Application No. 61/753,828, filed January 17, 2013.

82. The '033 patent issued with 23 claims. My co-inventors and I and formed a definite and permanent idea of the complete and operative invention described in each of these claims by no later than May 8, 2012. In particular, we had developed the particular solutions for analyzing nucleic acid samples from an individual utilizing the combination of capture probes and conducting sequencing assays according to the specific steps recited in the '033 patent claims. The definite and permanent idea we had was significantly more than a general research goal or plan. Further, a person of ordinary skill in the art would have been enabled to practice our invention as of May 8, 2012 without undue experimentation if they had been informed of our invention. Thus, we had conceived of the invention claimed by the '033 patent no later than May 8, 2012. Below is a discussion providing an explanation of our conception of each of the 23 claims of the '033 patent, along with corroborating evidence.

1. '033 Patent Claim 1

83. Claim 1 of the '033 patent 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

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- 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.

a. ‘033 Patent: Claim 1 - Preamble

84. The preamble of claim 1 of the ‘033 patent recites: “A method for analyzing a nucleic acid sample obtained from an individual.”

85. By no later than May 8, 2012, the Accuracy Program at Personalis included methods for analyzing a nucleic acid sample obtained from an individual. Conception of the preamble is reflected by, for example, Slide 5 of my May 8, 2012 CEO Overview Board of Director Presentation, which is entitled an “Overview of Personalis Accuracy Program,” and reproduced below with highlighting:

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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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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (highlighting added).

86. As shown in 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. Our Accuracy Program involved nucleic acid samples that would be sequenced by “whole genome sequencing”, supplemented by custom and/or semi-custom assays based on capture probe

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pullouts, and validated by, for example, “Sanger validation.” *See* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5.

87. Slide 13 of the same May 8, 2012 presentation provides additional details of the Accuracy Program, which included “receiv[ing]” and “de-identify[ing] samples” from our customers for analysis:

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

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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 13.

88. Work on the Accuracy Program from January 2012 that led up to the May 8, 2012 disclosure of our invention at the Board of Directors meeting provides additional evidence of conception of the preamble. For example, my January 5, 2012

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presentation at Slide 2 discusses taking responsibility for a customer's nucleic acid sample for analysis, and Slide 11 discusses several nucleic acid sample sources from "blood, saliva, tissue, [and] cell culture." *See* EX2046, January 5, 2012 Accuracy Framework PowerPoint. In addition, my April 2, 2012 email to Chrisitan Haudenschild and other Personalis employees discussed laboratory plans to include analysis of "multiple assays from the same sample" of a customer. *See* EX2036 (April 2, 2012 email to Christian Haudenschild and other Personalis employees).

89. Based on at least the foregoing, my co-inventors and I had conceived of the preamble recited by claim 1 by no later than May 8, 2012.

b. '033 Patent: Claim 1 – limitation 1(a)

90. Limitation 1(a) of claim 1 of the '033 patent recites: "[i]¹ producing, with the aid of a computer processor, a plurality of capture probes, [ii] 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 [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 Bracketed roman numerals, e.g. "[i]" and "[ii]", have been added to limitation 1(a) to organize the discussion of each portion of this limitation.

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i. Limitation 1(a)(i)

91. Limitation 1(a)(i) recites “producing, with the aid of a computer processor, a plurality of capture probes.”

92. By no later than May 8, 2012, the Accuracy Program at Personalis included producing a plurality of capture probes with the aid of a computer processor. Conception of this limitation is reflected by, for example, Slide 5 of my May 8, 2012 CEO Overview Board of Director Presentation which is entitled an “Overview of Personalis Accuracy Program,” and reproduced below with highlighting:

Overview of Personalis Accuracy Program

Characterize errors Analysis Rates by variant type & Q-score Underlying mechanisms Medical interpretation impact Regulatory impact Methods Comparison with literature Studies on limited regions Whole genome analysis: Single genome metrics Same person twice Family inheritance (MIE) Platform comparison Arrays ILMN / CGI / Ion T... Sanger capillary Prioritize solutions Bio-informatic approaches Laboratory approaches Content approaches	Informatic Solutions Advances in 3rd party alg's Aligner for > 200bp reads New versions, current alg's Other alg's (e.g. lobSTR) Advances in our alg's: SV's : Zygosity, accuracy Combine SV's & SNP's Broader use of Breakseq New Personalis alg's Alignment degeneracy Genome-aware alignment VNTR-specific Advances in reference Ethnic major-allele ref's Iterative Admixed InDel's / SV's Flag or Filter Out For problems not yet solved	Lab, Content Solutions Combine technologies WGS + exome Longer reads and/or inserts Multi-vendor Arrays (genotypes & SV's) Electrophoretic sizing Sanger validation Content-based semi-custom Array (genotypes & SV's) Pullout Custom sample preps Problematic motifs Degenerate regions Phasing Content Gold standard genomes Known healthy genomes
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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5
(highlighting added).

93. As shown in Slide 5, the Accuracy Program involved the use of “content-based semi-custom” capture probes to “pullout” genotypes and structural variants. Within Personalis, we used the term “pullout” to refer to a panel of capture probes conjoined to streptavidin-coated magnetic beads that would “pullout” target DNA via solution-phase hybridization and/or an array of capture probes. We used the terms “pullout,” “pulldown,” and “pull down” interchangeably within Personalis for this capture probe technology, as did others in the field. At least Mark Pratt and I were aware that custom and semi-custom capture probes could be purchased via Agilent (their “SureSelect” line of capture probes), Illumina (their “TruSeq” capture probes), and Roche (their “Nimblegen” capture probes). Members of the Personalis team were experienced in their use, and were also aware of the commercial release of a “cancer-gene pullout panel” of capture probes identified on Slide 4 of my May 8, 2012 presentation:

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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

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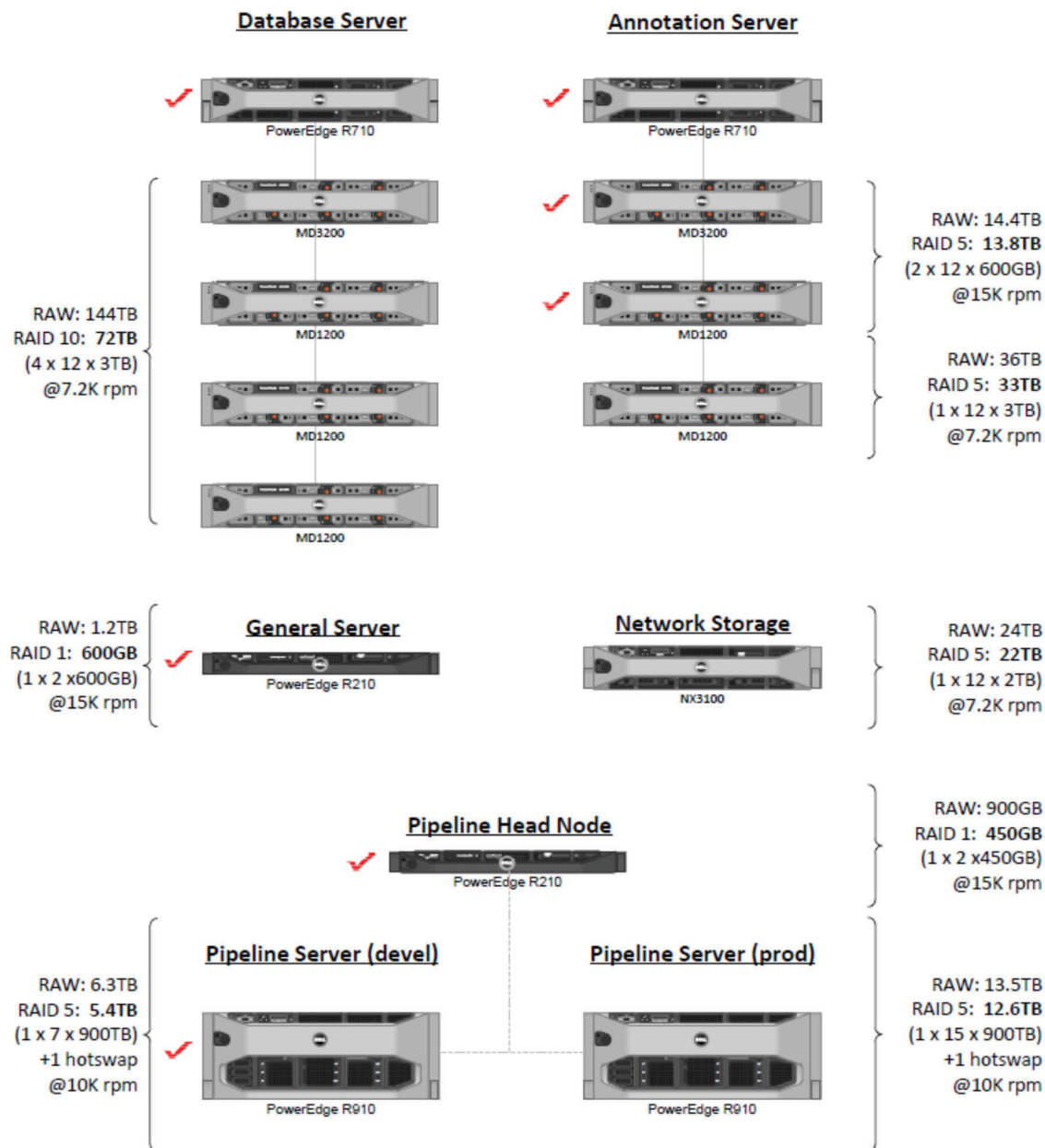
EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 4 (highlighting added).

94. The design of the capture probes to “pullout” the genotypes and structural variants involved “informatic solutions” that included “alg’s,” which stands for algorithms. *Id.* at Slide 5. The algorithms included “3rd party” “aligner for >200bp reads” and “advances in our” own algorithms to process the genomic data generated by “WGS” (whole genome sequencing) and validated by, for example, “Sanger validation” sequencing. *Id.* Such algorithms used the aid of a computer processor. Personalis had purchased and installed computer servers and

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processors to handle the genomic data generated by the WGS and validation sequencing called for by the Accuracy Program. For example, Exhibit 2044 is a true and correct copy of an email and attachment sent from Hugo Lam to Richard Chen and me on April 24, 2012 providing a pdf attachment depicting “our servers configuration.” *See* EX2044, April 24, 2012 email and attachment from Hugo Lam to John West and Richard Chen. The attachment is reproduced below:

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See EX2044, April 24, 2012 email attachment from Hugo Lam to John West and Richard Chen.

95. Each human genome we analyzed, such as the West family genomes, included billions of bases (the letters “G”, “A”, “T” or “C”) of data. It would have been impractical to process this data without the use of computers.

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96. Each SureSelect capture probe set that we designed involved thousands, and often tens of thousands of sequences. These also would have been impractical to design without the use of one or more computers.

97. Work on the Accuracy Program from January 2012 that led up to the May 8, 2012 disclosure of our invention at the Board of Directors meeting provides additional evidence of conception of the limitation 1(a)(i). For example, my January 13, 2012 presentation at Slide 2 discusses using “oligo-based pullout,” which is a reference to capture probes. *See* EX2109. In addition, my April 2, 2012 email to Chrisitan Haudenschild and other Personalis employees discussed laboratory plans to include “both whole genome and deeper sequencing of some regions selected by pull out. Mary Pratt is working on lists of regions we may want to pull out.” *See* EX2036 (April 2, 2012 email to Christian Haudenschild and other Personalis employees). We also held several meetings on, for example, May 4 and 5, 2012 to further develop the Accuracy Program leading up to the May 8, 2012 Board of Directors meeting. *See, e.g.*, EX2038, EX2040, EX2039.

98. Based on at least the foregoing, my co-inventors and I had conceived of limitation 1(a)(i) by no later than May 8, 2012.

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ii. Limitation 1(a)(ii)

99. Limitation 1(a)(ii) recites “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.”

100. By no later than May 8, 2012, the Accuracy Program at Personalis included a plurality of capture probes that hybridize to a plurality of polymorphisms in sequences encoding genes with known biomedically interpretable variants. Conception of this limitation is reflected by, for example, Slide 5 of my May 8, 2012 CEO Overview Board of Director Presentation, which includes identifying biomedically interpretable variants that were identified by the “analysis” of “whole genome sequencing,” which included identifying “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s” (insertions/deletions) having “medical interpretation impact.” *See* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (reproduced above with highlighting). Each of the “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s” (insertions/deletions) are a type of polymorphism. For our “analysis” to have “medical interpretation impact,” we were aware that the identified polymorphisms would include polymorphisms encoding genes (because the polymorphisms encoding genes would have the most

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medical impact as opposed to polymorphisms in non-encoding regions of the genome).

101. The capture probes were designed to “pullout” “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s” (insertions/deletions) polymorphisms encoding genes with known biomedically interpretable variants that were identified by the “analysis” of the “whole genome analysis” within the Accuracy Program. *See* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (reproduced above with highlighting). As discussed above, the purpose of the capture probes was to “pullout” those biomedically interpretable variants to provide a “medical interpretation impact” for each of our customers.

102. Work on the Accuracy Program from January 2012 that led up to the May 8, 2012 disclosure of our invention at the Board of Directors meeting provides additional evidence of conception of the limitation 1(a)(ii). For example, my January 13, 2012 presentation at Slide 2 discusses using “oligo-based pullout” with “long-fragment pullout to resolve repeats, particularly in approx. 3,000 genes with alignment problems due to gene-family homologies,” which is a reference to capture probes that hybridize to polymorphisms in sequences encoding genes with known biomedically interpretable variants. *See* Ex. EX2109. In addition, my April 2, 2012 email to Chrisitan Haudenschild and other Personalis employees discussed

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laboratory plans to include “both whole genome and deeper sequencing of some regions selected by pull out. Mary Pratt is working on lists of regions we may want to pull out.” *See* EX2036 (April 2, 2012 email to Christian Haudenschild and other Personalis employees). We also held several meetings on, for example, May 4 and 5, 2012 to further develop the Accuracy Program leading up to the May 8, 2012 Board of Directors meeting. *See, e.g.,* EX2038, EX2040, EX2039.

103. Based on at least the foregoing, my co-inventors and I had conceived of limitation 1(a)(ii) by no later than May 8, 2012.

iii. Limitation 1(a)(iii)

104. Limitation 1(a)(iii) recites “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.”

105. By no later than May 8, 2012, the Accuracy Program at Personalis included a plurality of capture probes that hybridize to a plurality of polymorphisms 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. As discussed above, the capture probes were designed to “pullout” “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s” (insertions/deletions) polymorphisms encoding genes with known biomedically interpretable variants that were identified by the “analysis” of the

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“whole genome analysis” within the Accuracy Program. *See* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (reproduced above with highlighting). 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” (whole genome sequencing) and validation by, for example, “Sanger validation” sequencing. The genotypes and structural variants would be stored in databases on the Personalis servers (which are described above with reference to, for example, EX2044 (April 24, 2012 email attachment from Hugo Lam to John West and Richard Chen describing the Personalis server configuration)) or elsewhere.

106. In August 2011, following a competitive requisition process, Personalis exclusively licensed a set of genetic databases from Stanford University. These included the PharmGKB database of genetic variants known to affect drug metabolism. It also included the MendelDB database, of genetic variants known to cause inherited genetic diseases (known as Mendelian diseases). Curation of that database had begun at Stanford and Personalis staff continued that curation after they joined Personalis from Stanford in 2011. It also included the Regulome database, of genetic variants in regulatory regions of genes. It also included the VariMed database of relationships between genetic variants and biomedical phenotypes, curated from the scientific literature. When Personalis licensed the Varimed

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database it already included tens of thousands of genetic variants. In 2011, Personalis took over and expanded the funding for this outsourced curation, growing the database still further. These databases, and our ongoing curation of the MendelDB and Varimed databases, were described in the R&D update of Rich Chen, our CSO, at the May 8th, 2012 meeting of our Board of Directors. *See* EX2042 at Slides 29-32. With the exception of Regulome, these databases each included a plurality of polymorphisms in sequences encoding genes with known biomedically interpretable variants. Regulome primarily included polymorphisms in regulatory regions, which are still biomedically important but generally outside the coding regions of genes.

107. The database of polymorphisms stored on the Personalis servers could also include polymorphisms observed in a population of one or more samples. *See, e.g.,* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slides 5 and 13 (reproduced above with highlighting). These included genome datasets we were allowed to use by collaborators such as the West family genomes, the 1,000 Genomes project, and genomes made public by Illumina, Complete Genomics and the Broad Institute. These included polymorphisms in sequences encoding genes with known biomedically interpretable variants, such as the variants in the Factor V gene of my genome, described above. These genome data sets could also include genomes we paid to have sequenced, for example from the CEPH 1463 family of 17

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individuals (payment for this was approved by the Personalis Board at its May 8, 2012 meeting). *See* EX2043 at 2. In some cases it could also include genome data from the sequencing of diagnostic patients and from our other customers. In fact, we had already been storing genotype and structural variant information in databases on the Personalis servers by no later than May 8, 2012.

108. Work on the Accuracy Program from January 2012 that led up to the May 8, 2012 disclosure of our invention at the Board of Directors meeting provides additional evidence of conception of the limitation 1(a)(iii). For example, my January 13, 2012 presentation at Slide 2 discusses using “oligo-based pullout” with “long-fragment pullout to resolve repeats, particularly in approx. 3,000 genes with alignment problems due to gene-family homologies,” which is a reference to capture probes that hybridize to polymorphisms extracted from a database of polymorphisms. *See* EX2109. In addition, my April 2, 2012 email to Chrisitan Haudenschild and other Personalis employees discussed laboratory plans to include “both whole genome and deeper sequencing of some regions selected by pull out. Mary Pratt is working on lists of regions we may want to pull out.” *See* EX2036 (April 2, 2012 email to Christian Haudenschild and other Personalis employees). We also held several meetings on, for example, May 4 and 5, 2012 to further develop the Accuracy Program leading up to the May 8, 2012 Board of Directors meeting. *See, e.g.*, EX2038, EX2040, EX2039.

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109. Based on at least the foregoing, my co-inventors and I had conceived of limitation 1(a)(iii) by no later than May 8, 2012.

c. ‘033 Patent: Claim 1 – limitation 1(b)

110. Limitation 1(b) of claim 1 of the ‘033 patent recites: “contacting said nucleic acid sample with said plurality of capture probes produced in (a).”

111. 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). As discussed above with respect to the preamble, Slide 13 of my May 8, 2012 CEO Board presentation shows that the Accuracy Program included “receiv[ing]” and “de-identify[ing] samples” from our customers.

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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

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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 13 (highlighting added).

112. As discussed above for limitation 1(a), Slide 5 from my May 8, 2012 CEO presentation 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" (whole genome sequencing).

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Overview of Personalis Accuracy Program

Characterize errors

Analysis

Rates by variant type & Qscore
Underlying mechanisms
Medical interpretation impact
Regulatory impact

Methods

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

Prioritize solutions

Bio-informatic approaches
Laboratory approaches
Content approaches

Informatic Solutions

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

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

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

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

Flag or Filter Out
For problems not yet solved

Lab, Content Solutions

Combine technologies

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

Content-based semicustom

Array (genotypes & SV's)
Pullout

Custom sample preps

Problematic motifs
Degenerate regions
Phasing

Content

Gold standard genomes
Known healthy genomes

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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (highlighting added).

113. Work on the Accuracy Program from January 2012 that led up to the May 8, 2012 disclosure of our invention at the Board of Directors meeting provides additional evidence of conception of the limitation 1(b). For example, my January 13, 2012 presentation at Slide 2 discusses using “oligo-based pullout” with “long-fragment pullout to resolve repeats, particularly in approx. 3,000 genes with alignment problems due to gene-family homologies,” which is a reference to capture probes that are used to contact a customer nucleic acid sample. *See* EX2109. In

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addition, my April 2, 2012 email to Chrisitan Haudenschild and other Personalis employees discussed laboratory plans to include analysis of “multiple assays from the same sample” of a customer that included “both whole genome and deeper sequencing of some regions selected by pull out. Mary Pratt is working on lists of regions we may want to pull out.” *See* EX2036 (April 2, 2012 email to Christian Haudenschild and other Personalis employees). We also held several meetings on, for example, May 4 and 5, 2012 to further develop the Accuracy Program leading up to the May 8, 2012 Board of Directors meeting. *See, e.g.*, EX2038, EX2040, EX2039.

114. Based on at least the foregoing, my co-inventors and I had conceived of limitation 1(b) by no later than May 8, 2012.

d. ‘033 Patent: Claim 1 – limitation 1(c)

115. Limitation 1(c) of claim 1 of the ‘033 patent recites: “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.”

116. 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. As

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described above, by January of 2012 our Accuracy Program involved supplementing a base whole genome or exome with hybrid capture probe sets to generate additional DNA sequencing reads which:

- (i) filled in some of the systematic gaps in sequencing coverage
- (ii) Included longer molecules to address alignment problems and
- (iii) Supplemented an exome (which focuses on the coding regions of genes) with additional content from outside the coding regions of the genes

These were the “Content-based” “Pullout” assay elements referred to in Slide 5 of my CEO Update to the Personalis Board of Directors on May 8th 2012, copied in below:

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Overview of Personalis Accuracy Program

Characterize errors <u>Analysis</u> Rates by variant type & Qscore Underlying mechanisms Medical interpretation impact Regulatory impact <u>Methods</u> Comparison with literature Studies on limited regions Whole genome analysis: Single genome metrics Same person twice Family inheritance (MIE) Platform comparison Arrays ILMN / CGI / Ion T... Sanger capillary <u>Prioritize solutions</u> Bio-informatic approaches Laboratory approaches Content approaches	Informatic Solutions <u>Advances in 3^d 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 semicustom</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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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (highlighting added). The additional sequencing reads are a subsequent sequencing assay.

117. Work on the Accuracy Program from January 2012 that led up to the May 8, 2012 disclosure of our invention at the Board of Directors meeting provides additional evidence of conception of the limitation 1(c). For example, my January 13, 2012 presentation at Slide 3 discusses “exon re-sequencing by pullout from customer sample (may be provided by customer)” and “additional re-sequencing by pullout, to capture regions outside the exons which are in VariMed, Regulome,

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lincRNA catalog & possibly others.” *See* EX2109. In addition, my April 2, 2012 email to Chrisitan Haudenschild and other Personalis employees discussed laboratory plans to include analysis of “multiple assays from the same sample” of a customer that included “both whole genome and deeper sequencing of some regions selected by pull out. Mary Pratt is working on lists of regions we may want to pull out.”. *See* EX2036 (April 2, 2012 email to Christian Haudenschild and other Personalis employees). We also held several meetings on, for example, May 4 and 5, 2012 to further develop the Accuracy Program leading up to the May 8, 2012 Board of Directors meeting. *See, e.g.,* EX2038, EX2040, EX2039.

118. Based on at least the foregoing, my co-inventors and I had conceived of limitation 1(c) by no later than May 8, 2012.

e. ‘033 Patent: Claim 1 – limitation 1(d)

119. Limitation 1(b) of claim 1 of the ‘033 patent recites: “repeating steps (b)-(c) on a subsequently obtained biological sample from said individual.”

120. By no later than May 8, 2012, the Accuracy Program at Personalis included repeating the steps recited by limitations 1(b)-1(c) on a subsequently obtained biological sample from said individual.

121. I was personally already very familiar with the idea of repeated blood testing due to a genetic condition. As described above, starting with my pulmonary embolism in December 2003, I had blood tests about monthly for over 8 years to

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confirm or adjust the dose of the drug warfarin that I had been prescribed. Although the condition causing this (a Factor V Leiden mutation in my genome) was genetic, the monthly tests I had to undergo were not genetic. Still, the idea of monthly blood testing related to a genetic condition was very personal to me.

122. I was also familiar with repeated blood tests for other conditions. This included the monthly “AlloMap” test developed and commercialized by XDX, Inc., for heart transplant patients, to check for transplant rejection. FDA approved in 2006, it used real-time PCR of a group of genes from a blood sample. XDX, Inc is now known as CareDx (Nasdaq : CDNA). Although this test did not use DNA sequencing, it was based on nucleic acids (RNA) extracted from a body fluid of the patient on an ongoing monthly basis.

123. I was also familiar with work by Stanford professor Steve Quake, who used whole genome sequencing of cell free DNA from the blood of transplant patients to look for genetic variants of a heart transplant donor in the heart transplant recipient, as an indication of transplant rejection. This was very inefficient because it did not use any type of hybrid capture to focus on variants.

124. It is fair to say that, by early 2012, the field had many efforts to test for various medical conditions based on blood samples taken periodically from a patient, but they were all inefficient because none used hybrid capture by capture probes,

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and in particular none used capture probes targeted to genetic variants which were specific to an individual person.

125. In my presentation from January 6, 2012, described above, I had already described sequencing an individual “twice (or more?)” or “multiple times” using a “Whole Genome Plus” or “Exome Plus” assay, to confirm results from an initial sample.

126. In March 2012, we made a key connection. Personalis employee and ‘033 patent co-inventor Hugo Lam was co-author on a publication (EX2030) which described the analysis of a patient at 20 time points over 400 days, during which time the patient suffered two viral infections and the onset of Type 2 diabetes. The patient was monitored using blood tests at each time point, using untargeted RNAseq, and took action based on the results that improved their clinical trajectory. This untargeted RNAseq revealed changes in both gene expression and also changes in the sequence of the RNA (RNA editing). This was very inefficient because the RNAseq was untargeted, but I realized that the technology being developed at Personalis, including targeted capture of genetic variants specific to an individual, could be an enormous improvement.

127. Slide 3 of my May 8, 2012 CEO Board presentation described the March 2012 publication as “seminal” because it sparked our invention connecting the frequent genetic analysis from blood with our development of targeted capture based on the

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genetic variants of an individual person. I highlighted for our Board of Directors “ongoing clinical use of genome-scale sequencing” and “not just a genome once in your life”

Publications & Upcoming Presentations

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

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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 3 (highlighting added).

128. Slide 3 of my presentation highlighted an important business aspect of the Accuracy Program. Earlier work on whole genome sequencing of individuals, such as the West family genomes, was only done at one time point. That meant that

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there were no repeat customers, which would have been a financial problem for a company offering the service. However, a program that involved “ongoing clinical use of genome-scale sequencing” would be used more than just “once in your [customer’s] lifetime” to provide a recurring revenue stream from each customer. The Accuracy Program involved initial “WGS” (whole genome sequencing) of a customer’s biological sample, and further supplementing that with additional sequencing of subsequently obtained biological samples from the customer to provide ongoing clinical use of their genomic information.

129. 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 algorithms used to analyze the data generated by “WGS” (whole genome sequencing). *See, e.g.*, Slide 5 of my May 8, 2012 CEO Board presentation, reproduced below.

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Overview of Personalis Accuracy Program

Characterize errors <u>Analysis</u> Rates by variant type & Qscore Underlying mechanisms Medical interpretation impact Regulatory impact <u>Methods</u> Comparison with literature Studies on limited regions Whole genome analysis: Single genome metrics Same person twice Family inheritance (MIE) Platform comparison Arrays ILMN / CGI / Ion T... Sanger capillary <u>Prioritize solutions</u> Bio-informatic approaches Laboratory approaches Content approaches	Informatic Solutions <u>Advances in 3^d 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 <u>Arrays (genotypes & SV's)</u> Electrophoretic sizing Sanger validation <u>Content-based semicustom</u> <u>Array (genotypes & SV's)</u> Pullout <u>Custom sample preps</u> Problematic motifs Degenerate regions Phasing <u>Content</u> Gold standard genomes Known healthy genomes
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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (highlighting added).

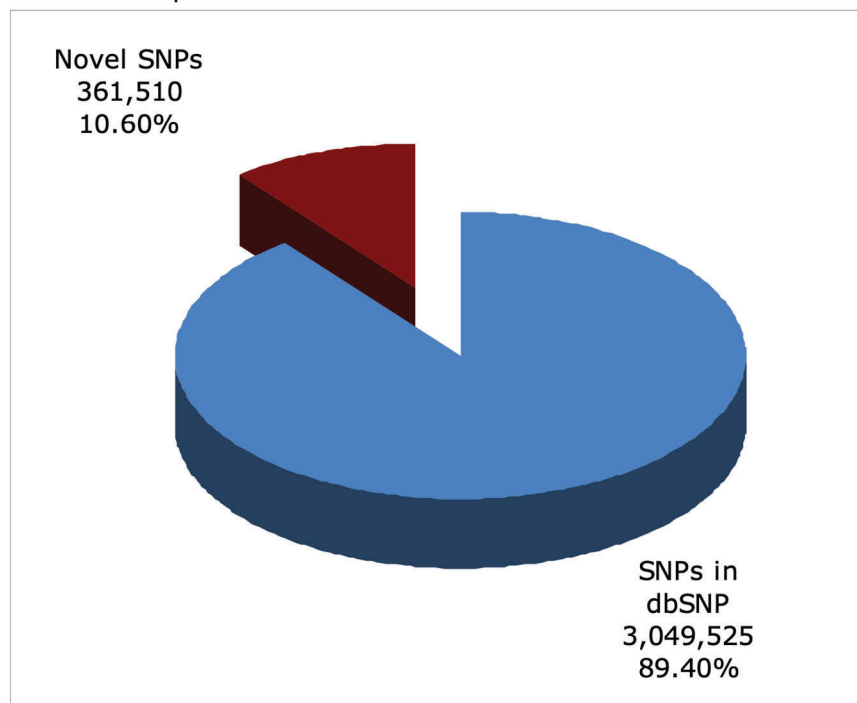
130. We envisioned performing the pullout sequencing analysis “two or more times.” For example, it would be done, e.g., monthly to check for organ transplant rejection. It would be done periodically, e.g., to test for changes in a patient’s cancer. It would be done 20 times over a 400 day period as had been used (but without targeted capture) in the paper published in March 2012 by Hugo Lam, Mike Snyder and others.

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131. The custom sample prep included focusing on genetic variants observed in just the patient. As I listed on slide 5 of my May 8, 2012 CEO update to the Personalis Board, a custom sample prep would include, e.g., problematic motifs, regions with alignment degeneracy, or variants to be phased (e.g. to determine whether they form a compound heterozygous combination, as described above). The custom sample prep would also include, e.g., genetic variants observed in one or more other individuals relevant to the condition of the specific patient, such as a parent, or such as the donor of the transplanted organ received by the patient.

132. The semi-custom sample prep would be part custom (as just described) and part based on genetic variants from a database. There would frequently be an overlap in the genetic variants observed in an individual and those in a database. As an example, Illumina's original (January 2010) report on my genome sequence identified about 3.4 million SNPs, of which just 361,510 (11%) were "novel", i.e. not already known in the dbSNP database. Thus 89% were both observed in my genome and included in the dbSNP database (version 129, which had 13 million known SNPs in it). The following is a screen capture from that January 2010 Illumina report on my genome, showing this distribution:

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EX2114 at 4.

133. We included “Sanger validation” sequencing, as an optional orthogonal technology, not based on hybrid capture, to independently verify individual genetic variants identified by our Whole Genome or Exome supplemented by semi-custom or custom hybrid capture pullout assays. *See* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (highlighting added).

134. Based on at least the foregoing, my co-inventors and I had conceived of limitation 1(d) by no later than May 8, 2012. Accordingly, my co-inventors and I had conceived of claim 1 of the ‘033 patent by no later than May 8, 2012.

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2. '033 Patent Claim 2

135. Claim 2 of the '033 patent recites:

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.

136. By no later than May 8, 2012, the Accuracy Program at Personalis included generating a biomedical report that includes biomedical information of the individual that was indicative of the result recited by limitation 1(c). Conception of this claim is reflected by, for example, Slide 5 of my May 8, 2012 CEO Overview Board of Director Presentation, which includes identifying biomedical information regarding interpretable variants that were identified by the “analysis” of “whole genome sequencing,” which included identifying “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s” (insertions/deletions) having “medical interpretation impact.” See EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5. For our “analysis” to have “medical interpretation impact,” we intended to provide a report to the customer to interpret the medically impactful “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s” (insertions/deletions) identified by the Accuracy Program.

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Overview of Personalis Accuracy Program

Characterize errors Analysis Rates by variant type & Q-score Underlying mechanisms Medical interpretation impact Regulatory impact Methods Comparison with literature Studies on limited regions Whole genome analysis: Single genome metrics Same person twice Family inheritance (MIE) Platform comparison Arrays ILMN / CGI / Ion T... Sanger capillary Prioritize solutions Bio-informatic approaches Laboratory approaches Content approaches	Informatic Solutions Advances in 3rd party alg's Aligner for > 200bp reads New versions, current alg's Other alg's (e.g. lobSTR) Advances in our alg's: SV's : Zygosity, accuracy Combine SV's & SNP's Broader use of Breakseq New Personalis alg's Alignment degeneracy Genome-aware alignment VNTR-specific Advances in reference Ethnic major-allele ref's Iterative Admixed InDel's / SV's Flag or Filter Out For problems not yet solved	Lab, Content Solutions Combine technologies WGS + exome Longer reads and/or inserts Multi-vendor Arrays (genotypes & SV's) Electrophoretic sizing Sanger validation Content-based semi-custom Array (genotypes & SV's) Pullout Custom sample preps Problematic motifs Degenerate regions Phasing Content Gold standard genomes Known healthy genomes
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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (highlighting added).

137. Slide 13 of the same May 8, 2012 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 our customer so that Personalis would provide “value-added” biomedical information about the customer’s genome.

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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

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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 13.

138. Based on at least the foregoing, my co-inventors and I had conceived of claim 2 by no later than May 8, 2012.

3. '033 Patent Claim 3

139. Claim 3 of the '033 patent recites:

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.

140. 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

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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, as discussed above for claim 2, Slide 5 of my May 8, 2012 CEO Board presentation includes identifying biomedical information regarding interpretable variants that were identified by the “analysis” of “whole genome sequencing,” which included identifying “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s” (insertions/deletions) having “medical interpretation impact.” *See* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5. For our “analysis” to have “medical interpretation impact,” we 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.

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141. Based on at least the foregoing, my co-inventors and I had conceived of claim 3 by no later than May 8, 2012.

4. '033 Patent Claim 4

142. Claim 4 of the '033 patent recites:

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.

143. 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, as discussed above for claim 1, Slide 5 of my May 8, 2012 CEO Overview Board of Director Presentation, includes identifying biomedically interpretable variants that were identified by the “analysis” of “whole genome sequencing,” which included identifying “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “InDel’s” (insertions/deletions) and “VNTRs” (Variable Number Tandem Repeats, also referred to as “Variable Length Tandem Repeats” or just “Short Tandem Repeats” (STRs)) having “medical interpretation impact.” Each of the “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “InDel’s” (insertions/deletions) and “VNTR’s” are a type of polymorphism.

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144. Based on at least the foregoing, my co-inventors and I had conceived of claim 4 by no later than May 8, 2012.

5. ‘033 Patent Claim 5

145. Claim 5 of the ‘033 patent recites:

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.

146. 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, the above discussion of claim 1. As discussed above for claim 1, Slide 4 of my May 8, 2012 CEO Overview Board of Director Presentation, described the use of a “cancer-gene pullout panel” of capture probes. The “cancer-gene pullout panel” would include sequences encoding genes associated with cancer.

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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

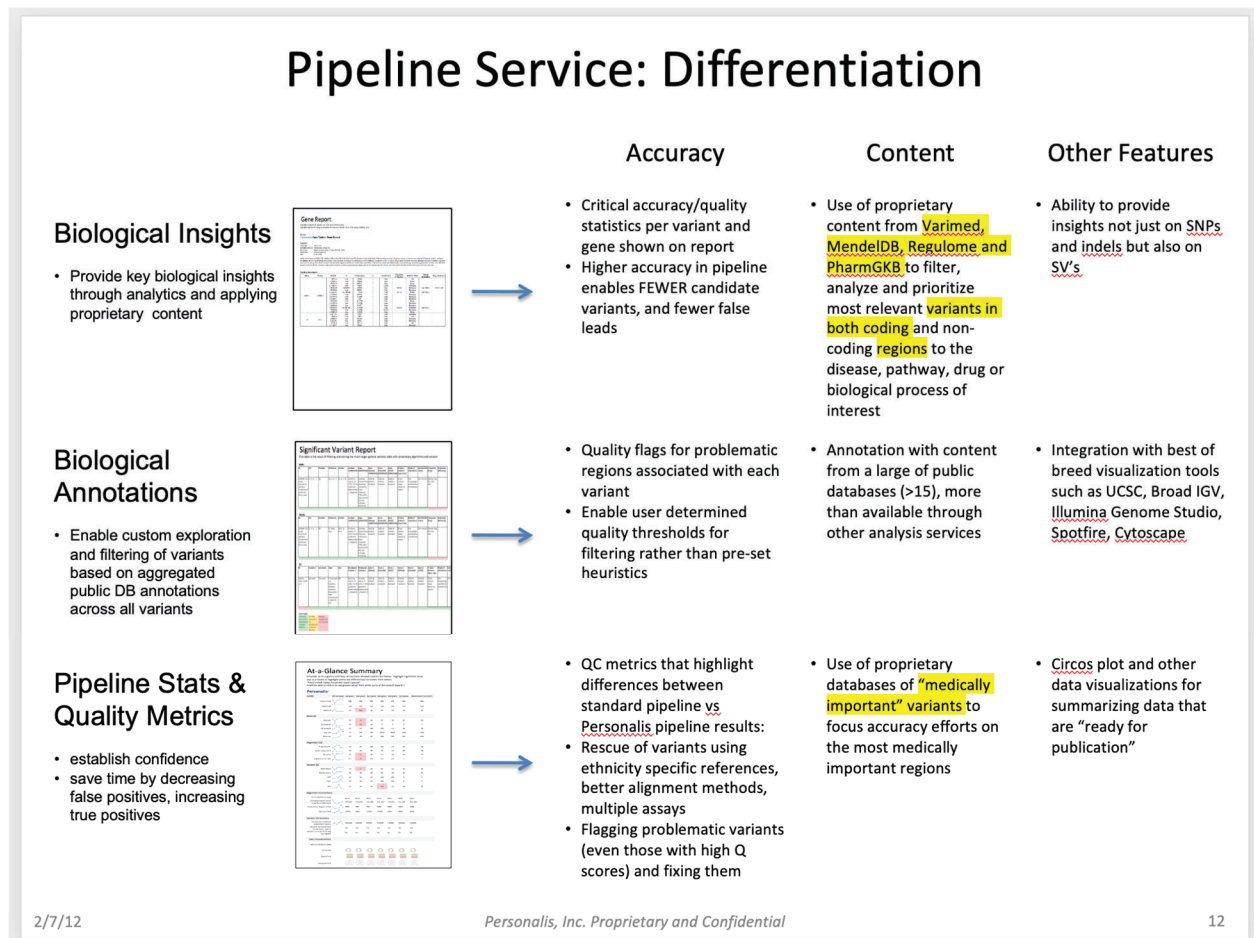
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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 4 (highlighting added).

147. In addition, the PharmGKB, MendelDB and Varimed databases we licensed from Stanford and continued to extend all included genes associated with cancer. Also at the May 8th 2012 Board Personalis meeting, our CSO Richard Chen provided an R&D update focused on our product development. Slide 12 from his presentation is copied below, with highlighted reference to these four databases of “medically important variants”:

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See EX2042 at Slide 12. On slides 29 - 32 of that presentation, he went into detail on our ongoing development of those databases. On slide 25, he showed an example of what a Personalis report would look like based on our invention at the time, and I have copied in a part here:

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Genome Results Overview

ID: John Smith
Ethnicity: Caucasian
Eye Color: Brown

Overall Risk by System

System	# Diseases with Overall Composite Genetic Risk > 5%	# Diseases with Above Average Genetic Risk Compared to Population	Ref
Cardiovascular	3	10	p 3
Congenital Disease	2	1	p 4
Dermatology	2	3	p 5
Endocrinology	1	2	p 6
ENT	-	-	p 7
Gastrointestinal	2	1	p 8
Gynecologic Disease and Pregnancy	-	-	p 9
Hematology Disease	1	-	p 10
Infectious Disease	-	-	p 11
Musculoskeletal Disease	2	1	p 12
Oncology/Neoplastic Disease	-	-	p 13
Nephrology	-	-	p 14
Neurology	-	-	p 15
Nutritional/Metabolic	1	1	p 16
Ophthalmology	-	-	p 17
Pharmacology	-	-	p 18
Pulmonary	-	-	p 19
Psychiatry	-	-	p 20
Rheumatology	-	-	p 20

See EX2042 at Slide 25. This alphabetized list of many medical conditions includes the entry “Oncology/Neoplastic Disease” showing that cancer was one of the categories of disease for inclusion in the report.

148. Based on at least the foregoing, my co-inventors and I had conceived of claim 5 by no later than May 8, 2012.

6. ‘033 Patent Claim 6

149. Claim 6 of the ‘033 patent recites:

6. The method of claim 1, further comprising identifying the presence or absence of said plurality of polymorphisms in said nucleic acid sample.

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150. 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 the above discussion of claim 1. For example, as discussed above for claim 1, Slide 5 of my May 8, 2012 CEO Overview Board of Director Presentation, 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 us 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.

151. Also at the May 8th 2012 meeting of our Board of Directors, our CSO Richard Chen provided an R&D update presentation (EX2042) focused on our product development. Slide 10 included some mock ups of reports we planned to generate for customers. It included a “General Variant Report” described as a “Very large table of every variant call”:

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	A	B	C	D	E	F	G	H	I	J	K	L
1	General Variant Report											
2	Very large table of every variant call intersected with important public databases											
3												
4	SNPs											
5	ID	Chr	Position	Reference	Variant	Context (ANNOVAR)	Type (ANNOVAR)	Gene (Refseq) (ANNOVAR)	Gene (Ensembl) (ANNOVAR)	Gene (UCSC) (ANNOVAR)	Frequency (Pop)	Frequency (Ethnicity)
6	[dbSNP rsid, evsid, internal ID - will be a hierarchy of preferred IDs to use]	[1, 2, 3, ...]	[#]	[A, C, G, T]	[T, G, C, A]	[intronic, exonic, 3'-UTR, 5'-UTR, downstream, intergenic]	[splicing, synonymous missense, nonsynonymous missense, TFBS, eQTL, hypersensitivity site, nonstop,	[ID(x) & relative location]	[ID(x) & relative location]	[ID(x) & relative location]	[dbamp, 1kg, CG, EVS, etc]	
7												
8												
9	Indels											
10	ID	Chr	Position	Reference	Variant	Context (ANNOVAR)	Type (ANNOVAR)	Gene (Refseq) (ANNOVAR)	Gene (Ensembl) (ANNOVAR)	Gene (UCSC) (ANNOVAR)	Frequency (Pop)	Frequency (Ethnicity)
11	[dbSNP rsid, evsid, internal ID - will be a hierarchy of preferred IDs to use]	[1, 2, 3, ...]	[#]	[C, AAG, etc.]	[CCT, G, etc.]	[intronic, exonic, 3'-UTR, 5'-UTR, downstream, intergenic]	[splicing, synonymous missense, nonsynonymous missense, TFBS, eQTL, hypersensitivity site, nonstop,	[ID(x) & relative location]	[ID(x) & relative location]	[ID(x) & relative location]	[dbamp, 1kg, CG, EVS, etc]	
12												
13												
14	SV											
15	ID	Junction 1	Junction2	Type	Size	Breakpoint Context 1	Breakpoint Context 2	Gene 1 (Refseq)	Gene 1 (Ensembl)	Gene 1 (UCSC)	Gene 2 (Refseq)	Gene 2 (Ensembl)
16	[dbVar, DGV, CHOP, etc]	[chrpos]	[chrpos]	[Translocation, Insertion, Deletion, Inversion,	[#]	[intronic, exonic, 3'-UTR, 5'-UTR, downstream,	[intronic, exonic, 3'-UTR, 5'-UTR, downstream,	[ID(x) & relative location]	[ID(x) & relative location]	[ID(x) & relative location]	[ID(x) & relative location]	[ID(x) & relative location]

See EX2042 at Slide 25. Variants included in this table were those detected in the sample and those not listed were those not detected.

152. Based on at least the foregoing, my co-inventors and I had conceived of claim 6 by no later than May 8, 2012.

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7. '033 Patent Claim 7

153. Claim 7 of the '033 patent recites:

7. The method of claim 2, wherein said identifying comprises observing an allele frequency of said plurality of polymorphisms.

154. By no later than May 8, 2012, the Accuracy Program at Personalis included observing an allele frequency of said plurality of polymorphisms. For example, Slide 11 of my May 8, 2012 CEO Overview Board of Director 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.

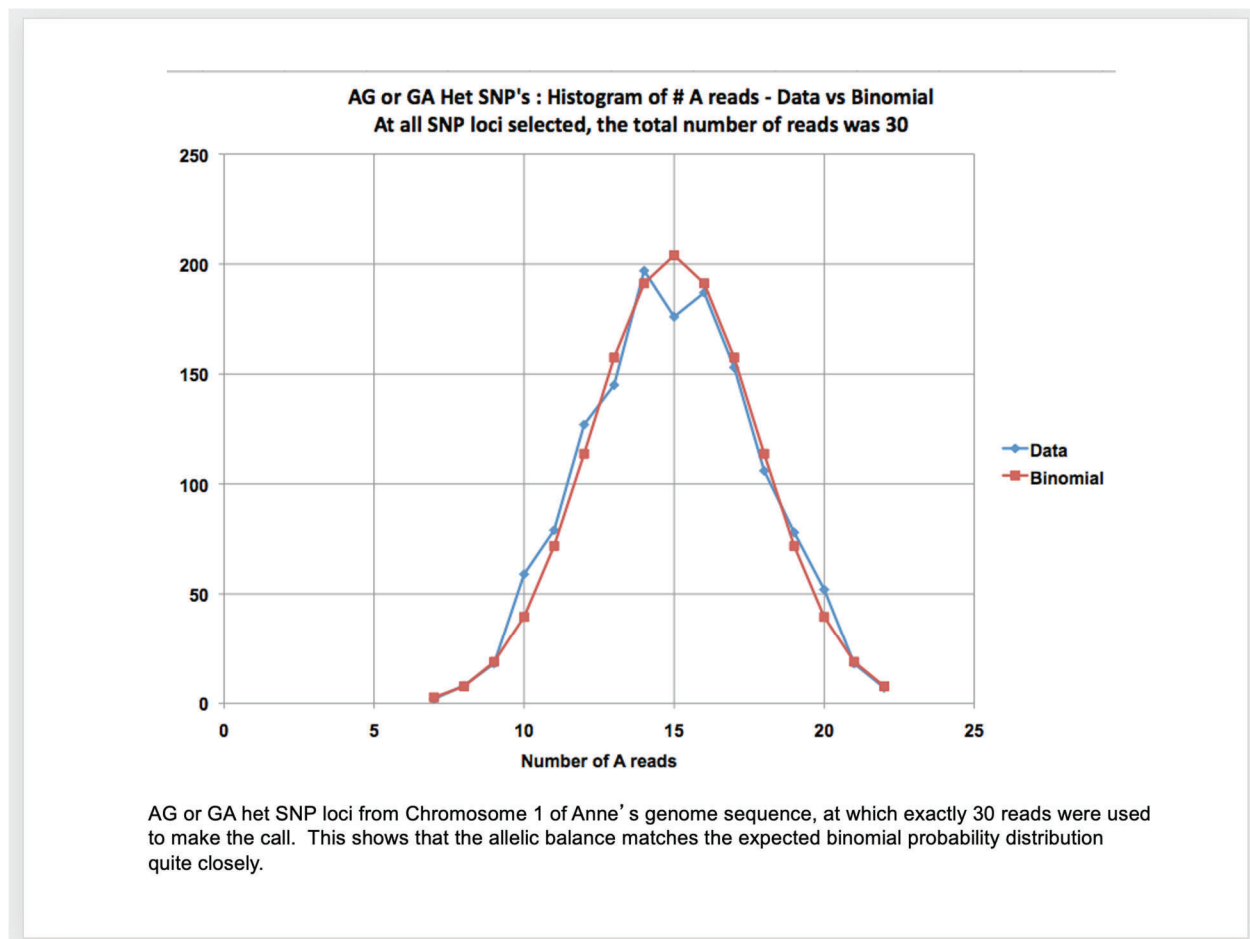
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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 11.

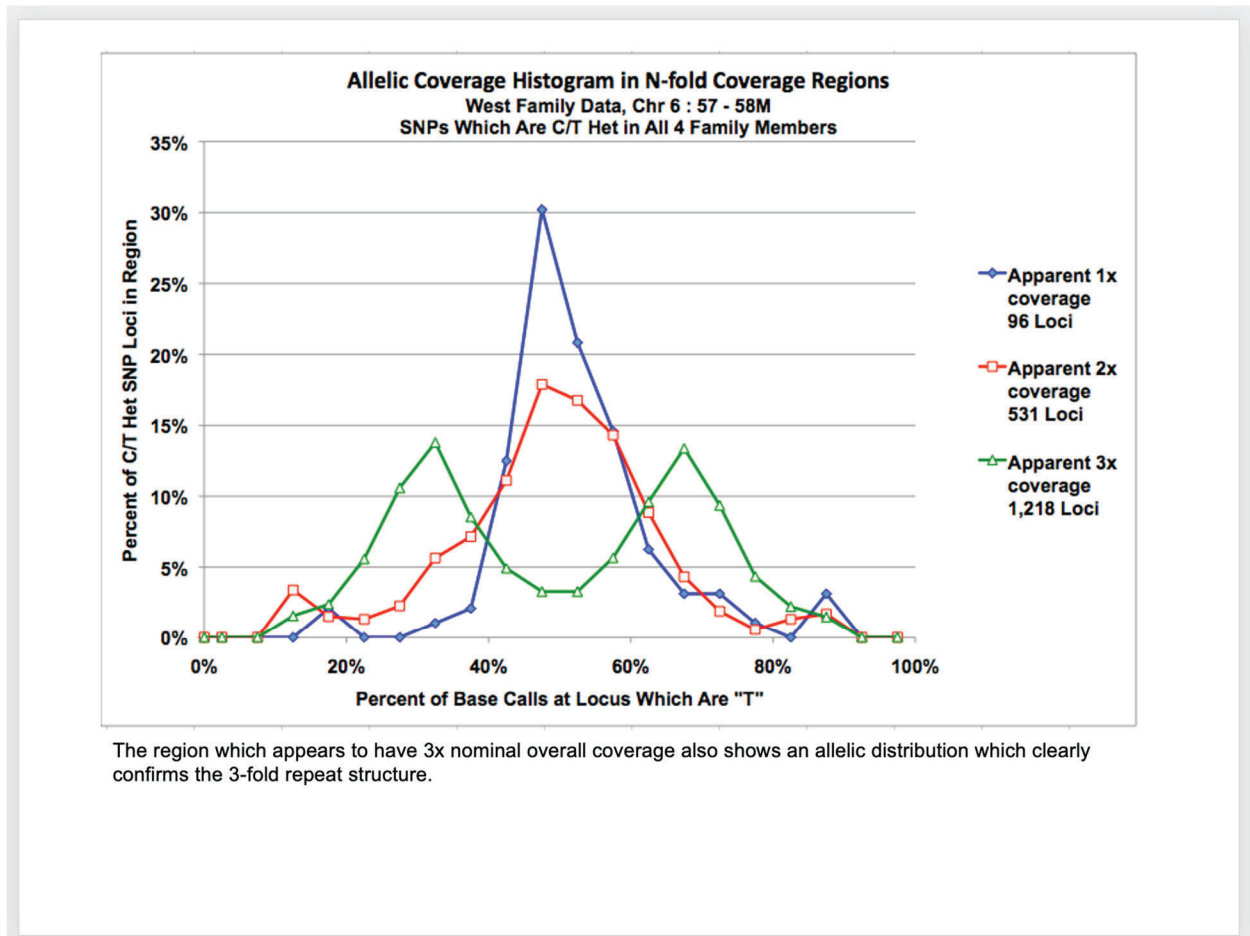
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155. We had also focused on the allele frequencies of individual genetic variants in the data from individuals. In an internal slide deck, on the subject of quality control, that I shared with the Personalis co-founders on June 18, 2011, I showed (slide 10) data on the allele frequency distribution observed in a part of my daughter's genome and how closely it matched the expected binomial distribution:



See EX2115, June 18, 2011 presentation at slide 10. Slide 12 then went on to show that allele frequencies deviated from that in a region with unusually high coverage:

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See EX2115, June 18, 2011 presentation at slide 12. This illustrated the use of allele frequencies to detect underlying structural variants in that part of the genome.

156. Based on at least the foregoing, my co-inventors and I had conceived of claim 7 by no later than May 8, 2012.

8. '033 Patent Claim 8

157. Claim 8 of the '033 patent recites:

8. The method of claim 1, wherein said plurality of capture probes are in a hybridization array.

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

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claim is reflected by, for example, the above discussion of claim 1. As discussed above for claim 1, Slide 5 of my May 8, 2012 CEO Overview Board of Director Presentation, involved the use of “content-based semi-custom” capture probes in “array (genotypes & SV’s)” to capture genotypes and structural variants. The “arrays” included in Slide 5 reference capture probes arranged in a hybridization array where the capture probes are designed to hybridize to the “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s” (insertions/deletions) that were identified by the “analysis” of the “whole genome analysis” within the Accuracy Program. EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5.

159. Based on at least the foregoing, my co-inventors and I had conceived of claim 8 by no later than May 8, 2012.

9. ‘033 Patent Claim 9

160. Claim 9 of the ‘033 patent recites:

9. The method of claim 1, wherein said plurality of capture probes are conjugated to beads.

161. 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 whole genome sequencing (“WGS”) with “semi-custom” assays using “pullout” technologies. As described above, the Accuracy Program included “pulling out” desired content from a genomic DNA sample by

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streptavidin-coated magnetic beads conjugated to biotin-labelled capture probes. At least Mark Pratt and I were aware that custom and semi-custom capture probes could be purchased via Agilent (their “SureSelect” line of capture probes), Illumina (their “TruSeq” capture probes), and Roche (their “Nimblegen” capture probes). Members of the Personalis team were experienced in their use, and the knowledge that such capture probes included streptavidin-coated magnetic beads conjugated to biotin-labelled capture probes. In particular, we were aware that Agilent supported custom customer-designed kits based on the customer’s own content that utilized biotinylated capture probes being conjugated to magnetic beads via the streptavidin coating on the beads.

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Overview of Personalis Accuracy Program

Characterize errors <u>Analysis</u> Rates by variant type & Q-score Underlying mechanisms Medical interpretation impact Regulatory impact <u>Methods</u> Comparison with literature Studies on limited regions Whole genome analysis: Single genome metrics Same person twice Family inheritance (MIE) Platform comparison Arrays ILMN / CGI / Ion T... Sanger capillary <u>Prioritize solutions</u> Bio-informatic approaches Laboratory approaches Content approaches	Informatic Solutions <u>Advances in 3rd party alg's</u> Aligner for > 200bp reads New versions, current alg's Other alg's (e.g. lobSTR) <u>Advances in our alg's:</u> SV's : Zygosity, accuracy Combine SV's & SNP's Broader use of Breakseq <u>New Personalis alg's</u> Alignment degeneracy Genome-aware alignment VNTR-specific <u>Advances in reference</u> Ethnic major-allele ref's Iterative Admixed InDel's / SV's <u>Flag or Filter Out</u> For problems not yet solved	Lab, Content Solutions <u>Combine technologies</u> WGS + exome Longer reads and/or inserts Multi-vendor Arrays (genotypes & SV's) Electrophoretic sizing Sanger validation <u>Content-based semi-custom</u> Array (genotypes & SV's) Pullout <u>Custom sample preps</u> Problematic motifs Degenerate regions Phasing <u>Content</u> Gold standard genomes Known healthy genomes
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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (highlighting added).

162. EX2045 is a true and correct copy of the Personalis July 26, 2011 Board of Directors meeting slides by Euan Ashley, one of the co-founders of Personalis. As mentioned above, I attended the July 2011 meeting with the following additional persons, all of whom are appropriately not named as inventors of the '033 patent: Michael Snyder, Russ Altman, Euan Ashley, Jonathan MacQuitty, Sue Siegel, Andrew Chung, Robin Bennet, and Lisa Kenkel (who was present by phone for a portion of the meeting). Slide 31 is reproduced below. I was aware through at least

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Slide 31 that “Custom Agilent SureSelect in solution hybridization” biotinylated capture probes for conjugation to streptavidin-coated magnetic beads were available to order from Agilent.

Prior expectation – CV disease genes

➤ Custom Agilent SureSelect in solution hybridization selected regions associated with 251 target genes implicated in myocardial disease and/or function:

- Exons +/- 100 base pairs
- TFBS within 1.5 kbp
- Enhancers/repressors within 1.5 Mbp
- Conserved regions from MSA within 2kbp of coding regions and in introns
- miRNA target sites
- miRNA coding regions
- Targets 3.5 Mbp of genomic sequence



EX2045, July 26, 2011 Euan Ashley Board of Directors Meeting at Slide 31.

163. Based on at least the foregoing, my co-inventors and I had conceived of claim 9 by no later than May 8, 2012.

10. ‘033 Patent Claim 10

164. Claim 10 of the ‘033 patent recites:

10. The method of claim 1, wherein said plurality of capture probes further comprises barcodes.

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

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inventors of the '033 patent, at least Mark Pratt and I were aware that it was possible to multiplex multiple samples into each lane of a sequencing instrument flow cell by adding a DNA barcode to the end of each molecule of DNA to be sequenced. We 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. Mark Pratt and I were familiar with the use of DNA barcodes as sample identifiers to multiplex samples for sequencing on the Illumina instruments based on our previous employment at Illumina, and the use of barcodes in some of Illumina's workflows. We were also aware of the use of DNA barcodes and sample indexes to multiplex samples for sequencing of DNA in some of the workflows for Roche's 454 sequencing instrument.

166. By no later than May 8, 2012, barcoding samples to multiplex them for DNA sequencing was part of the Accuracy Program at Personalis. The Accuracy Program combined technologies to supplement whole genome sequencing ("WGS") with "semi-custom" assays using "pullout" technologies. As described above, the Accuracy Program included "pulling" out desired content from a genomic DNA sample by streptavidin-coated magnetic beads conjugated to biotin-labelled capture probes. We were aware that custom and semi-custom capture probes could be

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purchased via Agilent (their “SureSelect” line of capture probes), Illumina (their “TruSeq” capture probes), and Roche (their “Nimblegen” capture probes). I was aware that Agilent’s Sure Select and Illumina’s TruSeq capture probes could include DNA barcode indexing systems, and members of the Personalis team were experienced in their use. In particular, we were aware that Agilent supported custom customer-designed kits based on the customer’s own content. We were also aware in particular that these customer-designed kits could be pooled for efficient sequencing by the use of indexed (barcoded) libraries.

Overview of Personalis Accuracy Program

Characterize errors <u>Analysis</u> Rates by variant type & Q-score Underlying mechanisms Medical interpretation impact Regulatory impact <u>Methods</u> Comparison with literature Studies on limited regions Whole genome analysis: Single genome metrics Same person twice Family inheritance (MIE) Platform comparison Arrays ILMN / CGI / Ion T... Sanger capillary <u>Prioritize solutions</u> Bio-informatic approaches Laboratory approaches Content approaches	Informatic Solutions <u>Advances in 3rd party alg's</u> Aligner for > 200bp reads New versions, current alg's Other alg's (e.g. lobSTR) <u>Advances in our alg's:</u> SV's : Zygosity, accuracy Combine SV's & SNP's Broader use of Breakseq <u>New Personalis alg's</u> Alignment degeneracy Genome-aware alignment VNTR-specific <u>Advances in reference</u> Ethnic major-allele ref's Iterative Admixed InDel's / SV's <u>Flag or Filter Out</u> For problems not yet solved	Lab, Content Solutions <u>Combine technologies</u> WGS + exome Longer reads and/or inserts Multi-vendor Arrays (genotypes & SV's) Electrophoretic sizing Sanger validation <u>Content-based semi-custom</u> Array (genotypes & SV's) Pullout <u>Custom sample preps</u> Problematic motifs Degenerate regions Phasing <u>Content</u> Gold standard genomes Known healthy genomes
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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5
(highlighting added).

167. EX2045 is a true and correct copy of the Personalis July 26, 2011 Board of Directors meeting slides by Euan Ashley, one of the co-founders of Personalis. As mentioned above, I attended the July 2011 meeting with the additional persons, all of whom are appropriately not named as inventors of the '033 patent. Slides 31 and 33 are reproduced below. I was aware through at least Slide 31 that “Custom Agilent SureSelect in solution hybridization” capture probes were available to order from Agilent, and through at least Slide 33 that studying subjects and follow-up work involving sequencing on Illumina’s HiSeq instrument could use “indexed primers and sample pooling for maximum sequencing efficiency.”

Prior expectation – CV disease genes

➤ Custom Agilent SureSelect in solution hybridization
selected regions associated with 251 target genes implicated
in myocardial disease and/or function:

- Exons +/- 100 base pairs
- TFBS within 1.5 kbp
- Enhancers/repressors within 1.5 Mbp
- Conserved regions from MSA within 2kbp of coding regions and in introns
- miRNA target sites
- miRNA coding regions
- Targets 3.5 Mbp of genomic sequence



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EX2045, July 26, 2011 Euan Ashley Board of Directors Meeting at Slide 31.

Study subjects and follow-up work

- 80 subjects with dilated and hypertrophic cardiomyopathy in whom clinical genetic testing has not identified a pathogenic mutation
 - 65 subjects have DNA already/15 subjects require DNA collection
- Plan for sequencing on Hi-Seq using indexed primers and sample pooling for maximum sequencing efficiency
- Ethnicity-specific variant identification as prior
- Targeted genotyping/re-sequencing/re-phenotyping contingent on results of discovery sequencing
- Potential clinical tool and tool for investigating modifier loci in other subjects



EX2045, July 26, 2011 Euan Ashley Board of Directors Meeting at Slide 33.

168. Based on at least the foregoing, my co-inventors and I had conceived of claim 10 by no later than May 8, 2012.

11. '033 Patent Claim 11

169. Claim 11 of the '033 patent recites:

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.

170. 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. For example, Slide 11 of my January 5, 2012 Accuracy Framework PowerPoint slides is entitled

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“Examples of process variability,” and the first line stated “sample source (blood, saliva, tissue, culture cell).” Thus, the Accuracy Program included sample sources obtained from our customer that included body fluid (e.g., blood, saliva), cell (e.g., culture cell), and tissues and organs.

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, January 5, 2012 Accuracy Framework PowerPoint slides at Slide 11.

171. Based on at least the foregoing, my co-inventors and I had conceived of claim 11 by no later than May 8, 2012.

12. ‘033 Patent Claim 12

172. Claim 12 of the ‘033 patent recites:

12. The method of claim 11, wherein said body fluid is blood plasma.

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173. By no later than May 8, 2012, the Accuracy Program at Personalis included nucleic acid sample obtained from blood plasma. For example, Slide 3 of my May 8, 2012 CEO Board presentation described a “seminal paper by Mike Snyder & team published in Cell” which supported my idea for the Accuracy Program to include “ongoing clinical use of genome -scale sequencing” and “not just a genome once in your life.”

Publications & Upcoming Presentations

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

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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 3 (highlighting added).

174. The referenced paper by Dr. Snyder was Chen and Snyder et al., “Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes,” Cell, 148:1293-1307 (March 2012), EX2030. The paper reported on a 54-year-old

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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. *Id.* at 3. The assays used at those 20 time points were chosen in part based on analysis of groups of genetic variants detected in his whole genome sequencing data. 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. *See, e.g., id.* at Figure 1(A). At each of the 20 time points, the analysis from the blood included assays on three different components of the blood: plasma, serum and PBMC’s (white blood cells). They used blood plasma for protein assays and PBMC’s for untargeted RNAseq. The RNAseq was used not only to measure changes in genes which were expressed (e.g., changes in genes of the immune system during the infections) but also, by comparison with the original genome sequence, variations in the nucleic acid sequence over time (RNA edits). Those changes in RNA sequences were dynamic, being detected at some points and not others. When they were detected, their allele frequencies were calculated from the data and changes in those were tracked.

175. My co-inventors and I realized that the Accuracy Program could be more efficient than the untargeted RNAseq used in the Snyder paper on PBMC’s by replacing it with a “content-based semi-custom” approach using “pullout” based on

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the plasma portion of a blood sample. *See* Slide 5 of my May 8, 2012 CEO Board Presentation, EX2112. Well before that time we were familiar with the genetic analysis of cell free DNA from blood plasma (for fetal diagnosis, cancer analysis and detection of transplant rejection) but not using hybrid capture probes targeted to the variants of the person, and not from a single individual at multiple time points. Our realization of this possibility to leverage our technology at so many time points was why we described this paper as seminal. The paper did not use or disclose our invention, but it sparked our creativity and that led to the invention. For at least these reasons, the Accuracy Program at Personalis included nucleic acid sample obtained from blood plasma by no later than May 8, 2012.

13. '033 Patent Claim 13

176. Claim 13 of the '033 patent recites:

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.

177. 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

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first time point. For example, as discussed above with respect to 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 above with respect to claim 12, the Accuracy Program further included that the additional nucleic acid samples would be isolated from a plasma sample obtained from our 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.” *See* Slide 3 of my May 8, 2012 CEO Board presentation, EX2112.

178. Based on at least the foregoing, my co-inventors and I had conceived of claim 13 by no later than May 8, 2012.

14. ‘033 Patent Claim 14

179. Claim 14 of the ‘033 patent recites:

14. The method of claim 13, wherein said first time point and said additional time point are at least 1 week apart, or more.

180. 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. For example, as discussed above with respect to claim 12, the Accuracy Program included using capture probes to generate an additional subset of nucleic acid molecules from an additional nucleic acid sample. As discussed above with respect to claim 12, I was aware of the paper authored by Dr. Snyder with Hugo Lam, that published in Cell in March of 2012. *See* Slide 3 of my May 8, 2012 CEO

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Board presentation, EX2112. 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. *See* EX2030 at 3. 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. *See, e.g., id.* at Figure 1(A). My co-inventors and I realized that the Accuracy Program would benefit from blood plasma samples being taken at different intervals from our customers, including a blood plasma sample taken at least 1 week or more after the first sample.

181. Based on at least the foregoing, my co-inventors and I had conceived of claim 14 by no later than May 8, 2012.

15. ‘033 Patent Claim 15

182. Claim 15 of the ‘033 patent recites:

15. The method of claim 13, wherein said first time point and said additional time point are at least 1 month apart, or more.

183. 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. For example, as discussed above with respect to claim 14, I was aware of a paper by Dr. Snyder that reported on a 54-year-old man who was whole genome sequenced at an initial time point, and then assessed using blood samples (including

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analysis of plasma) at 20 time points over a 400 day period. *See* EX2030 at 3. 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. *See, e.g., id.* at Figure 1(A). My co-inventors and I realized that the Accuracy Program would benefit from blood plasma samples being taken at different intervals from our customers, including a blood plasma sample taken at least 1 month or more after the first sample.

184. Based on at least the foregoing, my co-inventors and I had conceived of claim 15 by no later than May 8, 2012.

16. ‘033 Patent Claim 16

185. Claim 16 of the ‘033 patent recites:

16. The method of claim 13, wherein said additional time point is later than said first time point.

186. 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, my co-inventors and I realized that the Accuracy Program would benefit from blood plasma samples being taken at different intervals from our customers, including a blood plasma sample taken at least 1 week or more after the first sample. Based on at least the foregoing, my co-inventors and I had conceived of claim 16 by no later than May 8, 2012.

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17. '033 Patent Claim 17

187. Claim 17 of the '033 patent recites:

17. The method of claim 13, wherein said additional time point is earlier than said first time point.

188. 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, my co-inventors and I realized that the Accuracy Program would benefit from blood plasma samples being taken at different intervals from our customers. My co-inventors and I realized that the blood plasma sample could be taken earlier than the sample used for whole genome sequencing. This would allow us to verify, for example, that the capture probes discussed above effectively “pulled out” the targeted genotypes and structural variants of interest. This would allow us to validate the use of the capture probes in the customer’s blood plasma sample, and we realized that we could obtain the blood sample for validation purposes before or after the sample being used for WGS to generate the whole genome sequencing data. Based on at least the foregoing, my co-inventors and I had conceived of claim 17 by no later than May 8, 2012

18. '033 Patent Claim 18

189. Claim 18 of the '033 patent recites:

18. The method of claim 11, wherein said tissue is a tissue biopsy.

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190. 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. For example, Slide 11 of my January 5, 2012 Accuracy Framework PowerPoint slides is entitled “Examples of process variability,” and the first line stated “sample source (blood, saliva, tissue, culture cell).” Thus, the Accuracy Program included sample sources obtained from a tissue biopsy. *See, e.g.*, EX2046, January 5, 2012 Accuracy Framework PowerPoint slides at Slide 11. Based on at least the foregoing, my co-inventors and I had conceived of claim 18 by no later than May 8, 2012.

19. ‘033 Patent Claim 19

191. Claim 19 of the ‘033 patent recites:

19. The method of claim 1, wherein said subsequently obtained biological sample is a plasma sample.

192. 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.

20. ‘033 Patent Claim 20

193. Claim 20 of the ‘033 patent recites:

20. The method of claim 1, wherein said subsequently obtained biological sample is a tissue biopsy sample.

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194. 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.

21. '033 Patent Claim 21

195. Claim 21 of the '033 patent recites:

21. The method of claim 1, wherein said one or more databases of polymorphisms comprises a biomedical database.

196. By no later than May 8, 2012, the Accuracy Program at Personalis included one or more databases of polymorphisms that comprise a biomedical database. As described above, in August 2011 Personalis exclusively licensed four databases, two of which (MendelDB and VariMed) we continued to curate. The MendelDB database is a biomedical database which identifies genetic variants known to cause specific Mendelian diseases. The PharmGKB database we had licensed was considered the premier database in the world linking genetic variant to the metabolism and thus efficacy of pharmaceutical drugs. The VariMed database was being curated specifically to identify genetic variants identified in the published literature to be associated with specific phenotypes. The majority of entries in the database were for phenotypes which were diseases.

197. In addition, as discussed above with respect to limitation 1(a), the Accuracy Program included capture probes designed to “pullout” “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s”

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(insertions/deletions) polymorphisms encoding genes with known biomedically interpretable variants that were identified by the “analysis” of the “whole genome analysis” within the Accuracy Program. *See* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 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” (whole genome sequencing) and validated by, for example, “Sanger validation” sequencing. The genotypes and structural variants would be stored in databases on the Personalis servers (which are described above with reference to, for example, EX2044 (April 24, 2012 email attachment from Hugo Lam to John West and Richard Chen describing the Personalis server configuration)) or elsewhere. The database of polymorphisms stored on the Personalis servers could include polymorphisms observed in a population of one or more samples from our customers. *See, e.g.*, EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slides 5 and 13 (reproduced above with highlighting). The database of polymorphisms was kept for “medical interpretation impact.” *Id.* at Slide 5. Thus, the database of polymorphisms comprises a biomedical database. Based on at least the foregoing, my co-inventors and I had conceived of claim 21 by no later than May 8, 2012.

22. ‘033 Patent Claim 22

198. Claim 22 of the ‘033 patent recites:

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22. The method of claim 1, wherein said one or more polymorphisms are observed in a population of a single sample.

199. 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. In my CEO Update on May 8th 2012, slide 5, I highlighted “Custom Sample Preps” including for Phasing. As discussed above, custom sample preps, implemented by hybrid capture of a subset of long fragments, coupled with longer DNA sequence reads, could be used to phase pairs of genetic variants closely spaced on a chromosome. As further discussed above, this is key to the medical interpretation of pairs of heterozygous variants to determine whether or not they constitute compound heterozygosity. The pairs of heterozygous variants which have the potential to constitute compound heterozygosity will be different for almost every person. This is why a hybrid capture assay for this purpose would need to be custom. The individual genetic variants could be identified and determined to be heterozygous using exome or whole genome sequencing, but to capture long fragment molecules in the region of a pair of such variants, to enable phasing them, a custom assay would need to be designed based on the pairs of variants detected in the genome or exome.

200. We also realized that there were other diseases in which genetic variants might be largely unique to the individual, such as in cancer.

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201. When a new set of capture probes is synthesized, it can be quite expensive, but the synthesis can provide enough capture probe material to enable analysis of multiple samples. As an example, Personalis' first purchase of capture probes based on our own designs, September 2012, (EX2089) cost over \$29,000 but could provide enough material for the analysis of 32 samples. The cost of a custom capture probe set could only be amortized down to a reasonable level if there were many samples to be analyzed. This part of why we considered the March 2012 publication authored by Hugo Lam, Mike Snyder and others to be so seminal for us. The authors did not use a custom hybrid capture probe set, but the paper showed that it could be quite useful medically to assay genetic variants in the same person at many time points (twenty). We realized that it could be advantageous to design a custom assay based on the genetic variants of a single person and that could be cost effective by amortizing the rather high cost of synthesis over samples taken at many time points from that person.

202. As an additional example, as discussed above for claim 11, the sample obtained from our customer could be obtained from a blood, saliva, tissue, or cell culture sample from the patient. *See* EX2046, January 5, 2012 Accuracy Framework PowerPoint slides at Slide 11. The first sample from a patient would be contacted with the capture probes that were designed to “pullout” “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s”

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(insertions/deletions) polymorphisms encoding genes with known biomedically interpretable variants that were identified by the “analysis” of the first sample by “whole genome analysis.” *See* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 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” (whole genome sequencing) and “Sanger validation” sequencing. The genotypes and structural variants would be stored in a database on the Personalis servers (which are described above with reference to, for example, EX2044 (April 24, 2012 email attachment from Hugo Lam to John West and Richard Chen describing the Personalis server configuration)) or elsewhere. The database of polymorphisms stored on the Personalis servers could include polymorphisms observed in a population of the first (and single) sample from one of our customers. *See, e.g.,* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slides 5 and 13. This database of polymorphisms would be observed in a population of the first (and single) sample.

203. Based on at least the foregoing, my co-inventors and I had conceived of claim 22 by no later than May 8, 2012.

23. ‘033 Patent Claim 23

204. Claim 23 of the ‘033 patent recites:

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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.

205. By no later than May 8, 2012, the Accuracy Program 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, in the paper published in March 2012, authored by Hugo Lam, Mike Snyder and others, and which we had referenced as seminal, the study began not only with the whole genome sequencing of the primary subject of the study, but also of his mother. The utility of this was described in the paper as follows: “Analysis of the subject's mother's genome and imputation allowed a maternal/paternal chromosomal phasing of 92.5% of the subject's SNVs and indels (see Figure S2 and Extended Experimental Procedures). 139 phased genes contain predicted compound heterozygous deleterious and/or nonsense mutations.”

EX2030. As we have discussed, phasing and the identification of compound heterozygous mutations can help prioritize genetic variants of an individual for further study. While this publication did not create a custom hybrid capture panel, the utility it showed from the analysis of so many time points (twenty) inspired us to invent that. In the case of this paper, the plurality of samples was two – the sample of the subject, and separately the sample of the subject’s mother. We realized that another such plurality of two would be the comparison of sequence data from two

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samples of a cancer patient, one sample being of the tumor and the other sample being a non-tumor tissue or blood from the same person. By comparing the two, it becomes 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. Based on at least the foregoing, my co-inventors and I had conceived of claim 23 by no later than May 8, 2012.

Conclusion Regarding Conception for the ‘033 Patent

206. In conclusion, my co-inventors and I had conceived of the invention recited by claims 1-23 of the ‘033 patent by no later than May 8, 2012. Further, by no later than May 8, 2012, I recognized and appreciated that the Accuracy Program had the features that are now recited by claims 1-23 of the ‘033 patent. Further, a person of ordinary skill in the art would have been enabled to practice our invention as of May 8, 2012 without undue experimentation if they had been informed of our invention on that date.

207. In summary, our conception of the methods of this patent began in an effort to resolve the accuracy problems in whole genome and exome sequencing, by augmenting them with hybrid capture pullout sets. As described above, our plan for the initial products from the Accuracy Program, “Whole Genome Plus” and “Exome Plus,” involved three different supplements, each implemented as a separate

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Personalis-designed capture probe set involving thousands of probes. As we became more and more comfortable with the concepts around these large sets of capture probes, we began to realize that they could be customized for an individual person, but at considerable cost. It was in March 2012, when we saw the utility of analyzing genetic sequence changes in a single individual over blood samples from twenty time points, that we realized such a multiple time point analysis could amortize the expense of a custom hybrid capture panel and make it practical. That was the basis of the ‘033 patent.

C. Conception of the ‘394 patent

208. U.S. Patent Application No. 17/548,379 (“the ‘379 application”) was filed on December 10, 2021 and issued as U.S. Patent No. 11,384,394 (“the ‘394 patent”) on July 12, 2022. The ‘379 application is a continuation of U.S. Patent Application No. 17/078,857, filed on October 23, 2020, now U.S. Pat. No. 11,408,033, which is a continuation application of U.S. Patent Application No. 16/816,135, filed on March. 11, 2020, which application is a continuation application of U.S. Patent Application No. 16/526,928, filed July 30, 2019, which application is a continuation application of U.S. Patent Application No. 15/996,215, filed June 1, 2018, now U.S. Patent No. 10,415,091, which application is a continuation application of U.S. Patent Application No. 14/810,337, filed July 27,

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2015, now U.S. Pat. No. 10,266,890, which application is a divisional application of U.S. Patent Application No. 14/141,990, filed December 27, 2013, now U.S. Pat. No. 9,128,861, which claims priority to U.S. Provisional Application No. 61/753,828, filed January 17, 2013.

209. The ‘394 patent issued with 19 claims. My co-inventors and I and formed a definite and permanent idea of the complete and operative invention described in each of these claims by no later than May 8, 2012. In particular, we had developed the particular solutions for analyzing nucleic acid samples from an individual utilizing the combination of whole genome sequencing, capture probes, and conducting sequencing assays according to the specific steps recited in the ‘394 patent claims. The definite and permanent idea we had was significantly more than a general research goal or plan. Further, a person of ordinary skill in the art would have been enabled to practice our invention as of May 8, 2012 without undue experimentation if they had been informed of our invention. Thus, we had conceived of the invention claimed by the ‘394 patent no later than May 8, 2012. Below is a discussion providing an explanation of our conception of each of the 19 claims of the ‘394 patent, along with corroborating evidence.

1. ‘394 Patent Claim 1

210. Claim 1 of the ‘394 patent recites:

1. A method for analyzing a nucleic acid sample obtained from an individual, comprising:

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- (a) generating a first subset of nucleic acid molecules from a first nucleic acid sample obtained from said individual;
- (b) conducting a first sequencing assay on said first subset of nucleic acid molecules to yield a first result comprising a first nucleic acid sequence wherein said first sequencing assay comprises whole genome sequencing;
- (c) generating a second subset of nucleic acid molecules from a second nucleic acid sample of said individual by contacting said second nucleic acid sample with a plurality of capture probes, wherein said plurality of capture probes hybridize to one or more polymorphisms which are based on or extracted from one or more databases of polymorphisms, observed in a population of one or more samples, or a combination thereof, wherein said first sample or said second sample is obtained from said subject at a first time point;
- (d) conducting a second sequencing assay on said second subset of nucleic acid molecules to yield a second result comprising a second nucleic acid sequence;
- (e) using said plurality of capture probes to generate an additional subset of nucleic acid molecules from an additional nucleic acid sample isolated from an additional sample obtained from said subject at an additional time point different from said first time point;
- (f) conducting a third sequencing assay on said additional subset of nucleic acid molecules from said additional nucleic acid sample to yield a third result comprising a third nucleic acid sequence; and
- (g) generating a biomedical report that includes biomedical information of said subject, which biomedical information identifies the presence or absence of said one or more polymorphisms identified by said second result or said third result.

a. ‘394 Patent: Claim 1 - Preamble

211. The preamble of claim 1 of the ‘394 patent recites: “A method for analyzing a nucleic acid sample obtained from an individual.”

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212. By no later than May 8, 2012, the Accuracy Program at Personalis included methods for analyzing a nucleic acid sample obtained from an individual. Conception of the preamble is reflected by, for example, Slide 5 of my May 8, 2012 CEO Overview Board of Director Presentation, which is entitled an “Overview of Personalis Accuracy Program,” and reproduced below with highlighting:

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>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 Prioritize solutions Bio-informatic approaches Laboratory approaches Content approaches	<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 New Personalis alg's 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	<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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Ex2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (highlighting added).

213. As shown in Slide 5, the Accuracy Program involved “analysis” of nucleic acid samples by “methods” that included “whole genome analysis.” The

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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. Our Accuracy Program involved nucleic acid samples that would be sequenced by “whole genome sequencing”, supplemented by custom and/or semi-custom assays based on capture probe pullouts, and validated by, for example, “Sanger validation.” *See* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5.

214. Slide 13 of the same May 8, 2012 presentation provides additional details of the Accuracy Program, which included “receiv[ing]” and “de-identify[ing] samples” from our customers for analysis:

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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

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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 13.

215. Work on the Accuracy Program from January 2012 that led up to the May 8, 2012 disclosure of our invention at the Board of Directors meeting provides additional evidence of conception of the preamble. For example, my January 5, 2012 presentation at Slide 2 discusses taking responsibility for a customer's nucleic acid sample for analysis, and Slide 11 discusses several nucleic acid sample sources from "blood, saliva, tissue, [and] cell culture." See EX2046, January 5, 2012 Accuracy Framework PowerPoint. In addition, my April 2, 2012 email to Chrisitan Haudenschild and other Personalis employees discussed laboratory plans to include

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analysis of “multiple assays from the same sample” of a customer. *See* EX2036 (April 2, 2012 email to Christian Haudenschild and other Personalis employees).

216. Based on at least the foregoing, my co-inventors and I had conceived of the preamble recited by claim 1 by no later than May 8, 2012

b. ‘394 Patent: Claim 1 – limitations 1(a)-(b)

217. Limitations 1(a)-(b) of claim 1 of the ‘033 patent recite: “(a) generating a first subset of nucleic acid molecules from a first nucleic acid sample obtained from said individual; (b) conducting a first sequencing assay on said first subset of nucleic acid molecules to yield a first result comprising a first nucleic acid sequence wherein said first sequencing assay comprises whole genome sequencing.”

218. By no later than May 8, 2012, the Accuracy Program at Personalis included methods for generating a subset of nucleic acid molecules from a nucleic acid sample obtained from an individual and conducting a first sequencing assay on said first subset of nucleic acid molecules to yield a first result comprising a first nucleic acid sequence wherein said first sequencing assay comprises whole genome sequencing. Conception of these limitations is reflected by, for example, Slide 5 of my May 8, 2012 CEO Overview Board of Director Presentation, which is entitled an “Overview of Personalis Accuracy Program,” and reproduced below with highlighting:

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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> <u>WGS + exome</u> 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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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (highlighting added).

219. As shown in 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. Our Accuracy Program involved nucleic acid samples that would be sequenced by “whole genome sequencing”, supplemented by custom and/or semi-custom assays based on capture probe pullouts. The whole genome sequencing is a first sequencing assay conducted on a

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first sample from a customer, and that sample includes a first subset of nucleic acid molecules. The result of whole genome sequencing is the sequence of the first nucleic acid sample. *See* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5.

220. Slide 13 of the same May 8, 2012 presentation provides additional details of the Accuracy Program, which included “receiv[ing]” and “de-identify[ing] samples” from our customers for analysis:

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

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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 13.

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221. Work on the Accuracy Program from January 2012 that led up to the May 8, 2012 disclosure of our invention at the Board of Directors meeting provides additional evidence of conception of limitations 1(a)-(b). For example, my January 5, 2012 presentation at Slide 2 discusses taking responsibility for a customer's nucleic acid sample for analysis, and Slide 11 discusses several nucleic acid sample sources from "blood, saliva, tissue, [and] cell culture." *See* EX2046, January 5, 2012 Accuracy Framework PowerPoint. My January 13, 2012 presentation at Slide 1 discusses "generic genome-scale assays which can be applied to any sample without prior knowledge of the sample" such as "whole genome plus" and Slide 2 discusses "whole genome sequence." *See* EX2109. In addition, my April 2, 2012 email to Chrisitan Haudenschild and other Personalis employees discussed laboratory plans to include analysis of "multiple assays from the same sample" of a customer that included "both whole genome and deeper sequencing of some regions selected by pull out." *See* EX2036 (April 2, 2012 email to Christian Haudenschild and other Personalis employees). We also held several meetings on, for example, May 4 and 5, 2012 to further develop the Accuracy Program leading up to the May 8, 2012 Board of Directors meeting. *See, e.g.,* EX2038, EX2040, EX2039.

222. Based on at least the foregoing, my co-inventors and I had conceived of the limitations 1(a)-(b) by no later than May 8, 2012.

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c. ‘394 Patent: Claim 1 – limitation 1(c)

223. Limitation 1(c) of claim 1 of the ‘394 patent recites: “[i]² generating a second subset of nucleic acid molecules from a second nucleic acid sample of said individual by contacting said second nucleic acid sample with a plurality of capture probes, [ii] wherein said plurality of capture probes hybridize to one or more polymorphisms which are based on or extracted from one or more databases of polymorphisms, observed in a population of one or more samples, or a combination thereof, wherein said first sample or said second sample is obtained from said subject at a first time point.”

224. By no later than May 8, 2012, the Accuracy Program at Personalis included [i] generating a second subset of nucleic acid molecules from a second nucleic acid sample of said individual by contacting said second nucleic acid sample with a plurality of capture probes, [ii] wherein said plurality of capture probes hybridize to one or more polymorphisms which are based on or extracted from one or more databases of polymorphisms, observed in a population of one or more samples, or a combination thereof, wherein said first sample or said second sample is obtained from said subject at a first time point.

² Bracketed roman numerals, e.g. “[i]” and “[ii]”, have been added to limitation 1(a) to organize the discussion of each portion of this limitation.

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225. First I address limitation 1(c)(ii), then I address limitation 1(c)(i).

i. Limitation 1(c)(ii)

226. Conception of limitation 1(c)(ii) is reflected by, for example, Slide 5 of my May 8, 2012 CEO Overview Board of Director Presentation which is entitled an “Overview of Personalis Accuracy Program,” and reproduced below with highlighting:

Overview of Personalis Accuracy Program

Characterize errors

Analysis

Rates by variant type & Q-score

Underlying mechanisms

Medical interpretation impact

Regulatory impact

Methods

Comparison with literature

Studies on limited regions

Whole genome analysis:

- Single genome metrics
- Same person twice
- Family inheritance (MIE)
- Platform comparison
- Arrays
- ILMN / CGI / Ion T...
- Sanger capillary

Prioritize solutions

Bio-informatic approaches

Laboratory approaches

Content approaches

Informatic Solutions

Advances in 3rd party alg's

Aligner for > 200bp reads

New versions, current alg's

Other alg's (e.g. lobSTR)

Advances in our alg's:

SV's : Zygosity, accuracy

Combine SV's & SNP's

Broader use of Breakseq

New Personalis alg's

Alignment degeneracy

Genome-aware alignment

VNTR-specific

Advances in reference

Ethnic major-allele ref's

Iterative

Admixed

InDel's / SV's

Flag or Filter Out

For problems not yet solved

Lab, Content Solutions

Combine technologies

WGS + exome

Longer reads and/or inserts

Multi-vendor

Arrays (genotypes & SV's)

Electrophoretic sizing

Sanger validation

Content-based semi-custom

Array (genotypes & SV's)

Pullout

Custom sample preps

Problematic motifs

Degenerate regions

Phasing

Content

Gold standard genomes

Known healthy genomes

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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (highlighting added).

227. As shown in Slide 5, the Accuracy Program involved the use of “content-based semi-custom” capture probes to “pullout” genotypes and structural

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variants. Within Personalis, we used the term “pullout” to refer to a panel of capture probes conjoined to streptavidin-coated magnetic beads that would “pullout” target DNA via solution-phase hybridization and/or an array of capture probes. We used the terms “pullout,” “pulldown,” and “pull down” interchangeably within Personalis for this capture probe technology, as did others in the field. At least Mark Pratt and I were aware that custom and semi-custom capture probes could be purchased via Agilent (their “SureSelect” line of capture probes), Illumina (their “TruSeq” capture probes), and Roche (their “Nimblegen” capture probes). Members of the Personalis team were experienced in their use, and were also aware of the commercial release of a “cancer-gene pullout panel” of capture probes identified on Slide 4 of my May 8, 2012 presentation:

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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

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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 4 (highlighting added).

228. Further, Slide 5 of my May 8, 2012 CEO Overview Board of Director Presentation includes identifying interpretable variants that were identified by the “analysis” of “whole genome sequencing,” which included identifying “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s” (insertions/deletions). *See* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (reproduced above with highlighting). Each of

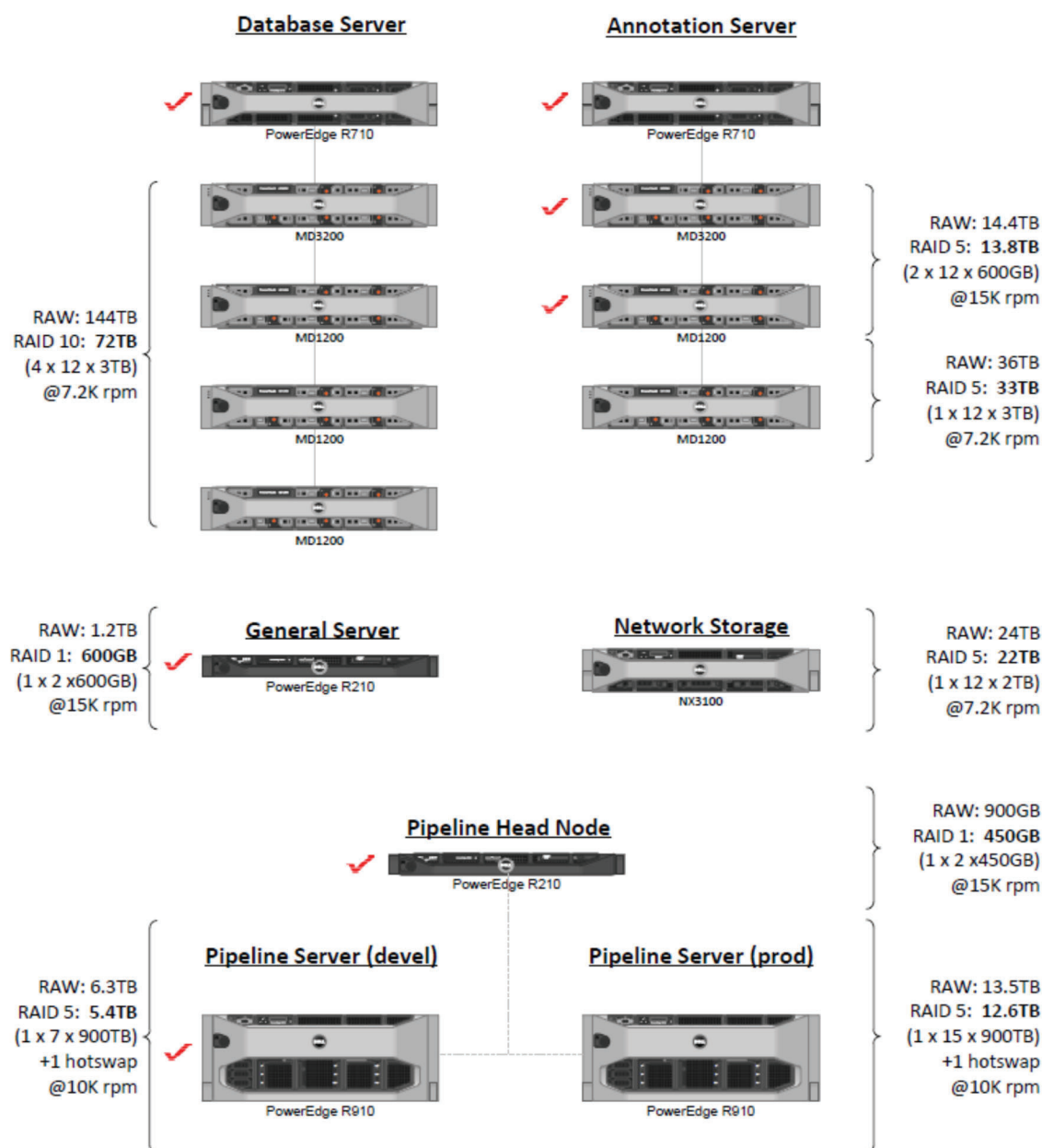
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the “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s” (insertions/deletions) are a type of polymorphism.

229. The capture probes were designed to “pullout” “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s” (insertions/deletions) polymorphisms encoding genes with known biomedically interpretable variants that were identified by the “analysis” of the “whole genome analysis” within the Accuracy Program. *See* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (reproduced above with highlighting). 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” (whole genome sequencing) and validation by, for example, “Sanger validation” sequencing.

230. The genotypes and structural variants would be stored in databases on, for example, the Personalis servers. Personalis had purchased and installed computer servers and processors to handle the genomic data generated by the WGS and validation sequencing called for by the Accuracy Program. For example, EX2044 is a true and correct copy of an email and attachment sent from Hugo Lam to Richard Chen and me on April 24, 2012 providing a pdf attachment depicting “our servers configuration.” *See* EX2044, April 24, 2012 email and attachment from Hugo Lam to John West and Richard Chen. The attachment is reproduced below:

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See EX2044, April 24, 2012 email attachment from Hugo Lam to John West and Richard Chen.

231. In August 2011, following a competitive requisition process, Personalis exclusively licensed a set of genetic databases from Stanford University. These included the PharmGKB database of genetic variants known to affect drug

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metabolism. It also included the MendelDB database, of genetic variants known to cause inherited genetic diseases (known as Mendelian diseases). Curation of that database had begun at Stanford and Personalis staff continued that curation after they joined Personalis from Stanford in 2011. It also included the Regulome database, of genetic variants in regulatory regions of genes. It also included the VariMed database of relationships between genetic variants and biomedical phenotypes, curated from the scientific literature. When Personalis licensed the Varimed database it already included tens of thousands of genetic variants. In 2011, Personalis took over and expanded the funding for this outsourced curation, growing the database still further. These databases, and our ongoing curation of the MendelDB and Varimed databases, were described in the R&D update of Rich Chen, our CSO, at the May 8th, 2012 meeting of our Board of Directors. *See* EX2042 at Slides 29-32. With the exception of Regulome, these databases each included a plurality of polymorphisms in sequences encoding genes with known biomedically interpretable variants. Regulome primarily included polymorphisms in regulatory regions, which are still biomedically important but generally outside the coding regions of genes.

232. The database of polymorphisms stored on the Personalis servers could also include polymorphisms observed in a population of one or more samples. *See, e.g.,* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slides

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5 and 13 (reproduced above with highlighting). These included genome datasets we were allowed to use by collaborators such as the West family genomes, the 1,000 Genomes project, and genomes made public by Illumina, Complete Genomics and the Broad Institute. These included polymorphisms in sequences encoding genes with known biomedically interpretable variants, such as the variants in the Factor V gene of my genome, described above. These genome data sets could also include genomes we paid to have sequenced, for example from the CEPH 1463 family of 17 individuals (payment for this was approved by the Personalis Board at its May 8, 2012 meeting). *See* EX2043 at 2. In some cases it could also include genome data from the sequencing of diagnostic patients and from our other customers. In fact, we had already been storing genotype and structural variant information in databases on the Personalis servers by no later than May 8, 2012.

ii. Limitation 1(c)(i)

233. By no later than May 8, 2012, the Accuracy Program involved contacting a second subset of nucleic acid molecules from a second nucleic acid sample with a plurality of capture probes. By May 8, 2012, I was personally already very familiar with the idea of repeated blood testing due to a genetic condition. As described above, starting with my pulmonary embolism in December 2003, I had blood tests about monthly for over 8 years to confirm or adjust the dose of the drug warfarin that I had been prescribed. Although the condition causing this (a Factor

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V Leiden mutation in my genome) was genetic, the monthly tests I had to undergo were not genetic. Still, the idea of monthly blood testing related to a genetic condition was very personal to me.

234. I was also familiar with repeated blood tests for other conditions. This included the monthly “AlloMap” test developed and commercialized by XDX, Inc., for heart transplant patients, to check for transplant rejection. FDA approved in 2006, it used real-time PCR of a group of genes from a blood sample. XDX, Inc is now known as CareDx (Nasdaq : CDNA). Although this test did not use DNA sequencing, it was based on nucleic acids (RNA) extracted from a body fluid of the patient on an ongoing monthly basis.

235. I was also familiar with work by Stanford professor Steve Quake, who used whole genome sequencing of cell free DNA from the blood of transplant patients to look for genetic variants of a heart transplant donor in the heart transplant recipient, as an indication of transplant rejection. This was very inefficient because it did not use any type of hybrid capture to focus on variants.

236. It is fair to say that, by early 2012, the field had many efforts to test for various medical conditions based on blood samples taken periodically from a patient, but they were all inefficient because none used hybrid capture by capture probes, and in particular none used capture probes targeted to genetic variants which were specific to an individual person.

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237. In my presentation from January 6, 2012, described above, I had already described sequencing an individual “twice (or more?)” or “multiple times” using a “Whole Genome Plus” or “Exome Plus” assay, to confirm results from an initial sample.

238. In March 2012, we made a key connection. Personalis employee and ‘033 patent co-inventor Hugo Lam was co-author on a publication (EX2030) which described the analysis of a patient at 20 time points over 400 days, during which time the patient suffered two viral infections and the onset of Type 2 diabetes. The patient was monitored using blood tests at each time point, using untargeted RNAseq, and took action based on the results that improved their clinical trajectory. This untargeted RNAseq revealed changes in both gene expression and also changes in the sequence of the RNA (RNA editing). This was very inefficient because the RNAseq was untargeted, but I realized that the technology being developed at Personalis, including targeted capture of genetic variants specific to an individual, could be an enormous improvement.

239. Slide 3 of my May 8, 2012 CEO Board presentation described the March 2012 publication as “seminal” because it sparked our invention connecting the frequent genetic analysis from blood with our development of targeted capture based on the genetic variants of an individual person. I highlighted for our Board of Directors

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“ongoing clinical use of genome-scale sequencing” and “not just a genome once in your life”:

Publications & Upcoming Presentations

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

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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 3 (highlighting added).

240. Slide 3 of my presentation highlighted an important business aspect of the Accuracy Program. Earlier work on whole genome sequencing of individuals, such as the West family genomes, was only done at one time point. That meant that there were no repeat customers, which would have been a financial problem for a company offering the service. However, a program that involved “ongoing clinical

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use of genome-scale sequencing” would be used more than just “once in your [customer’s] lifetime” to provide a recurring revenue stream from each customer. The Accuracy Program involved initial “WGS” (whole genome sequencing) of a customer’s biological sample, and further supplementing that with additional sequencing of subsequently obtained biological samples from the customer to provide ongoing clinical use of their genomic information.

241. 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 algorithms used to analyze the data generated by “WGS” (whole genome sequencing). *See, e.g.*, Slide 5 of my May 8, 2012 CEO Board presentation, reproduced above.

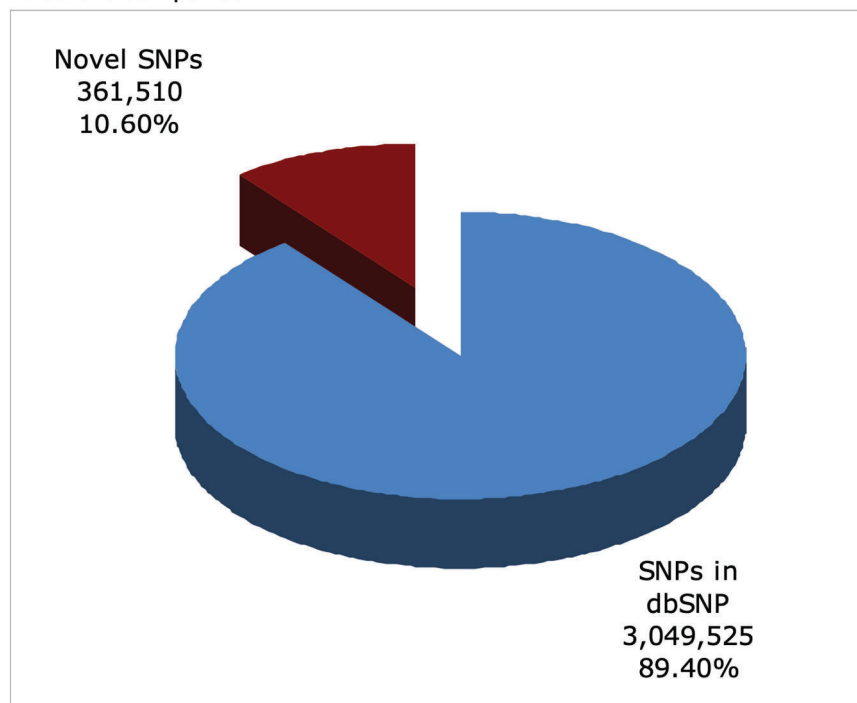
242. We envisioned performing the pullout sequencing analysis “two or more times.” For example, it would be done, e.g., monthly to check for organ transplant rejection. It would be done periodically, e.g., to test for changes in a patient’s cancer. It would be done 20 times over a 400 day period as had been used (but without targeted capture) in the paper published in March 2012 by Hugo Lam, Mike Snyder and others.

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243. The custom sample prep included focusing on genetic variants observed in just the patient. As I listed on slide 5 of my May 8, 2012 CEO update to the Personalis Board, a custom sample prep would include, e.g., problematic motifs, regions with alignment degeneracy, or variants to be phased (e.g. to determine whether they form a compound heterozygous combination, as described above). The custom sample prep would also include, e.g., genetic variants observed in one or more other individuals relevant to the condition of the specific patient, such as a parent, or such as the donor of the transplanted organ received by the patient.

244. The semi-custom sample prep would be part custom (as just described) and part based on genetic variants from a database. There would frequently be an overlap in the genetic variants observed in an individual and those in a database. As an example, Illumina's original (January 2010) report on my genome sequence identified about 3.4 million SNPs, of which just 361,510 (11%) were "novel", i.e. not already known in the dbSNP database. Thus 89% were both observed in my genome and included in the dbSNP database (version 129, which had 13 million known SNPs in it). The following is a screen capture from that January 2010 Illumina report on my genome, showing this distribution:

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EX2114 at 4.

245. Work on the Accuracy Program from January 2012 that led up to the May 8, 2012 disclosure of our invention at the Board of Directors meeting provides additional evidence of conception of the limitation 1(c)(i)-(ii). For example, my January 13, 2012 presentation at Slide 2 discusses using “oligo-based pullout” with “long-fragment pullout to resolve repeats, particularly in approx. 3,000 genes with alignment problems due to gene-family homologies,” which is a reference to capture probes that hybridize to polymorphisms extracted from a database of polymorphisms. *See* EX2109. In addition, my April 2, 2012 email to Chrisitan Haudenschild and other Personalis employees discussed laboratory plans to include analysis of “multiple assays from the same sample” of a customer that included “both

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whole genome and deeper sequencing of some regions selected by pull out. Mary Pratt is working on lists of regions we may want to pull out.” *See* EX2036 (April 2, 2012 email to Christian Haudenschild and other Personalis employees). We also held several meetings on, for example, May 4 and 5, 2012 to further develop the Accuracy Program leading up to the May 8, 2012 Board of Directors meeting. *See, e.g.,* EX2038, EX2040, EX2039.

246. Based on at least the foregoing, my co-inventors and I had conceived of limitation 1(c) by no later than May 8, 2012.

d. ‘394 Patent: Claim 1 – limitation 1(d)

247. Limitation 1(d) of claim 1 of the ‘394 patent recites: “conducting a second sequencing assay on said second subset of nucleic acid molecules to yield a second result comprising a second nucleic acid sequence.”

248. By no later than May 8, 2012, the Accuracy Program at Personalis included conducting a second sequencing assay on said second subset of nucleic acid molecules to yield a second result comprising a second nucleic acid sequence. As described above, by January of 2012 our Accuracy Program involved supplementing a base whole genome or exome with hybrid capture probe sets to generate additional DNA sequencing reads which:

- (i) filled in some of the systematic gaps in sequencing coverage
- (ii) Included longer molecules to address alignment problems and

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

These were the “Content-based” “Pullout” assay elements referred to in Slide 5 of my CEO Update to the Personalis Board of Directors on May 8th 2012, copied in below:

Overview of Personalis Accuracy Program

Characterize errors <u>Analysis</u> Rates by variant type & Qscore Underlying mechanisms Medical interpretation impact Regulatory impact <u>Methods</u> Comparison with literature Studies on limited regions Whole genome analysis: Single genome metrics Same person twice Family inheritance (MIE) Platform comparison Arrays ILMN / CGI / Ion T... Sanger capillary <u>Prioritize solutions</u> Bio-informatic approaches Laboratory approaches Content approaches	Informatic Solutions <u>Advances in 3^d 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 semicustom</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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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (highlighting added). The additional sequencing reads are a subsequent (e.g., second) sequencing assay conducted on a subsequent (e.g., second) subset of nucleic

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acid molecules and the results of the subsequent sequencing assay is the sequence of the subsequent subset of nucleic acid molecules.

249. Work on the Accuracy Program from January 2012 that led up to the May 8, 2012 disclosure of our invention at the Board of Directors meeting provides additional evidence of conception of the limitation 1(d). For example, my January 13, 2012 presentation at Slide 3 discusses “exon re-sequencing by pullout from customer sample (may be provided by customer)” and “additional re-sequencing by pullout, to capture regions outside the exons which are in VariMed, Regulome, lincRNA catalog & possibly others.” *See* EX2109. In addition, my April 2, 2012 email to Chrisitan Haudenschild and other Personalis employees discussed laboratory plans to include analysis of “multiple assays from the same sample” of a customer that included “both whole genome and deeper sequencing of some regions selected by pull out. Mary Pratt is working on lists of regions we may want to pull out.” *See* EX2036 (April 2, 2012 email to Christian Haudenschild and other Personalis employees). We also held several meetings on, for example, May 4 and 5, 2012 to further develop the Accuracy Program leading up to the May 8, 2012 Board of Directors meeting. *See, e.g.,* EX2038, EX2040, EX2039.

250. Based on at least the foregoing, my co-inventors and I had conceived of limitation 1(d) by no later than May 8, 2012.

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e. '394 Patent: Claim 1 – limitations 1(e)-(f)

251. Limitations 1(e)-(f) of claim 1 of the '394 patent recite: “(e) using said plurality of capture probes to generate an additional subset of nucleic acid molecules from an additional nucleic acid sample isolated from an additional sample obtained from said subject at an additional time point different from said first time point; (f) conducting a third sequencing assay on said additional subset of nucleic acid molecules from said additional nucleic acid sample to yield a third result comprising a third nucleic acid sequence.”

252. By no later than May 8, 2012, the Accuracy Program at Personalis included using the plurality of capture probes to generate an additional subset of nucleic acid molecules from an additional nucleic acid sample isolated from an additional sample obtained from said subject at an additional time point different from said first time point. For example, as discussed above with respect to limitation 1(c), the Accuracy Program included using capture probes to generate an additional subset of nucleic acid molecules from an additional nucleic acid sample. The additional plasma sample would be obtained at a different (e.g., later) time point than the first sample to provide “ongoing clinical use of genome-scale sequencing.” *See* Slide 3 of my May 8, 2012 CEO Board presentation, EX2112.

253. For reasons discussed above with respect to limitation 1(d), the Accuracy Program at Personalis included conducting a sequencing assay on said a

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third subset of nucleic acid molecules to yield a third result comprising a third nucleic acid sequence. As described above, by January of 2012 our Accuracy Program involved supplementing a base whole genome or exome with hybrid capture probe sets to generate additional DNA sequencing reads which:

- (i) filled in some of the systematic gaps in sequencing coverage
- (ii) Included longer molecules to address alignment problems and
- (iii) Supplemented an exome (which focuses on the coding regions of genes) with additional content from outside the coding regions of the genes

These were the “Content-based” “Pullout” assay elements referred to in Slide 5 of my CEO Update to the Personalis Board of Directors on May 8th 2012. The additional sequencing reads are a subsequent (e.g., third) sequencing assay conducted on a subsequent (e.g., third) subset of nucleic acid molecules that are pulled out by the capture probes in a subsequent (e.g., third) assay and the results of the subsequent sequencing assay is the sequence of the subsequent subset of nucleic acid molecules.

254. Work on the Accuracy Program from January 2012 that led up to the May 8, 2012 disclosure of our invention at the Board of Directors meeting provides additional evidence of conception of the limitations 1(e)-(f). For example, my January 13, 2012 presentation at Slide 3 discusses “exon re-sequencing by pullout from customer sample (may be provided by customer)” and “additional re-

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sequencing by pullout, to capture regions outside the exons which are in VariMed, Regulome, lincRNA catalog & possibly others.” *See* EX2109. In addition, my April 2, 2012 email to Chrisitan Haudenschild and other Personalis employees discussed laboratory plans to include analysis of “multiple assays from the same sample” of a customer that included “both whole genome and deeper sequencing of some regions selected by pull out. Mary Pratt is working on lists of regions we may want to pull out.”. *See* EX2036 (April 2, 2012 email to Christian Haudenschild and other Personalis employees). We also held several meetings on, for example, May 4 and 5, 2012 to further develop the Accuracy Program leading up to the May 8, 2012 Board of Directors meeting. *See, e.g.,* EX2038, EX2040, EX2039.

255. Based on at least the foregoing, my co-inventors and I had conceived of limitations 1(e)-(f) by no later than May 8, 2012.

f. ‘394 Patent: Claim 1 – limitation 1(g)

256. Limitation 1(g) of claim 1 of the ‘394 patent recites: “generating a biomedical report that includes biomedical information of said subject, which biomedical information identifies the presence or absence of said one or more polymorphisms identified by said second result or said third result.”

257. By no later than May 8, 2012, the Accuracy Program at Personalis included generating a biomedical report that includes biomedical information of said subject, which biomedical information identifies the presence or absence of said one

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or more polymorphisms identified by said second result or said third result. Conception of this limitation is reflected by, for example, Slide 5 of my May 8, 2012 CEO Overview Board of Director Presentation, which includes identifying biomedical information regarding interpretable variants that were identified by the “analysis” of “whole genome sequencing,” which included identifying “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s” (insertions/deletions) having “medical interpretation impact.” *See* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5. For our “analysis” to have “medical interpretation impact,” we intended to provide a report to the customer to interpret the medically impactful “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s” (insertions/deletions) identified by the Accuracy Program.

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Overview of Personalis Accuracy Program

Characterize errors Analysis Rates by variant type & Q-score Underlying mechanisms Medical interpretation impact Regulatory impact Methods Comparison with literature Studies on limited regions Whole genome analysis: Single genome metrics Same person twice Family inheritance (MIE) Platform comparison Arrays ILMN / CGI / Ion T... Sanger capillary Prioritize solutions Bio-informatic approaches Laboratory approaches Content approaches	Informatic Solutions Advances in 3rd party alg's Aligner for > 200bp reads New versions, current alg's Other alg's (e.g. lobSTR) Advances in our alg's: SV's : Zygosity, accuracy Combine SV's & SNP's Broader use of Breakseq New Personalis alg's Alignment degeneracy Genome-aware alignment VNTR-specific Advances in reference Ethnic major-allele ref's Iterative Admixed InDel's / SV's Flag or Filter Out For problems not yet solved	Lab, Content Solutions Combine technologies WGS + exome Longer reads and/or inserts Multi-vendor Arrays (genotypes & SV's) Electrophoretic sizing Sanger validation Content-based semi-custom Array (genotypes & SV's) Pullout Custom sample preps Problematic motifs Degenerate regions Phasing Content Gold standard genomes Known healthy genomes
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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (highlighting added).

258. Slide 13 of the same May 8, 2012 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 our customer so that Personalis would provide “value-added” biomedical information about the customer’s genome.

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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

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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 13.

259. Also at the May 8th 2012 meeting of our Board of Directors, our CSO Richard Chen provided an R&D update presentation (EX2042) focused on our product development. Slide 10 included some mock ups of reports we planned to generate for customers. It included a "General Variant Report" described as a "Very large table of every variant call":

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	A	B	C	D	E	F	G	H	I	J	K	L
1	General Variant Report											
2	Very large table of every variant call intersected with important public databases											
3												
4	SNPs											
5	ID	Chr	Position	Reference	Variant	Context (ANNOVAR)	Type (ANNOVAR)	Gene (Refseq) (ANNOVAR)	Gene (Ensembl) (ANNOVAR)	Gene (UCSC) (ANNOVAR)	Frequency (Pop)	Frequency (Ethnicity)
6	[dbSNP rsid, evsid, internal ID - will be a hierarchy of preferred IDs to use]	[1, 2, 3, ...]	[#]	[A, C, G, T]	[T, G, C, A]	[intronic, exonic, 3'-UTR, 5'-UTR, downstream, intergenic]	[splicing, synonymous missense, nonsynonymous missense, TFBS, eQTL, hypersensitivity site, nonstop]	[ID(x) & relative location]	[ID(x) & relative location]	[ID(x) & relative location]	[dbamp, 1kg, CG, EVS, etc]	
7												
8												
9	Indels											
10	ID	Chr	Position	Reference	Variant	Context (ANNOVAR)	Type (ANNOVAR)	Gene (Refseq) (ANNOVAR)	Gene (Ensembl) (ANNOVAR)	Gene (UCSC) (ANNOVAR)	Frequency (Pop)	Frequency (Ethnicity)
11	[dbSNP rsid, evsid, internal ID - will be a hierarchy of preferred IDs to use]	[1, 2, 3, ...]	[#]	[C, AAG, etc.]	[CCT, G, etc.]	[intronic, exonic, 3'-UTR, 5'-UTR, downstream, intergenic]	[splicing, synonymous missense, nonsynonymous missense, TFBS, eQTL, hypersensitivity site, nonstop]	[ID(x) & relative location]	[ID(x) & relative location]	[ID(x) & relative location]	[dbamp, 1kg, CG, EVS, etc]	
12												
13												
14	SV											
15	ID	Junction 1	Junction2	Type	Size	Breakpoint Context 1	Breakpoint Context 2	Gene 1 (Refseq)	Gene 1 (Ensembl)	Gene 1 (UCSC)	Gene 2 (Refseq)	Gene 2 (Ensembl)
16	[dbVar, DGV, CHOP, etc]	[chr:pos]	[chr:pos]	[Translocation, Insertion, Deletion, Inversion]	[#]	[intronic, exonic, 3'-UTR, 5'-UTR, downstream]	[intronic, exonic, 3'-UTR, 5'-UTR, downstream]	[ID(x) & relative location]	[ID(x) & relative location]	[ID(x) & relative location]	[ID(x) & relative location]	[ID(x) & relative location]

See EX2042 at Slide 25. Variants included in this table were those detected in the sample and those not listed were those not detected.

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260. Based on at least the foregoing, my co-inventors and I had conceived of limitation 1(g) by no later than May 8, 2012. Accordingly, my co-inventors and I had conceived of claim 1 of the ‘394 patent by no later than May 8, 2012.

2. ‘394 Patent Claim 2

261. Claim 2 of the ‘394 patent recites:

2. The method of claim 1, wherein said biomedical information of said subject is predictive, prognostic, or diagnostic of one or more biomedical features selected from the group consisting of disease state, efficacy of a drug therapy, prediction of optimal drug dosage, recommendation of one or more therapies, and recommendation of a course of treatment of a disease.

262. By no later than May 8, 2012, the Accuracy Program at Personalis included generating a biomedical report that includes biomedical information of said subject is predictive, prognostic, or diagnostic of one or more biomedical features selected from the group consisting of disease state, efficacy of a drug therapy, prediction of optimal drug dosage, recommendation of one or more therapies, and recommendation of a course of treatment of a disease. Conception of this claim is reflected by, for example the above discussion of limitation 1(g). For example, as discussed above for limitation 1(g), Slide 5 of my May 8, 2012 CEO Board presentation includes identifying biomedical information regarding interpretable variants that were identified by the “analysis” of “whole genome sequencing,” which included identifying “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s” (insertions/deletions) having “medical interpretation impact.” *See* EX2112, May 8, 2012 CEO Overview Board of Director

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Presentation at Slide 5. For our “analysis” to have “medical interpretation impact,” we 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.

263. Based on at least the foregoing, my co-inventors and I had conceived of claim 2 by no later than May 8, 2012.

3. ‘394 Patent Claim 3

264. Claim 3 of the ‘394 patent recites:

3. The method of claim 1, wherein said one or more polymorphisms comprise one or more insertions, deletions, structural variant junctions, variable length tandem repeats, single nucleotide mutations, or a combination thereof.

265. By no later than May 8, 2012, the Accuracy Program at Personalis included one or more 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, as discussed above for claim 1, Slide 5 of my May 8, 2012 CEO Overview Board of Director Presentation,

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includes identifying biomedically interpretable variants that were identified by the “analysis” of “whole genome sequencing,” which included identifying “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “InDel’s” (insertions/deletions) and “VNTRs” (Variable Number Tandem Repeats, also referred to as “Variable Length Tandem Repeats” or just “Short Tandem Repeats” (STRs)) having “medical interpretation impact.” Each of the “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “InDel’s” (insertions/deletions) and “VNTR’s” are a type of polymorphism.

266. Based on at least the foregoing, my co-inventors and I had conceived of claim 3 by no later than May 8, 2012.

4. ‘394 Patent Claim 4

267. Claim 4 of the ‘394 patent recites:

4. The method of claim 1, wherein said one or more polymorphisms are in a set of genes with known biomedically interpretable variants.

268. By no later than May 8, 2012, the Accuracy Program at Personalis included one or more polymorphisms that are in a set of genes with known biomedically interpretable variants. Conception of claim 4 is reflected by, for example, Slide 5 of my May 8, 2012 CEO Overview Board of Director Presentation, which includes identifying biomedically interpretable variants that were identified by the “analysis” of “whole genome sequencing,” which included identifying

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“SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s” (insertions/deletions) having “medical interpretation impact.” *See* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (reproduced above with highlighting). Each of the “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s” (insertions/deletions) are a type of polymorphism. For our “analysis” to have “medical interpretation impact,” we 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).

269. The capture probes were designed to “pullout” “SV’s” (structural variants), “SNP’s” (single nucleotide polymorphisms), “allele[s]”, “InDel’s” (insertions/deletions) polymorphisms encoding genes with known biomedically interpretable variants that were identified by the “analysis” of the “whole genome analysis” within the Accuracy Program. *See* EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5. As discussed above, the purpose of the capture probes was to “pullout” those biomedically interpretable variants to provide a “medical interpretation impact” for each of our customers.

270. Work on the Accuracy Program from January 2012 that led up to the May 8, 2012 disclosure of our invention at the Board of Directors meeting provides

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additional evidence of conception of claim 4. For example, my January 13, 2012 presentation at Slide 2 discusses using “oligo-based pullout” with “long-fragment pullout to resolve repeats, particularly in approx. 3,000 genes with alignment problems due to gene-family homologies,” which is a reference to capture probes that hybridize to polymorphisms in sequences encoding genes with known biomedically interpretable variants. *See* EX2109. In addition, my April 2, 2012 email to Chrisitan Haudenschild and other Personalis employees discussed laboratory plans to include “both whole genome and deeper sequencing of some regions selected by pull out. Mary Pratt is working on lists of regions we may want to pull out.” *See* EX2036 (April 2, 2012 email to Christian Haudenschild and other Personalis employees). *See, e.g.,* EX2038, EX2040, EX2039.

271. Based on at least the foregoing, my co-inventors and I had conceived of claim 4 by no later than May 8, 2012.

5. ‘394 Patent Claim 5

272. Claim 5 of the ‘394 patent recites:

5. The method of claim 4, wherein said set of genes with known biomedically interpretable variants comprise one or more genes or variants associated with cancer.

273. By no later than May 8, 2012, the Accuracy Program at Personalis included a set of genes with known biomedically interpretable variants that comprise one or more genes or variants associated with cancer. Conception of this claim is

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reflected by, for example, Slide 4 of my May 8, 2012 CEO Overview Board of Director Presentation, which described the use of a “cancer-gene pullout panel” of capture probes. The “cancer-gene pullout panel” would include sequences encoding genes associated with cancer.

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

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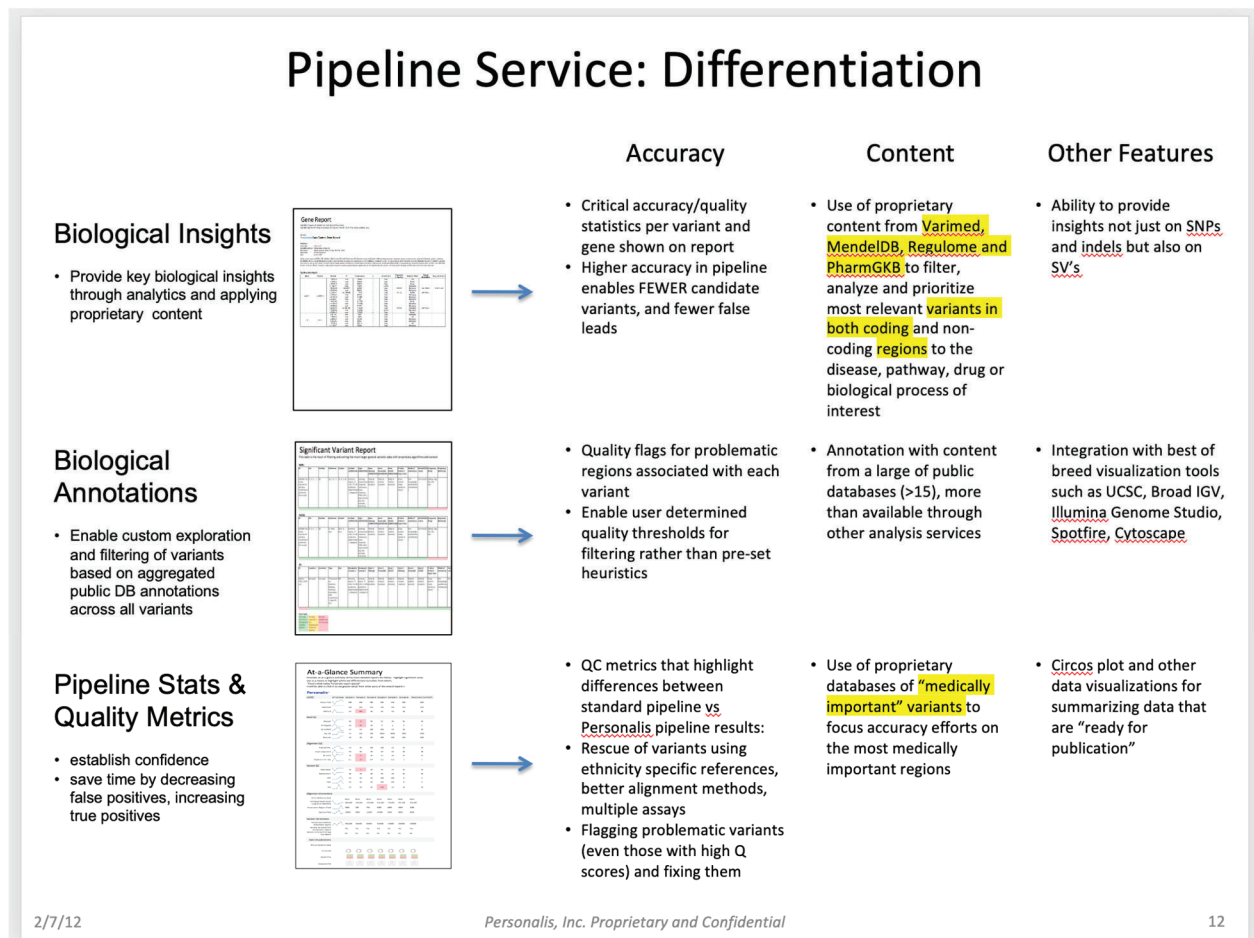
4

EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 4 (highlighting added).

274. In addition, the PharmGKB, MendelDB and Varimed databases we licensed from Stanford and continued to extend all included genes associated with cancer. Also at the May 8th 2012 Board Personalis meeting, our CSO Richard Chen

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provided an R&D update focused on our product development. Slide 12 from his presentation is copied below, with highlighted reference to these four databases of “medically important variants”:



See EX2042 at Slide 12. On slides 29 - 32 of that presentation, he went into detail on our ongoing development of those databases. On slide 25, he showed an example of what a Personalis report would look like based on our invention at the time, and I have copied in a part here:

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Genome Results Overview

ID: John Smith
Ethnicity: Caucasian
Eye Color: Brown

Overall Risk by System

System	# Diseases with Overall Composite Genetic Risk > 5%	# Diseases with Above Average Genetic Risk Compared to Population	Ref
Cardiovascular	3	10	p 3
Congenital Disease	2	1	p 4
Dermatology	2	3	p 5
Endocrinology	1	2	p 6
ENT	-	-	p 7
Gastrointestinal	2	1	p 8
Gynecologic Disease and Pregnancy	-	-	p 9
Hematology Disease	1	-	p 10
Infectious Disease	-	-	p 11
Musculoskeletal Disease	2	1	p 12
Oncology/Neoplastic Disease	-	-	p 13
Nephrology	-	-	p 14
Neurology	-	-	p 15
Nutritional/Metabolic	1	1	p 16
Ophthalmology	-	-	p 17
Pharmacology	-	-	p 18
Pulmonary	-	-	p 19
Psychiatry	-	-	p 20
Rheumatology	-	-	p 20

See EX2042 at Slide 25. This alphabetized list of many medical conditions includes the entry “Oncology/Neoplastic Disease” showing that cancer was one of the categories of disease for inclusion in the report.

275. Based on at least the foregoing, my co-inventors and I had conceived of claim 5 by no later than May 8, 2012.

6. ‘394 Patent Claim 6

276. Claim 6 of the ‘394 patent recites:

6. The method of claim 1, wherein said first time point and said additional time point are at least 1 week apart, or more.

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277. 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. For example, Slide 3 of my May 8, 2012 CEO Board presentation described a “seminal paper by Mike Snyder & team published in Cell” which supported my idea for the Accuracy Program to include “ongoing clinical use of genome -scale sequencing” and “not just a genome once in your life.”

Publications & Upcoming Presentations

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

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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 3 (highlighting added).

278. The referenced paper by Dr. Snyder was Chen and Snyder et al., “Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes,” Cell, 148:1293-1307 (March 2012), EX2030. The paper reported on a 54-year-old

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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. *Id.* at 3. The assays used at those 20 time points were chosen in part based on analysis of groups of genetic variants detected in his whole genome sequencing data. 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. *See, e.g., id.* at Figure 1(A). At each of the 20 time points, the analysis from the blood included assays on three different components of the blood: plasma, serum and PBMC’s (white blood cells). They used blood plasma for protein assays and PBMC’s for untargeted RNAseq. The RNAseq was used not only to measure changes in genes which were expressed (e.g., changes in genes of the immune system during the infections) but also, by comparison with the original genome sequence, variations in the nucleic acid sequence over time (RNA edits). Those changes in RNA sequences were dynamic, being detected at some points and not others. When they were detected, their allele frequencies were calculated from the data and changes in those were tracked.

279. My co-inventors and I realized that the Accuracy Program could be more efficient than the untargeted RNAseq used in the Snyder paper on PBMC’s by replacing it with a “content-based semi-custom” approach using “pullout” based on

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the plasma portion of a blood sample. *See* Slide 5 of my May 8, 2012 CEO Board Presentation, EX2112. Well before that time we were familiar with the genetic analysis of cell free DNA from blood plasma (for fetal diagnosis, cancer analysis and detection of transplant rejection) but not using hybrid capture probes targeted to the variants of the person, and not from a single individual at multiple time points. Our realization of this possibility to leverage our technology at so many time points was why we described this paper as seminal. The paper did not use or disclose our invention, but it sparked our creativity and that led to the invention. My co-inventors and I realized that the Accuracy Program would benefit from samples being taken at different intervals from our customers, including a sample taken at least 1 week or more after the first sample.

280. Based on at least the foregoing, my co-inventors and I had conceived of claim 6 by no later than May 8, 2012.

7. '394 Patent Claim 7

281. Claim 7 of the '394 patent recites:

7. The method of claim 1, wherein said first time point and said additional time point are at least 1 month apart, or more.

282. 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. For example, as discussed above with respect to claim 6, I was aware of a paper by Dr. Snyder that reported on a 54-year-old man who was whole genome

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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. *See* EX2030 (Chen and Snyder) at 3. 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. *See, e.g., id.* at Figure 1(A). My co-inventors and I realized that the Accuracy Program would benefit from blood plasma samples being taken at different intervals from our customers, including a blood plasma sample taken at least 1 month or more after the first sample.

283. Based on at least the foregoing, my co-inventors and I had conceived of claim 7 by no later than May 8, 2012.

8. ‘394 Patent Claim 8

284. Claim 8 of the ‘394 patent recites:

8. The method of claim 1, wherein said additional time point is later than said first time point.

285. 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 5-7, my co-inventors and I realized that the Accuracy Program would benefit from samples being taken at different intervals from our customers, including a sample taken at least 1 week or more after the first

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sample. Based on at least the foregoing, my co-inventors and I had conceived of claim 8 by no later than May 8, 2012.

9. ‘394 Patent Claim 9

286. Claim 9 of the ‘394 patent recites:

9. The method of claim 1, further comprising comparing said first result and said second result.

287. By no later than May 8, 2012, the Accuracy Program at Personalis included comprising comparing said first result and said second result. For example, As discussed above for limitation 1(c), an important business aspect of the Accuracy Program was to further 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.” EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 3. The ongoing clinical use of the genome-scale sequencing would involve contacting subsequently obtained biological samples 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” (whole genome sequencing). EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5.

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288. As described above, by January of 2012 our Accuracy Program involved supplementing a base whole genome or exome with hybrid capture probe sets to generate additional DNA sequencing reads which:

- (i) filled in some of the systematic gaps in sequencing coverage
- (ii) Included longer molecules to address alignment problems and
- (iii) Supplemented an exome (which focuses on the coding regions of genes) with additional content from outside the coding regions of the genes

These were the “Content-based” “Pullout” assay elements referred to in Slide 5 of my CEO Update to the Personalis Board of Directors on May 8th 2012. The additional sequencing reads are a subsequent sequencing assay, and the results of the subsequent sequencing assay would be compared with the results from the previous sequencing assay(s).

289. Based on at least the foregoing, my co-inventors and I had conceived of claim 9 by no later than May 8, 2012

10. ‘394 Patent Claim 10

290. Claim 10 of the ‘394 patent recites:

10. The method of claim 1, further comprising identifying the presence or absence of said one or more polymorphisms in said second nucleic acid sample.

291. By no later than May 8, 2012, the Accuracy Program at Personalis included identifying the presence or absence of said one or more polymorphisms in

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said second nucleic acid sample. Conception of this claim is reflected by, for example the above discussion of claim 1. For example, as discussed above for claim 1, Slide 5 of my May 8, 2012 CEO Overview Board of Director Presentation, 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 us 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.

292. Also at the May 8th 2012 meeting of our Board of Directors, our CSO Richard Chen provided an R&D update presentation (EX2042) focused on our product development. Slide 10 included some mock ups of reports we planned to generate for customers. It included a “General Variant Report” described as a “Very large table of every variant call”:

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	A	B	C	D	E	F	G	H	I	J	K	L
1	General Variant Report											
2	Very large table of every variant call intersected with important public databases											
3												
4	SNPs											
5	ID	Chr	Position	Reference	Variant	Context (ANNOVAR)	Type (ANNOVAR)	Gene (Refseq) (ANNOVAR)	Gene (Ensembl) (ANNOVAR)	Gene (UCSC) (ANNOVAR)	Frequency (Pop)	Frequency (Ethnicity)
6	[dbSNP rsid, evsid, internal ID - will be a hierarchy of preferred IDs to use]	[1, 2, 3, ...]	[#]	[A, C, G, T]	[T, G, C, A]	[intronic, exonic, 3'-UTR, 5'-UTR, downstream, intergenic]	[splicing, synonymous missense, nonsynonymous missense, TFBS, eQTL, hypersensitivity site, nonstop]	[ID(x) & relative location]	[ID(x) & relative location]	[ID(x) & relative location]	[dbamp, 1kg, CG, EVS, etc]	
7												
8												
9	Indels											
10	ID	Chr	Position	Reference	Variant	Context (ANNOVAR)	Type (ANNOVAR)	Gene (Refseq) (ANNOVAR)	Gene (Ensembl) (ANNOVAR)	Gene (UCSC) (ANNOVAR)	Frequency (Pop)	Frequency (Ethnicity)
11	[dbSNP rsid, evsid, internal ID - will be a hierarchy of preferred IDs to use]	[1, 2, 3, ...]	[#]	[C, AAG, etc.]	[CCT, G, etc.]	[intronic, exonic, 3'-UTR, 5'-UTR, downstream, intergenic]	[splicing, synonymous missense, nonsynonymous missense, TFBS, eQTL, hypersensitivity site, nonstop]	[ID(x) & relative location]	[ID(x) & relative location]	[ID(x) & relative location]	[dbamp, 1kg, CG, EVS, etc]	
12												
13												
14	SV											
15	ID	Junction 1	Junction2	Type	Size	Breakpoint Context 1	Breakpoint Context 2	Gene 1 (Refseq)	Gene 1 (Ensembl)	Gene 1 (UCSC)	Gene 2 (Refseq)	Gene 2 (Ensembl)
16	[dbVar, DGV, CHOP, etc]	[chrpos]	[chrpos]	[Translocation, Insertion, Deletion, Inversion]	[#]	[intronic, exonic, 3'-UTR, 5'-UTR, downstream]	[intronic, exonic, 3'-UTR, 5'-UTR, downstream]	[ID(x) & relative location]	[ID(x) & relative location]	[ID(x) & relative location]	[ID(x) & relative location]	[ID(x) & relative location]

See EX2042 at Slide 25. Variants included in this table were those detected in the sample and those not listed were those not detected.

293. Based on at least the foregoing, my co-inventors and I had conceived of claim 10 by no later than May 8, 2012.

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11. '394 Patent Claim 11

294. Claim 11 of the '394 patent recites:

11. The method of claim 10, wherein said identifying comprises observing an allele frequency of said one or more polymorphisms.

295. By no later than May 8, 2012, the Accuracy Program at Personalis included observing an allele frequency of said one or more of polymorphisms. For example, Slide 11 of my May 8, 2012 CEO Overview Board of Director Presentation included observing parental allele frequencies in children in the "CEPH1463 Pedigree Analysis."

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

All 11 children

Several optimal subsets with 5 of the 11 children

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

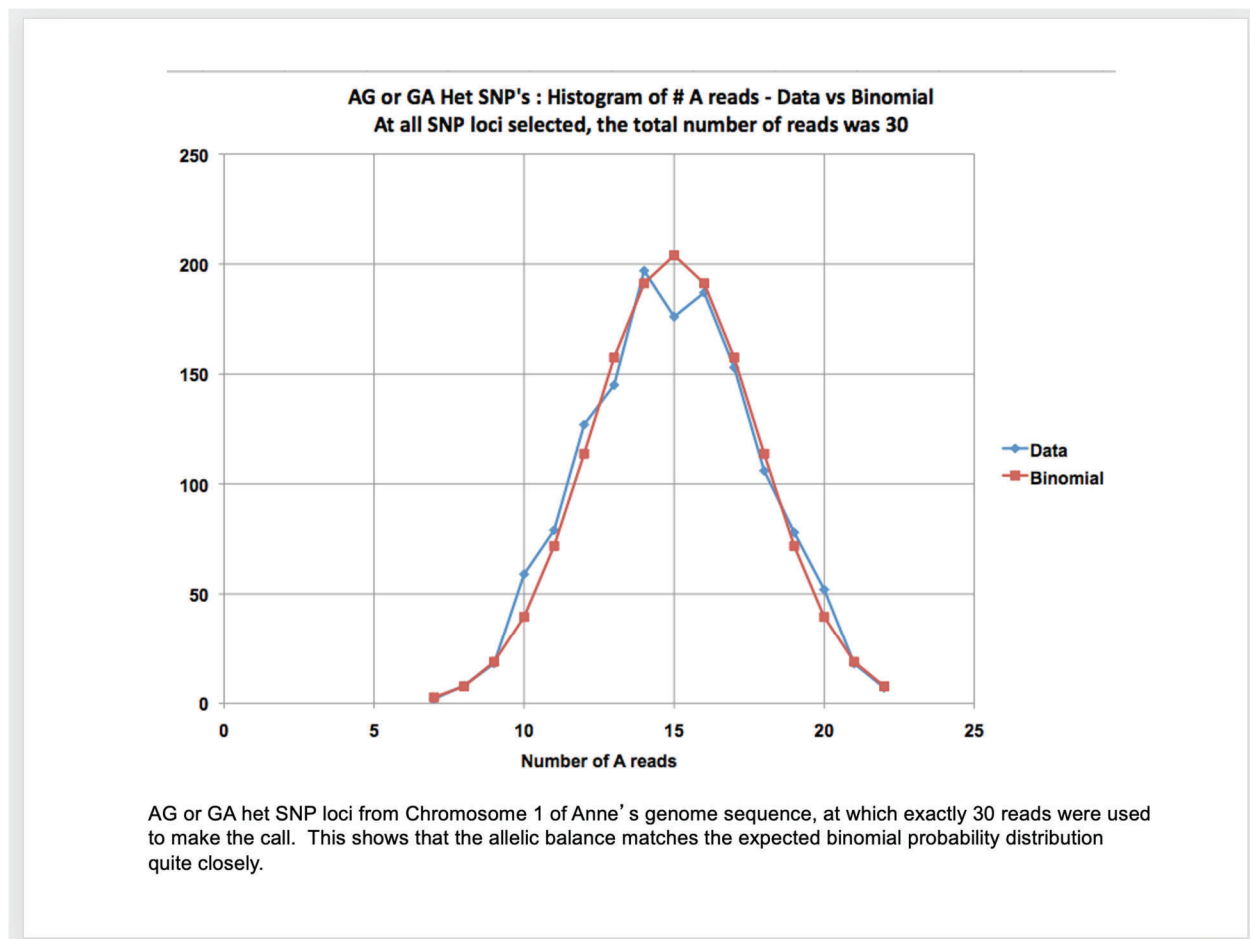
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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 11.

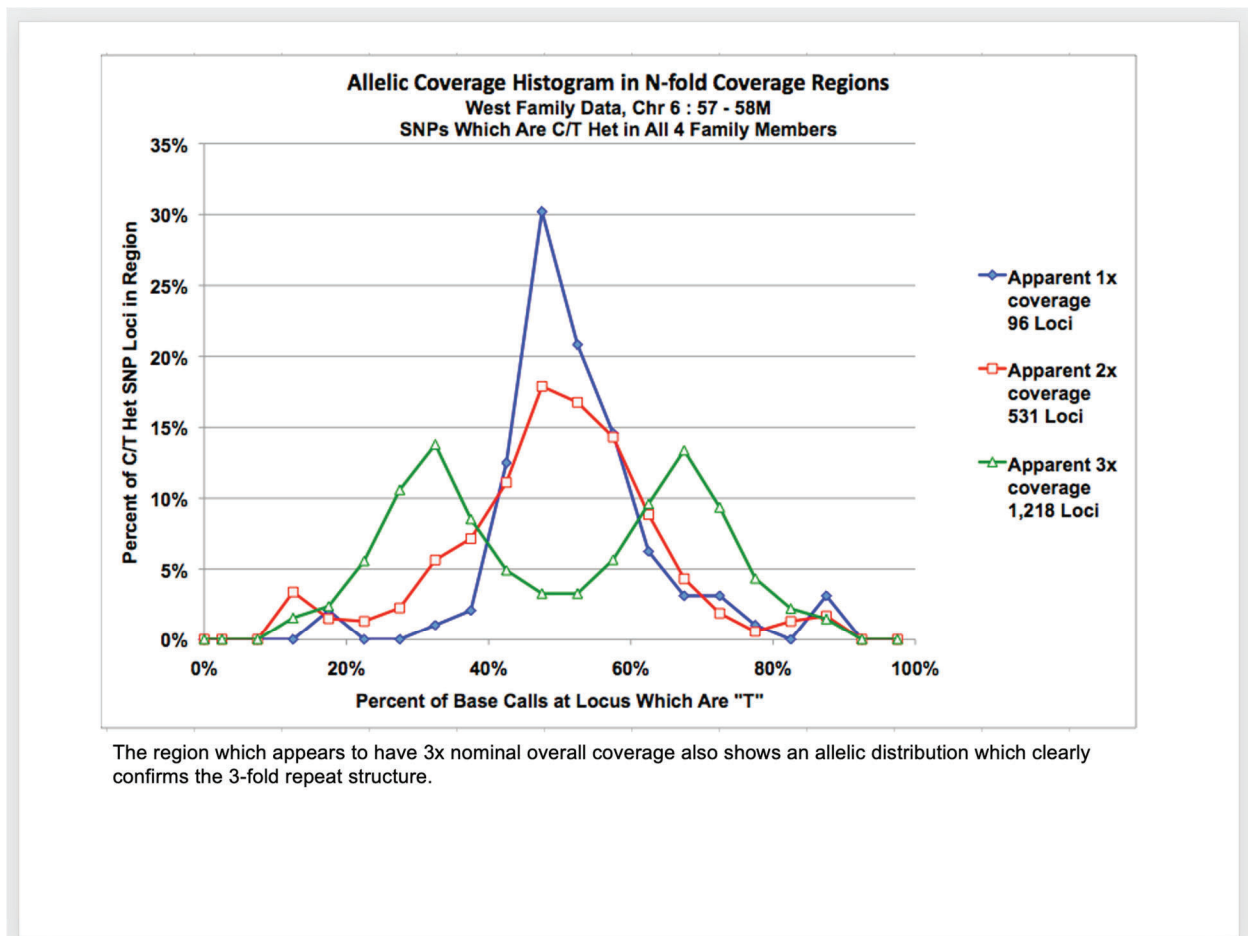
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296. We had also focused on the allele frequencies of individual genetic variants in the data from individuals. In an internal slide deck, on the subject of quality control, that I shared with the Personalis co-founders on June 18, 2011, I showed (slide 10) data on the allele frequency distribution observed in a part of my daughter's genome and how closely it matched the expected binomial distribution:



See EX2115, June 18, 2011 presentation at slide 10. Slide 12 then went on to show that allele frequencies deviated from that in a region with unusually high coverage:

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See EX2115, June 18, 2011 presentation at slide 12. This illustrated the use of allele frequencies to detect underlying structural variants in that part of the genome.

297. Based on at least the foregoing, my co-inventors and I had conceived of claim 11 by no later than May 8, 2012.

12. '394 Patent Claim 12

298. Claim 12 of the '394 patent recites:

12. The method of claim 1, wherein said plurality of capture probes are conjugated to beads.

299. 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

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technologies to supplement whole genome sequencing (“WGS”) with “semi-custom” assays using “pullout” technologies. As described above, 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 Mark Pratt and I were aware that custom and semi-custom capture probes could be purchased via Agilent (their “SureSelect” line of capture probes), Illumina (their “TruSeq” capture probes), and Roche (their “Nimblegen” capture probes). Members of the Personalis team were experienced in their use, and the knowledge that such capture probes included streptavidin-coated magnetic beads conjugated to biotin-labelled capture probes. In particular, we were aware that Agilent supported custom customer-designed kits based on the customer’s own content that utilized biotinylated capture probes being conjugated to magnetic beads via the streptavidin coating on the beads.

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Overview of Personalis Accuracy Program

Characterize errors <u>Analysis</u> Rates by variant type & Q-score Underlying mechanisms Medical interpretation impact Regulatory impact <u>Methods</u> Comparison with literature Studies on limited regions Whole genome analysis: Single genome metrics Same person twice Family inheritance (MIE) Platform comparison Arrays ILMN / CGI / Ion T... Sanger capillary <u>Prioritize solutions</u> Bio-informatic approaches Laboratory approaches Content approaches	Informatic Solutions <u>Advances in 3rd party alg's</u> Aligner for > 200bp reads New versions, current alg's Other alg's (e.g. lobSTR) <u>Advances in our alg's:</u> SV's : Zygosity, accuracy Combine SV's & SNP's Broader use of Breakseq <u>New Personalis alg's</u> Alignment degeneracy Genome-aware alignment VNTR-specific <u>Advances in reference</u> Ethnic major-allele ref's Iterative Admixed InDel's / SV's <u>Flag or Filter Out</u> For problems not yet solved	Lab, Content Solutions <u>Combine technologies</u> WGS + exome Longer reads and/or inserts Multi-vendor Arrays (genotypes & SV's) Electrophoretic sizing Sanger validation <u>Content-based semi-custom</u> Array (genotypes & SV's) Pullout <u>Custom sample preps</u> Problematic motifs Degenerate regions Phasing <u>Content</u> Gold standard genomes Known healthy genomes
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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5 (highlighting added).

300. EX2045 is a true and correct copy of the Personalis July 26, 2011 Board of Directors meeting slides by Euan Ashley, one of the co-founders of Personalis. As mentioned above, I attended the July 2011 meeting with the following additional persons, all of whom are appropriately not named as inventors of the '033 patent: Michael Snyder, Russ Altman, Euan Ashley, Jonathan MacQuitty, Sue Siegel, Andrew Chung, Robin Bennet, and Lisa Kenkel (who was present by phone for a portion of the meeting). Slide 31 is reproduced below. I was aware through at least

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Slide 31 that “Custom Agilent SureSelect in solution hybridization” biotinylated capture probes for conjugation to streptavidin-coated magnetic beads were available to order from Agilent.

Prior expectation – CV disease genes

➤ Custom Agilent SureSelect in solution hybridization selected regions associated with 251 target genes implicated in myocardial disease and/or function:

- Exons +/- 100 base pairs
- TFBS within 1.5 kbp
- Enhancers/repressors within 1.5 Mbp
- Conserved regions from MSA within 2kbp of coding regions and in introns
- miRNA target sites
- miRNA coding regions
- Targets 3.5 Mbp of genomic sequence



EX2045, July 26, 2011 Euan Ashley Board of Directors Meeting at Slide 31.

301. Based on at least the foregoing, my co-inventors and I had conceived of claim 12 by no later than May 8, 2012.

13. ‘394 Patent Claim 13

302. Claim 13 of the ‘394 patent recites:

13. The method of claim 1, wherein said plurality of capture probes further comprise barcodes.

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

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inventors of the '394 patent, at least Mark Pratt and I were aware that it was possible to multiplex multiple samples into each lane of a sequencing instrument flow cell by adding a DNA barcode to the end of each molecule of DNA to be sequenced. We 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. Mark Pratt and I were familiar with the use of DNA barcodes as sample identifiers to multiplex samples for sequencing on the Illumina instruments based on our previous employment at Illumina, and the use of barcodes in some of Illumina's workflows. We were also aware of the use of DNA barcodes and sample indexes to multiplex samples for sequencing of DNA in some of the workflows for Roche's 454 sequencing instrument.

304. By no later than May 8, 2012, barcoding samples to multiplex them for DNA sequencing was part of the Accuracy Program at Personalis. The Accuracy Program combined technologies to supplement whole genome sequencing ("WGS") with "semi-custom" assays using "pullout" technologies. As described above, the Accuracy Program included "pulling" out desired content from a genomic DNA sample by streptavidin-coated magnetic beads conjugated to biotin-labelled capture probes. We were aware that custom and semi-custom capture probes could be

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purchased via Agilent (their “SureSelect” line of capture probes), Illumina (their “TruSeq” capture probes), and Roche (their “Nimblegen” capture probes). I was aware that Agilent’s Sure Select and Illumina’s TruSeq capture probes could include DNA barcode indexing systems, and members of the Personalis team were experienced in their use. In particular, we were aware that Agilent supported custom customer-designed kits based on the customer’s own content. We were also aware in particular that these customer-designed kits could be pooled for efficient sequencing by the use of indexed (barcoded) libraries.

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	

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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 5
(highlighting added).

305. EX2045 is a true and correct copy of the Personalis July 26, 2011 Board of Directors meeting slides by Euan Ashley, one of the co-founders of Personalis. As mentioned above, I attended the July 2011 meeting with the additional persons, all of whom are appropriately not named as inventors of the '033 patent. Slides 31 and 33 are reproduced below. I was aware through at least Slide 31 that “Custom Agilent SureSelect in solution hybridization” capture probes were available to order from Agilent, and through at least Slide 33 that studying subjects and follow-up work involving sequencing on Illumina’s HiSeq instrument could use “indexed primers and sample pooling for maximum sequencing efficiency.”

Prior expectation – CV disease genes

➤ Custom Agilent SureSelect in solution hybridization
selected regions associated with 251 target genes implicated
in myocardial disease and/or function:

- Exons +/- 100 base pairs
- TFBS within 1.5 kbp
- Enhancers/repressors within 1.5 Mbp
- Conserved regions from MSA within 2kbp of coding
regions and in introns
- miRNA target sites
- miRNA coding regions
- Targets 3.5 Mbp of genomic sequence



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EX2045, July 26, 2011 Euan Ashley Board of Directors Meeting at Slide 31.

Study subjects and follow-up work

- 80 subjects with dilated and hypertrophic cardiomyopathy in whom clinical genetic testing has not identified a pathogenic mutation
 - 65 subjects have DNA already/15 subjects require DNA collection
- Plan for sequencing on Hi-Seq using indexed primers and sample pooling for maximum sequencing efficiency
- Ethnicity-specific variant identification as prior
- Targeted genotyping/re-sequencing/re-phenotyping contingent on results of discovery sequencing
- Potential clinical tool and tool for investigating modifier loci in other subjects



EX2045, July 26, 2011 Euan Ashley Board of Directors Meeting at Slide 33.

306. Based on at least the foregoing, my co-inventors and I had conceived of claim 13 by no later than May 8, 2012.

14. '394 Patent Claim 14

307. Claim 14 of the '394 patent recites:

14. The method of claim 1, wherein said samples isolated from said individual are isolated from a body fluid, cell, skin, tissue, organ, or combination thereof.

308. By no later than May 8, 2012, the Accuracy Program at Personalis included the nucleic acid sample obtained from the individual being isolated from a body fluid, cell, skin, tissue, organ, or combination thereof. For example, Slide 11 of my January 5, 2012 Accuracy Framework PowerPoint slides is entitled

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“Examples of process variability,” and the first line stated “sample source (blood, saliva, tissue, culture cell).” Thus, the Accuracy Program included sample sources obtained from our customer that included body fluid (e.g., blood, saliva), cell (e.g., culture cell), and tissues and organs.

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, January 5, 2012 Accuracy Framework PowerPoint slides at Slide 11.

309. Based on at least the foregoing, my co-inventors and I had conceived of claim 14 by no later than May 8, 2012.

15. ‘394 Patent Claim 15

310. Claim 15 of the ‘394 patent recites:

15. The method of claim 14, wherein said body fluid sample is a blood plasma sample.

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311. By no later than May 8, 2012, the Accuracy Program at Personalis included a nucleic acid sample obtained from blood plasma. For example, Slide 3 of my May 8, 2012 CEO Board presentation described a “seminal paper by Mike Snyder & team published in Cell” which supported my idea for the Accuracy Program to include “ongoing clinical use of genome -scale sequencing” and “not just a genome once in your life.”

Publications & Upcoming Presentations

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

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EX2112, May 8, 2012 CEO Overview Board of Director Presentation at Slide 3 (highlighting added).

312. The referenced paper by Dr. Snyder was Chen and Snyder et al., “Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes,” Cell, 148:1293-1307 (March 2012), EX2030. The paper reported on a 54-year-old

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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. *Id.* at 3. The assays used at those 20 time points were chosen in part based on analysis of groups of genetic variants detected in his whole genome sequencing data. 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. *See, e.g., id.* at Figure 1(A). At each of the 20 time points, the analysis from the blood included assays on three different components of the blood: plasma, serum and PBMC’s (white blood cells). They used blood plasma for protein assays and PBMC’s for untargeted RNAseq. The RNAseq was used not only to measure changes in genes which were expressed (e.g., changes in genes of the immune system during the infections) but also, by comparison with the original genome sequence, variations in the nucleic acid sequence over time (RNA edits). Those changes in RNA sequences were dynamic, being detected at some points and not others. When they were detected, their allele frequencies were calculated from the data and changes in those were tracked.

313. My co-inventors and I realized that the Accuracy Program could be more efficient than the untargeted RNAseq used in the Snyder paper on PBMC’s by replacing it with a “content-based semi-custom” approach using “pullout” based on

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the plasma portion of a blood sample. *See* Slide 5 of my May 8, 2012 CEO Board Presentation, EX2112. Well before that time we were familiar with the genetic analysis of cell free DNA from blood plasma (for fetal diagnosis, cancer analysis and detection of transplant rejection) but not using hybrid capture probes targeted to the variants of the person, and not from a single individual at multiple time points. Our realization of this possibility to leverage our technology at so many time points was why we described this paper as seminal. The paper did not use or disclose our invention, but it sparked our creativity and that led to the invention. For at least these reasons, the Accuracy Program at Personalis included a nucleic acid sample obtained from blood plasma by no later than May 8, 2012.

16. '394 Patent Claim 16

314. Claim 16 of the '394 patent recites:

16. The method of claim 14, wherein said tissue sample is a tissue biopsy sample.

315. By no later than May 8, 2012, the Accuracy Program at Personalis included nucleic acid sample isolated from the individual being isolated from a tissue biopsy. For example, Slide 11 of my January 5, 2012 Accuracy Framework PowerPoint slides is entitled "Examples of process variability," and the first line stated "sample source (blood, saliva, tissue, culture cell)." Thus, the Accuracy Program included sample sources obtained from a tissue biopsy. *See, e.g.*, EX2046, January 5, 2012 Accuracy Framework PowerPoint slides at Slide 11. Based on at

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least the foregoing, my co-inventors and I had conceived of claim 16 by no later than May 8, 2012.

17. ‘394 Patent Claims 17-18

316. Claims 17-18 of the ‘394 patent recites:

17. The method of claim 1, wherein said whole genome sequencing produces at least 750,000,000 sequencing reads.

18. The method of claim 1, wherein said whole genome sequencing produces at least 1,000,000,000 sequencing reads.

317. By no later than May 8, 2012, the Accuracy Program at Personalis included whole genome sequencing producing at least 750,000,000 and 1,000,000,000 sequencing reads. Personalis’ plan was to augment human whole genome sequence (WGS) data with other assays based on hybrid capture (“pullout”), to achieve biomedically superior accuracy. This was described in my CEO Update to the Board, May 8th 2012, including on slide 5, copied here:

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Overview of Personalis Accuracy Program

Characterize errors

Analysis

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

Methods

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

Prioritize solutions

Bio-informatic approaches
Laboratory approaches
Content approaches

Informatic Solutions

Advances in 3rd party alg's

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

Advances in our alg's:

SV's : Zygosity, accuracy
Combine SV's & SNP's
Broader use of Breakseq

New Personalis alg's

Alignment degeneracy
Genome-aware alignment
VNTR-specific

Advances in reference

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

Flag or Filter Out

For problems not yet solved

Lab, Content Solutions

Combine technologies

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

Content-based semi-custom

Array (genotypes & SV's)
Pullout

Custom sample preps

Problematic motifs
Degenerate regions
Phasing

Content

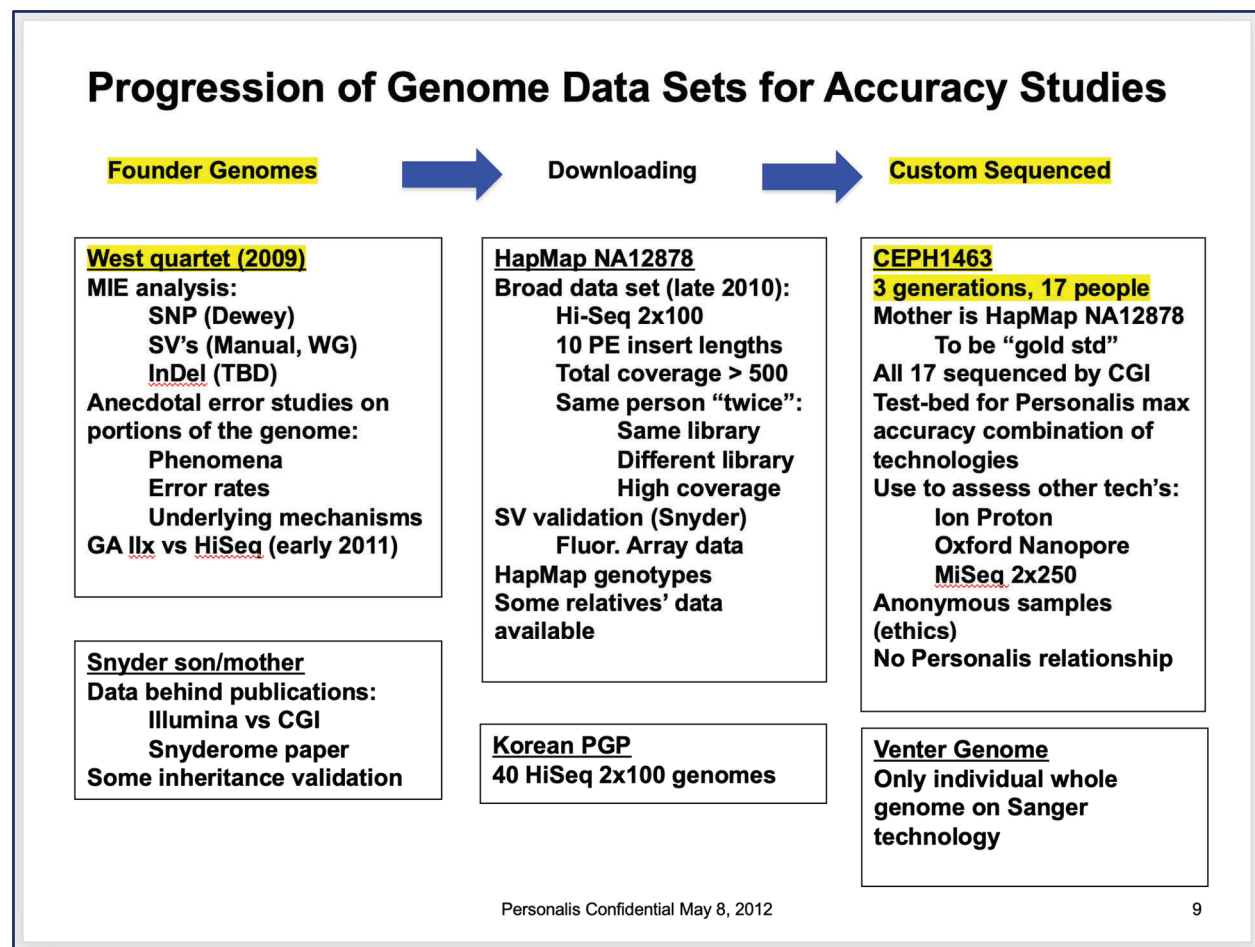
Gold standard genomes
Known healthy genomes

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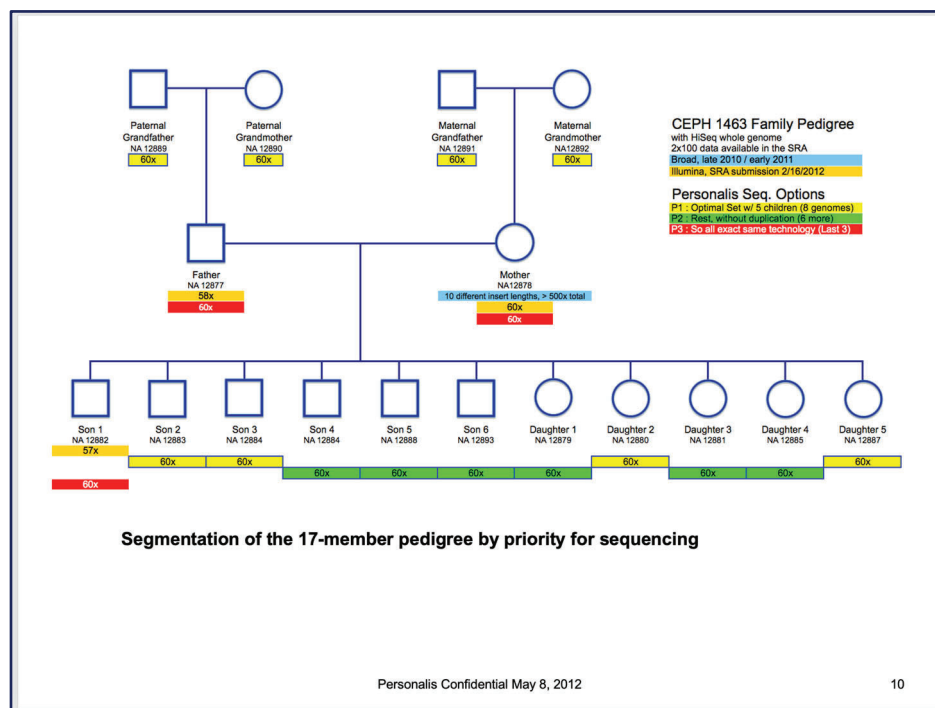
See Slide 5 of my May 8, 2012 CEO Board Presentation, EX2112. In the same presentation, on slide 9, I described the progression of data sets the company planned to use for its accuracy development program:

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See Slide 9 of my May 8, 2012 CEO Board Presentation, EX2112. This began with use of the West family genome data sets from 2009 blood draws. I proposed that Personalis have a further data set generated, based on DNA samples from a three-generation family of 17 individuals collected and made available internationally by the French research organization CEPH (Centre d'Etude du Polymorphisme Humain). The custom sequencing proposed was described on the next slide (Slide 10), copied here:

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See Slide 10 of my May 8, 2012 CEO Board Presentation, EX2112. It called for sequencing most of these samples at 60x coverage, double the depth used as a minimum for the Illumina sequencing of the West family genomes in 2009. This was confirmed in the budget for the project, shown on slide 12 of the same presentation, copied here:

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"GOLD STANDARD GENOME" PROJECT BUDGET	
Amount is within budget but requires Board approval	
Additional semi-custom work based on Personalis content may be proposed later in the year.	
Samples de-identified before shipment to vendors	
Whole genome sequencing	
By Illumina Genome Network at Illumina	\$ 122,000
20 samples at 60x coverage	
17 CEPH1463 pedigree	
2 replicates	
Venter	
Complete Genomics Sequencing	\$ 10,000
2 Samples at 80x coverage	
Venter	
CEPH1463 Mother (replicate)	
Array analysis	\$ 5,000
Genotypes	
SV validation	
Karyotyping, exomes & other assays	\$ 20,000
TOTAL	\$ 157,000

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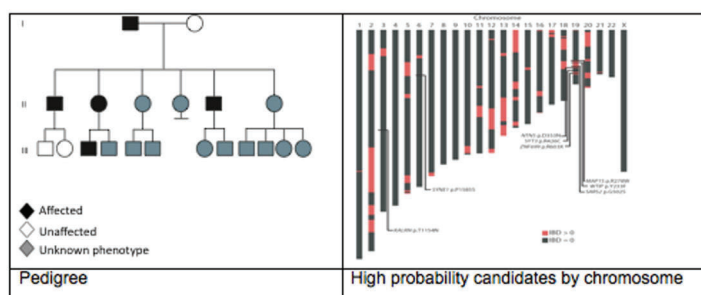
See Slide 12 of my May 8, 2012 CEO Board Presentation, EX2112. Whole genome sequencing (WGS) at 60x could be expensive, as seen in this budget (which the Personalis Board did approve, given that we were planning to create a “Gold Standard” data set).

318. In other applications, it was clear to us that it might be helpful to use more than 30x sequencing, but we might not need (or be able to afford) 60x sequencing. At the same May 8, 2012 Personalis Board meeting, Dr. Richard Chen, Personalis’ Chief Technology Officer, also made a presentation. It included some examples of what we planned the reports from our service to look like. One example, from slide 19, is copied in here:

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Summary

Disease: Hypertrophic Cardiomyopathy
Mode of inheritance: Autosomal dominant
Population prevalence: 1/500
Subjects sequenced: 6 (5 affected, 1 unaffected)
Sequencing platform: Illumina HiSeq 2000
Enrichment platform: none



Methods: Whole genome sequencing was performed in five affected individuals and one unaffected individual. Ninety-seven percent of bases in targeted regions were confidently genotyped, and mean haploid coverage depth was 46x. Variants were filtered according to co-segregation with disease and prioritized by variant type, frequency in ethnically concordant population data, and functional annotation.

Consanguinity: none reported and no abnormal autozygosity identified.

Interpretation: No variants previously implicated in Hypertrophic Cardiomyopathy were identified. Four missense SNVs were identified in six tier 1 regions (exons) that co-segregated with disease, all in heterozygous state. These six variants have not been previously seen in exome sequencing of 5,400 subjects unselected with regard to Mendelian phenotypes, 1,094 subjects undergoing whole genome sequencing (1000 genomes phase 1 project), and are not catalogued in dbSNP. One variant, LAMP2 p.Y233E, disrupts a highly conserved nucleotide in a gene that is highly expressed in myocardial tissue; LAMP2 has been implicated in the closely related disorder, Danon disease. The other three candidate variants occur in genes (SARS2, GLA) with as-yet undetermined roles in hypertrophic cardiomyopathy, though they have been implicated in similar Mendelian disorders. These results are provided for research purposes only and are not intended for clinical use.

Frederick Dewey, MD

Sarah Garcia, PhD, MS

PERSONALIS INC., PROPRIETARY AND CONFIDENTIAL 2012

See EX2042 at slide 19. It shows a family of six people in which five are afflicted by a potentially fatal genetic heart disease “Hypertrophic cardiomyopathy”. To identify the genetic variants underlying this specific family’s disease, the study used whole genome sequencing (WGS) at an average coverage of 46x.

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319. To allow for applications like these we added an alternative deeper sequencing level described in the '394 patent claim 18, increasing the minimum number of DNA sequencing reads from 750 million to one billion.

320. Based on at least the foregoing, my co-inventors and I had conceived of claims 17-18 by no later than May 8, 2012.

18. '394 Patent Claim 19

321. Claim 19 of the '394 patent recites:

19. The method of claim 1, further comprising:
(i) repeating said third sequencing assay one or more times on one or more subsequent samples to yield an additional result comprising a fourth nucleic acid sequence; and
(ii) generating an additional biomedical report that includes biomedical information of said subject, which biomedical information identifies the presence or absence of said one or more polymorphisms identified by said additional result.

322. By no later than May 8, 2012, the Accuracy Program at Personalis included repeating said third sequencing assay one or more times on one or more subsequent samples to yield an additional result comprising a fourth nucleic acid sequence and generating an additional biomedical report that includes biomedical information of said subject, which biomedical information identifies the presence or absence of said one or more polymorphisms identified by said additional result for the same reasons discussed above regarding limitations 1(e)-(g). Based on at least the foregoing, my co-inventors and I had conceived of claim 19 by no later than May 8, 2012.

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Conclusion Regarding Conception for the ‘394 Patent

323. In conclusion, my co-inventors and I had conceived of the invention recited by claims 1-19 of the ‘394 patent by no later than May 8, 2012. Further, by no later than May 8, 2012, I recognized and appreciated that the Accuracy Program had the features that are now recited by claims 1-19 of the ‘394 patent. Further, a person of ordinary skill in the art would have been enabled to practice our invention as of May 8, 2012 without undue experimentation if they had been informed of our invention on that date.

324. In summary, our conception of the methods of this patent began in an effort to resolve the accuracy problems in whole genome and exome sequencing, by augmenting them with hybrid capture pullout sets. As described above, our plan for the initial products from the Accuracy Program, “Whole Genome Plus” and “Exome Plus,” involved three different supplements, each implemented as a separate Personalis-designed capture probe set involving thousands of probes. As we became more and more comfortable with the concepts around these large sets of capture probes, we began to realize that they could be customized for an individual person, but at considerable cost. It was in March 2012, when we saw the utility of analyzing genetic sequence changes in a single individual over blood samples from twenty time points, that we realized such a multiple time point analysis could amortize the

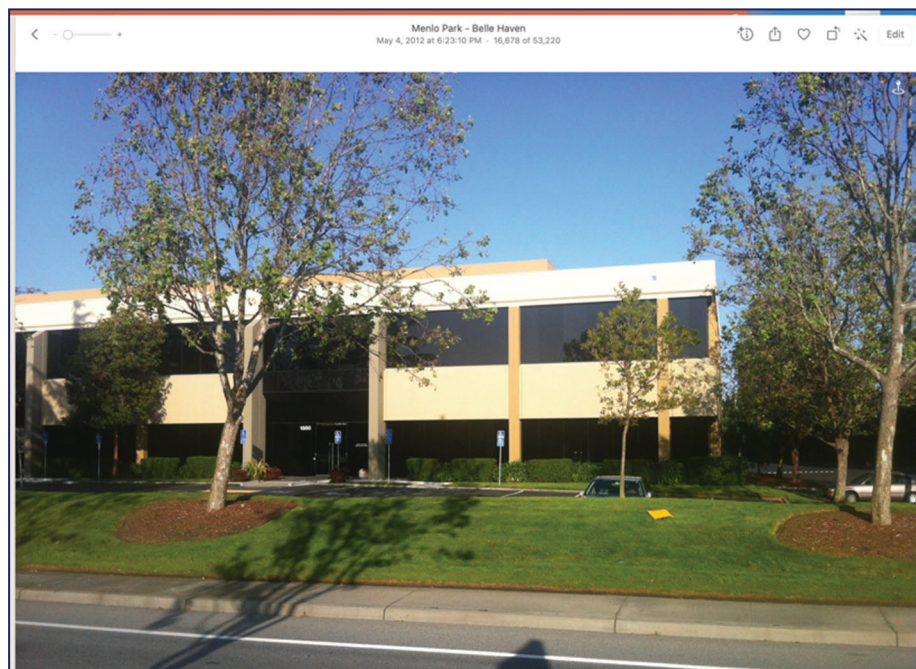
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expense of a custom hybrid capture panel and make it practical. That was the basis of the '394 patent.

IV. DILIGENCE

325. My co-inventors and I diligently pursued the Accuracy Program from May 9, 2012 thorough the January 17, 2013 filing date of U.S. Provisional Application No. 61/753,828.

326. In October 2011 Personalis began to rent its first offices, at a Regus facility in downtown Palo Alto. Over the following months we added a few more rooms at Regus but they were just for use as offices. We had no laboratory. By the spring of 2012 we found a building at 1350 Willow in Menlo Park that we could rent a somewhat larger space in (part of the 2nd floor).



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327. It did not have a laboratory, but the landlord was open to us building a modest laboratory there. On May 4th, 2012, our whole team went to visit the new space and we had this group photograph taken:

Company photo May 4, 2012



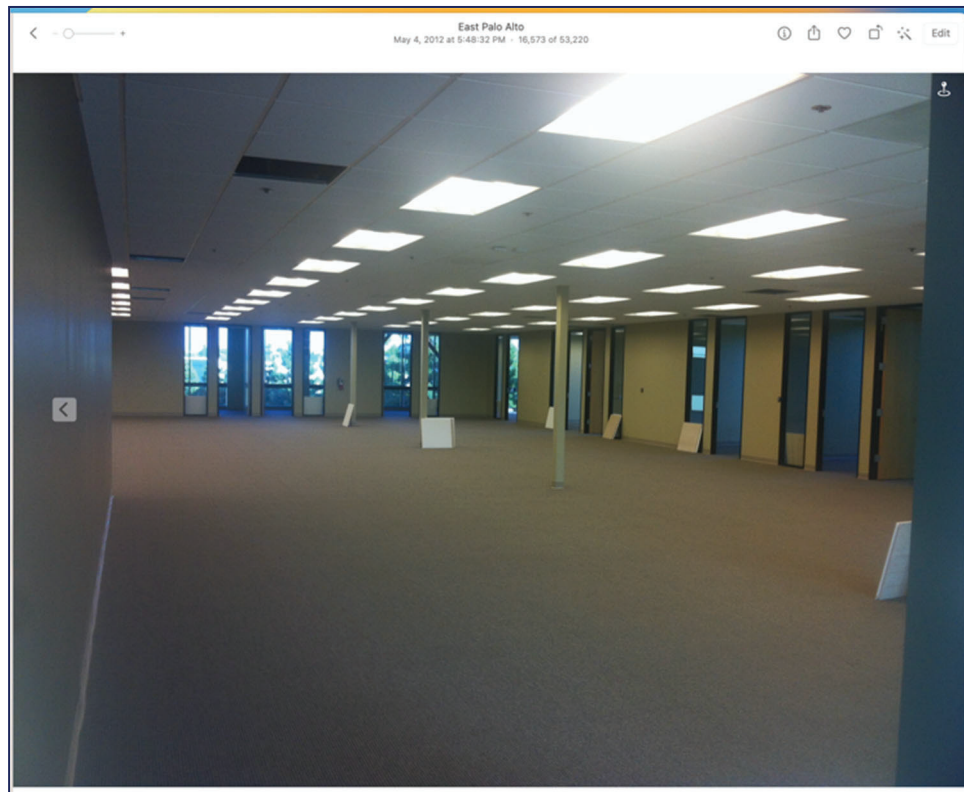
Left to right : Michael Clark, Rich Chen, Carol Tillis, Christian Haudenschild, Russ Altman, Carlos Bustamante, Euan Ashley, Gemma Chandratillake, Atul Butte, John West, Sarah Garcia, Hugo Lam, Rong Chen, Scott Kirk, Gabor Bartha, Namhai Nguyen, Mark Pratt, Eliane Sousa, Nan Leng

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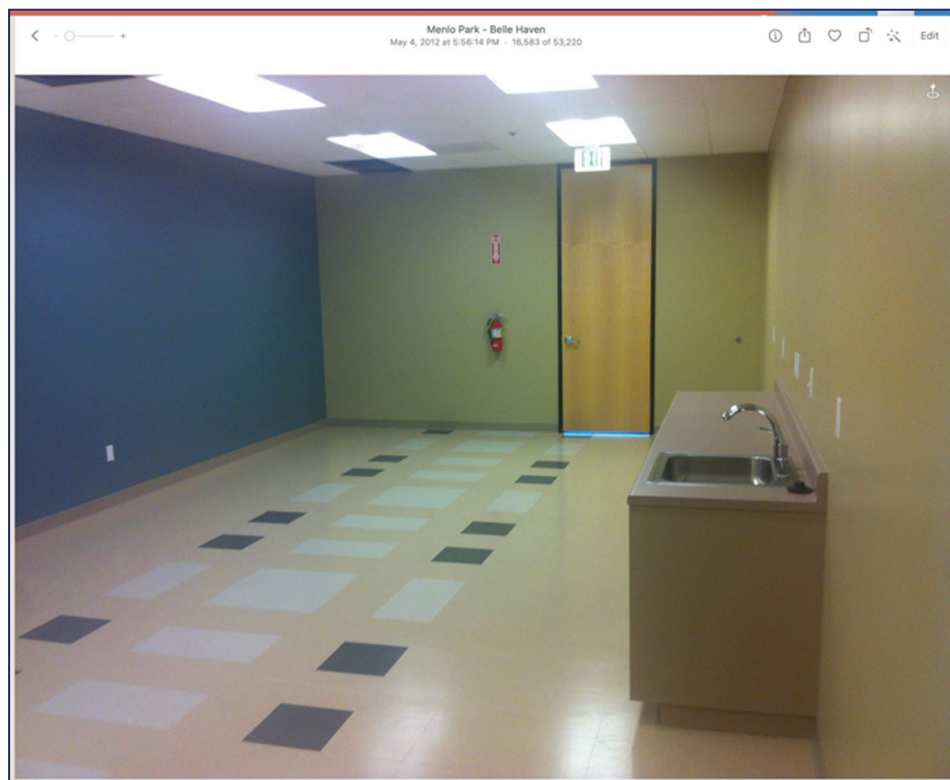
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There were some built-in offices but no cubicles or furniture:



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There was a small kitchen / lunch room with one sink. Over the coming months, we would turn it into a small lab:



328. At our Board meeting May 8th 2012, we proposed that we rent this space, add furniture and cubicles, and build a small lab. We also proposed a program, largely outsourced, to create a reference set of genome sequences from the 17-member 3-generation CEPH 1463 pedigree, and a new genome sequence of Craig Venter. Our Board of Directors approved leasing 12,000 square feet of space at 1350 Willow Road in Menlo Park, CA, with an expected cost of \$30,000 per month and up to \$157,000 for third party sequencing of genomes of the 17-person, 3-generation CEPH 1463 family, and Craig Venter. *See* May 8, 2012 Meeting Minutes at page 2.

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329. Over the following months we worked to build the new laboratory. It would be modest by the standards of the time, but it would let us generate data to show potential customers our planned product results. We did, and launched the product at the AGBT (Advances in Genome Biology and Technology) conference in February 2013. The data generated also reduced our invention to practice, and provided material for some of the examples included in our Provisional Patent Filing on January 17, 2013.

330. Prior to building our own lab and our May 8, 2012 Board approval to purchase outsourced sequencing services, the genome data sets we had available to work with were the West family genomes, sequenced by Illumina starting November 2009. In February 2012, we also identified a source of whole genome sequence raw data that we could download – the NIH’s Sequence Read Archive, entries by the MIT/Harvard Broad Institute. By May 8, 2012 we had downloaded 38 whole genome raw data sets. Not all were full 30x genomes but we were able to aggregate the to reach 30x. This gave us some whole genome data to work with, but no data from a hybrid capture panel. For that we would need to design our own panels, have them manufactured, and then perform the DNA sequencing.

331. The following subsections provide representative examples of the diligence we exercised during each month from May 9, 2012 through January 17, 2013.

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A. Evidence of diligence from May 9-30, 2012

332. My co-inventors and I were reasonably continuous and diligent in our pursuit of the Accuracy Program from May 9-30, 2012. Evidence of our diligence includes, for example, EX2047, which is a true and correct copy of a Google Calendar invitation for the Personalis Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. The meeting took place on Friday, May 11, 2012, from 4-6pm. During this weekly team meeting, we discussed updates on the Accuracy Program.

333. EX2051 is a true and correct copy of an email and attachment Richard Chen sent to me, among others, on May 14, 2012. Dr. Chen is a named inventor on the '394 patent and the '033 patent. The email and attachment describe Dr. Chen's proposal to form a Founder-led work group that "meet weekly for 2-4 hrs and present updates every 4-6 weeks." In the attachment, Dr. Chen proposes that I would be the Founder leader for the Accuracy Program, and Mark Pratt would be the Personalis leader. The attachment states that the purpose of the work groups was "to keep making progress on" the various projects within Personalis, including the Accuracy Program. The Founder-led work group was implemented within Personalis, and I did, in fact, serve as the Founder leader for the Accuracy Program to ensure that we diligently pursued it.

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334. EX2052 is a true and correct copy of an email and PowerPoint presentation I received from Mark Pratt, a named inventor on the '394 patent and the '033 patent, on May 15, 2012. This email discusses a PowerPoint that Mark began working on in February or March of 2012. Slide 1 of the PowerPoint attachment describes, for example, “facets” of the Accuracy Program including the use of “complementary assays and analytical methods for production use” including “targeted pullout and tailored insert sequencing libraries.”

335. EX2053 is a true and correct copy of an email I received from Scott Kirk, a Personalis employee, on May 15, 2012. Several non-inventors of the '033 and '394 patents were cc'd on this email, including Rong Chen, Nan Leng, and others. This email discusses notes that Scott took during a “planning meeting” and includes a summary of the Personalis discussion regarding how the technical advances of the Accuracy Program should involve a “meeting to define [a] path for how accuracy folds into the greater picture” of Personalis’ commercial business plan.

336. Exhibit 2120 is a true and correct copy of an email I sent on May 17, 2012 to Personalis employees and founders, including Richard Chen, Mark Pratt, and Carol Tillis. In this email, I approved a job description for Shujun Luo.

337. Exhibit 2116 is a true and correct copy of an email I sent on June 18, 2012 to Personalis employees and founders, including Richard Chen and Mark Pratt,

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regarding Shujun Luo beginning employment at Personalis. In this email, I discuss bringing Shujun Luo up to speed on the Accuracy Program.

338. EX2048 is a true and correct copy of a Google Calendar invitation for the Personalis Accuracy Review and Brainstorm Meeting that was attended by several Personalis employees and founders, including Hugo Lam, Mark Pratt, and myself, among others. The meeting took place on Monday, May 21, 2012, from 5:45-6:45pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

339. EX2054 is a true and correct copy of an email and Excel sheet I sent on May 22, 2012. The Excel sheet includes meeting notes from a team meeting that occurred on May 21, 2013. My Excel sheet notes explain how Personalis can further differentiate and advance the Accuracy Program beyond existing technologies in the field.

340. EX2055 is a true and correct copy of an email and PowerPoint Presentation I sent to Mark Pratt on May 22, 2012. The PowerPoint describes an overview of the Accuracy Program, including genomic sequencing and laboratory strategies. For example, Slide 2 of this PowerPoint includes an “overview of the Personalis Accuracy Program” that duplicates Slide 5 of my May 8, 2012 CEO Board presentation. Slides 4-19 provide data related to the Accuracy Program. This email (EX2055) also noted that the meeting had so much material to cover that we

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had run out of time and not been able to cover it all. Specifically, Gabor Bartha had attended the May 21st meeting and brought results of his MIE (Mendelian Inheritance Error) analysis of the quartet genomes, and review of those results had to be deferred until a later meeting when there could be more time.

341. EX2050 is a true and correct copy of an email thread dated May 25, 2012. This email discusses two Personalis team meetings. The first meeting was for Personalis founders to discuss, among other things, the strategy for the Accuracy Program. The second meeting was for the Personalis weekly team meeting, which also included team discussions related to the Accuracy Program.

342. EX2049 is a true and correct copy of a Google Calendar invitation for the Personalis Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. The meeting took place on Friday, May 25, 2012, from 4-6pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

343. EX2056 is a true and correct copy of an email and attachments I sent to several Personalis employees and founders, including Richard Chen, Mark Pratt, and Scott Kirk, on May 29, 2012. The email contains two Excel sheet attachments and seven PowerPoint presentation attachments. This email and attachments explain the development of the Accuracy Program since January 2012.

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B. Evidence of diligence in June 2012

344. My co-inventors and I were reasonably continuous and diligent in our pursuit of the Accuracy Program throughout June 2012. Evidence of our diligence includes, for example, EX2057, which is a Google Calendar invitation for the Personalis Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. The meeting took place on Friday, June 1, 2012, from 4-6pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

345. EX2061 is a true and correct copy of an email and attached Excel sheet I sent to Richard Chen, a named inventor on the '394 patent and the '033 patent, on June 7, 2012. I created the Excel sheet to explain how Personalis can detect and eliminate various data error types to further increase the precision and accuracy within the Accuracy Program.

346. EX2062 is an email and attached PowerPoint presentation from Richard Chen to me dated June 11, 2012. This email and PowerPoint presentation are for a Personalis Board of Directors meeting regarding the Accuracy Program, including research and development milestones and goals. The PowerPoint presentation further lists me and Mark Pratt as the Personalis Leads for the Accuracy Program.

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347. EX2063 is an email and attached PowerPoint presentation I sent on June 11, 2012. The PowerPoint presentation is my CEO Overview that I sent to Richard Chen, Carol Tillis, and Christian Haudenschild in advance of the June 12, 2012 Board of Directors meeting. The PowerPoint presentation discusses genome sequencing related to the Accuracy Program.

348. In June 2012, the Board of Directors approved up to \$240,000 in expenditures for the purchase of computing and storage equipment, as well as up to \$620,000 in expenditures for the purchase of sequencing equipment. *See* EX2064, June 12, 2012 Meeting Minutes at page 2. The DNA sequencing equipment was one Illumina HiSeq-2000 DNA sequencing instrument and one Illumina MiSeq instrument.

349. EX2058 is a Google Calendar invitation for the Personalis Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. The meeting took place on Friday, June 15, 2012, from 4-6pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

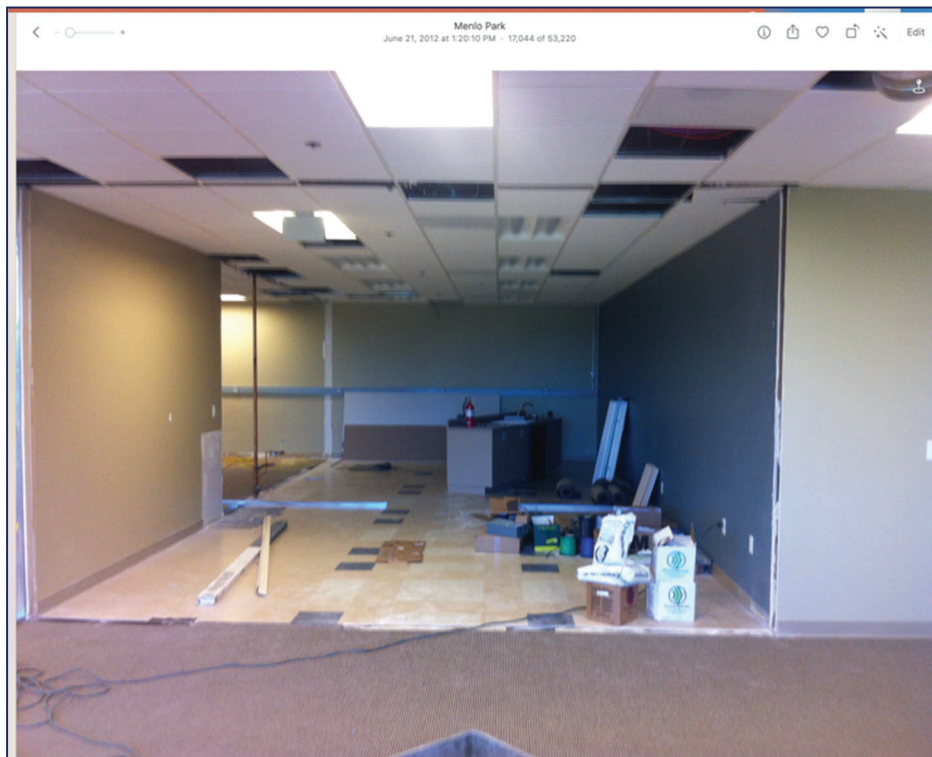
350. EX2065 is a true and correct copy of an email I sent on June 17, 2012 to Personalis employees and founders, including Richard Chen, Mark Pratt, and

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others. This email describes my top three goals for Accuracy Program, including Shujun Luo's involvement in the program.

351. On June 21st, 2012, both the HiSeq-2000 instrument and the MiSeq instruments were delivered. Because the HiSeq instrument requires on-site optical alignment, it could not be installed until we completed construction of our lab and could move the instrument there. The much smaller MiSeq did not have the same requirement and it could be used shortly after delivery.

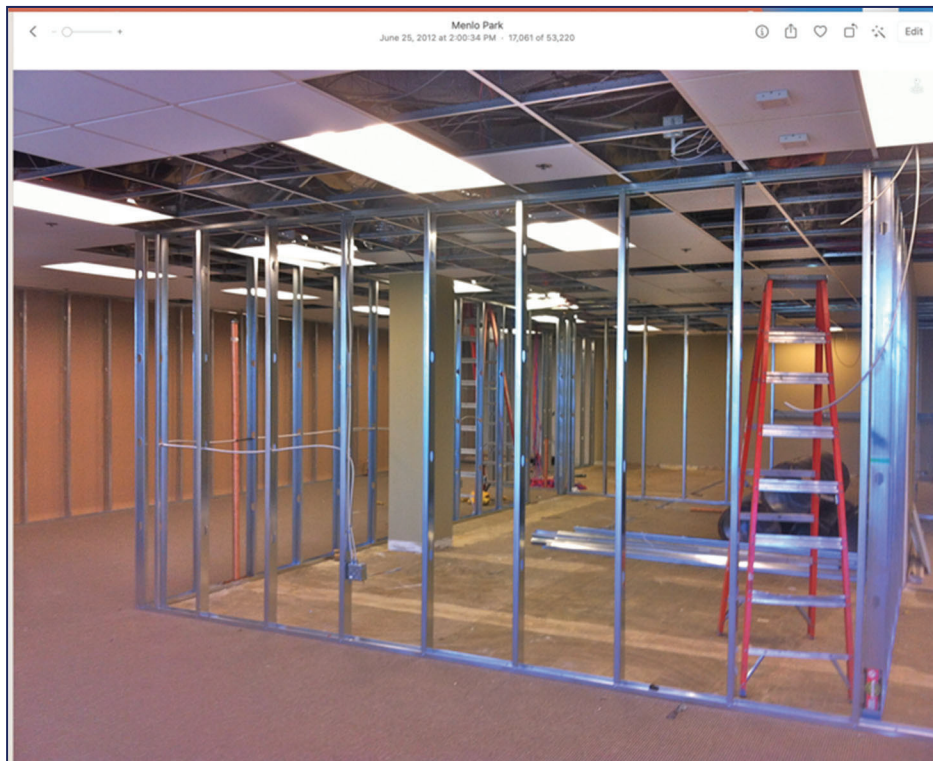
352. On June 21st, 2012, I took this photo, showing that the construction of our lab had started. Here you see that a wall of what had previously been a kitchen and break room had been torn down and the sink which had been there had been removed.



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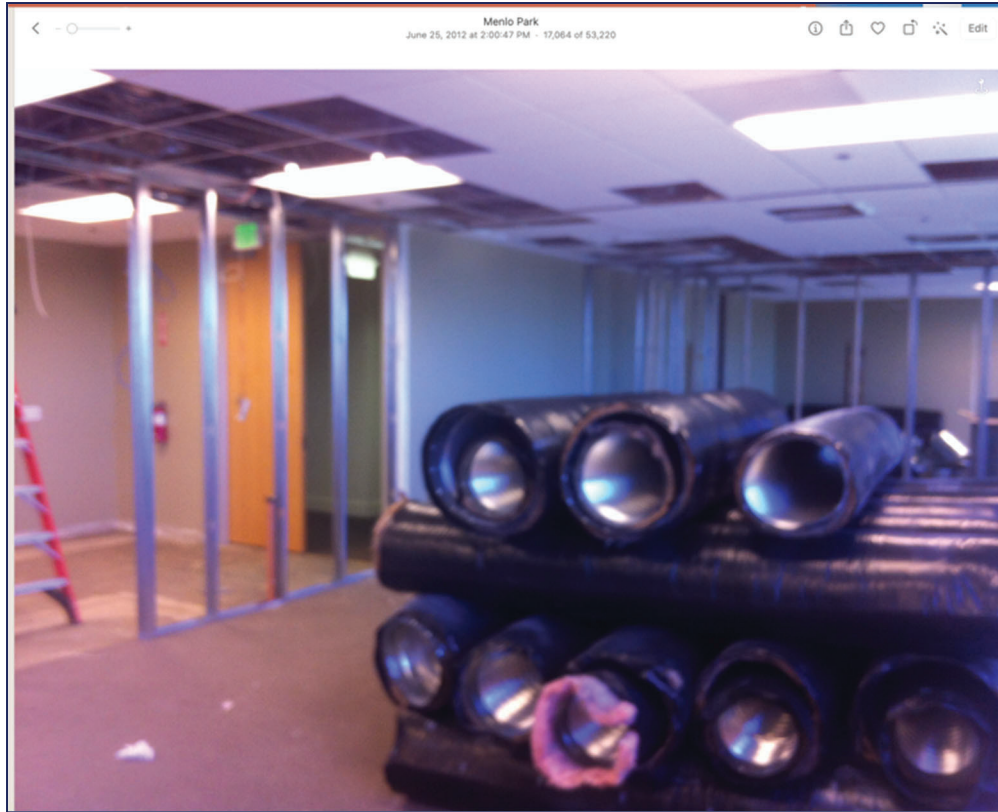
353. EX2059 is a Google Calendar invitation for the Personalis Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. The meeting took place on Friday, June 22, 2012, from 4-6pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

354. On June 25th, 2012 I took this photo of studs for walls of our new lab installed as part of the construction:



The same day I took this photo of ducts waiting to be installed, to implement the air flow required for the lab:

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355. On June 29th, 2012, we began our first DNA sequencing run on the MiSeq instrument. It was a test run using an Illumina-standard test DNA sample of the virus Phi-X. We sequenced it with 2 x 150 base paired-end reads, which was standard for the MiSeq at that time.

356. EX2060 is a Google Calendar invitation for the Personalis Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. The meeting took place on Friday, June 29, 2012, from 4-6pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

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C. Evidence of diligence in July 2012

357. My co-inventors and I were reasonably continuous and diligent in our pursuit of the Accuracy Program throughout July 2012. Evidence of our diligence includes, for example, EX2066, which is a Google Calendar invitation for the Personalis Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. The meeting took place on Friday, July 6, 2012, from 4-6pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

358. EX2067 is a Google Calendar invitation for the Personalis Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. The meeting took place on Friday, July 13, 2012, from 4-6pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

359. EX2070 is a true and correct copy of an email and PowerPoint presentation I received from Richard Chen on July 17, 2012. This PowerPoint was prepared for the Personalis Board of Directors July Meeting, and includes updates on research and development within Personalis, including an update on the Accuracy Program.

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360. EX2071 is an email and attached PowerPoint presentation I sent on July 18, 2012. The PowerPoint presentation is my CEO Overview that I sent to Richard Chen, Carol Tillis, Eliane Sousa, and Christian Haudenschild in advance of the July 2012 Board of Directors meeting. The PowerPoint presentation discusses genome sequencing related to the Accuracy Program.

361. EX2072 is a Google Calendar invitation for Personalis' July Board of Director Meeting. The meeting took place on Wednesday, July 18, 2012, from 1:30-3:30pm. During the Board of Directors meeting, we discussed updates on the Accuracy Program.

362. On July 19th, 2012, Shujun Luo reported that she had completed our first low coverage human genome sequencing experiment on the MiSeq instrument, using the NIST-standard human DNA sample NA12878.

363. EX2068 is a Google Calendar invitation for the Personalis Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. The meeting took place on Friday, July 20, 2012, from 4-6pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

364. EX2074 is a true and correct copy of an email I received from Mark Pratt on July 24, 2012. This email contains Mark Pratt's notes from a Personalis lab

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sequencing discussion that I attended. This email further discusses the development of Exome+, which was a product from the Accuracy Program before it became known as ACE Exome.

365. On July 25th, 2012, Shujun Luo reported completion of another low coverage whole human genome sequence run on our MiSeq instrument, also using the NA12878 DNA sample. In this case though we set up the MiSeq in a non-standard way, to achieve 2x300 base paired-end reads. This was beyond the normal specification of the MiSeq, but we speculated that it would be able to achieve useful results and our later analysis supported that. We pushed the limits on paired-end read length because our product plan included supplementing a whole genome or exome with hybrid capture and then long-read sequencing of parts of the genome with alignment degeneracy. This was beyond the capability of the HiSeq, which could provide sequencing of the majority of a genome at much lower cost than a MiSeq.

366. EX2069 is a Google Calendar invitation for the Personalis Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. The meeting took place on Friday, July 27, 2012, from 4-6pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

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D. Evidence of diligence in August 2012

367. My co-inventors and I were reasonably continuous and diligent in our pursuit of the Accuracy Program throughout August 2012. Evidence of our diligence includes, for example, EX2079, which is a Google Calendar invitation for the Personalis Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, and Mark Pratt, among others. The meeting took place on Friday, August 3, 2012, from 4-6pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

368. On August 4th, 2012, our labs had been completed and Christian Haudenschild reported that Illumina had arrived to begin installation of our HiSeq instrument and that it should be available for our experimental work by August 13th, 2012.

369. EX2075 and EX2076 are true and correct copies of an email thread and attachment I received and responded to on August 8, 2012. Shujun Luo created the attached PowerPoint Presentation, which discusses lab options and data for the Accuracy Program. This showed that Shujun had identified a DNA sequencing chemistry which could provide enough reads in regions of certain difficult VNTR's (variable length tandem repeats) that the lobSTR algorithm could correctly call them. One such example was the Huntington's disease locus in the HTT gene, which I had

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examined in my own genome data in 2010 and found no coverage. Shujun also provided data on our ability to sequence through difficult motifs, particularly long homopolymers.

370. EX2077 is a true and correct copy of an email thread dated August 10, 2012. This email discusses Personalis projects, including the Accuracy Program. Specifically, this email discusses computing infrastructure that we installed for data processing and metrics propagation regarding the Accuracy Program.

371. EX2080 is a Google Calendar invitation for the Personalis Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. The meeting took place on Friday, August 10, 2012, from 4-6pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

372. Exhibit 2118 is a Google Calendar invitation for the Personalis Board of Director Meeting. The meeting took place on Tuesday, August 14, 2012, from 9am-11am. During the Board of Directors meeting, we discussed updates on the Accuracy Program.

373. EX2081 is a Google Calendar invitation for the Personalis Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark

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Pratt, and myself, among others. The meeting took place on Friday, August 17, 2012, from 4-6pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

374. EX2082 is a true and correct copy of an email and finalized PowerPoint presentation I sent on August 20, 2012. The PowerPoint presentation discusses an overview of Personalis, including its ability to obtain Series A funding. Slide 13 of the presentation provides a summary of the Accuracy Program, including “Accuracy at the laboratory level” and “Accuracy in medical interpretation.”

375. EX2078 is a true and correct copy of an email thread dated August 28, 2012. This email thread discusses sequencing reagents and testing results related to the development of the Accuracy Program.

E. Evidence of diligence in September 2012

376. My co-inventors and I were reasonably continuous and diligent in our pursuit of the Accuracy Program throughout September 2012. Evidence of our diligence includes, for example, EX2083, which is a true and correct copy of an email and attached PowerPoint presentation from Richard Chen to me dated September 4, 2012. This email and PowerPoint presentation are for a Board of Directors meeting regarding research and development milestones and goals for Personalis as a company, including the Accuracy Project.

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377. EX2084 is a true and correct copy of an email I sent on September 4, 2012, regarding the upcoming Personalis Board of Directors meeting. This email explains Personalis' progress in genome sequencing as it relates to the Accuracy Program, including expanded data processing capabilities.

378. EX2086 is a true and correct copy of an email and attached PowerPoint presentation I sent on September 5, 2012. The PowerPoint presentation is my CEO Overview that I sent to Richard Chen, Carol Tillis, Eliane Sousa, and Christian Haudenschild in advance of the September 2012 Board of Directors meeting. The PowerPoint presentation discusses implementation of the proprietary content in lab assays related to Exome Plus, which was previously referred to as the Accuracy Program.

379. EX2085 is a Google Calendar reminder for the Personalis Board of Directors Meeting that was attended by several Personalis employees and founders, including Richard Chen and myself, among others. The meeting took place on Wednesday, September 5, 2012, from 9-11am. During the weekly team meeting, we discussed updates on the Accuracy Program, including project development and prioritized tasks.

380. EX2088 is a Google Calendar invitation for the Personalis Monthly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark

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Pratt, and myself, among others. The meeting took place on Friday, September 7, 2012, from 4-6pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

381. In September 2012, the Board approved expenditure of up to \$560,000 plus taxes and shipping to acquire a second HiSeq-2000 DNA sequencing instrument. See September 5, 2012 Meeting Minutes at page 2.

382. EX2089 is a true and correct copy of a Purchase Order submitted by Shujun Luo to Agilent Technologies for custom SureSelectXT capture probe libraries that was submitted to Agilent on September 27, 2012. This purchase, for over \$29,000, included three Personalis-designed capture probe sets, for filling in coverage gaps caused by High %GC sequences, for adding content to an exome outside the coding regions of genes, and for capture and long-read sequencing of molecules from portions of the genome with alignment degeneracy.

F. Evidence of diligence in October 2012

383. My co-inventors and I were reasonably continuous and diligent in our pursuit of the Accuracy Program throughout October 2012. Evidence of our diligence includes, for example, EX2094, which is a true and correct copy of an email I received from Scott Kirk on October 4, 2012. This email describes status updates for various Personalis projects, including Exome Plus (formerly referred to as the Accuracy Program). Specifically, research and development goals for Exome

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Plus included determining when to supplement the project with experimental plans based on the original concept.

384. EX2090 is a Google Calendar invitation for the Personalis Monthly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. The meeting took place on Friday, October 5, 2012, from 4-6pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

385. EX2096 is a true and correct copy of an email and PowerPoint presentation I sent to Richard Chen and Mark Pratt, named inventors on the '394 patent and the '033 patent, among others, on October 9, 2012. This PowerPoint presentation summarizes the current status of the Accuracy Program, and served as a discussion guide for an upcoming team meeting.

386. EX2091 is a true and correct copy of a Google Calendar invitation for the Accuracy Requirements Walk Through Meeting that was attended by several Personalis employees and founders, including Richard Chen, Mark Pratt, and myself, among others. The meeting took place on Tuesday, October 9, 2012, from 3-5pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

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387. EX2095 is a true and correct copy of an email and attachment I received from Scott Kirk on October 10, 2012. The attachment is a Word document titled “Personalis Genome Service.” The attachment further explains the key differentiators and industry issues that Personalis’ Exome Plus (formerly referred to as the Accuracy Program) overcomes. The attachment took many months to complete and describes the data analysis Personalis performed in developing Exome Plus.

388. EX2092 is a true and correct copy of a Google Calendar invitation for the Personalis Accuracy Bi-Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Mark Pratt, Shujun Luo, and myself, among others. The meeting took place on Wednesday, October 10, 2012, from 3-4pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

389. EX2097 is a true and correct copy of an email and PowerPoint presentation I sent to several Personalis employees and founders, including Richard Chen, Mark Pratt, and others, on October 12, 2012. The PowerPoint presentation discusses current Personalis projects and prioritization, including at Slide 5 a discussion of “Exome-Plus testing” (formerly referred to as the Accuracy Program) and that “Mark is developing a whole project plan & wants to review it” and “first round pullout kits are due in about 3 weeks.”

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390. EX2098 is a true and correct copy of an email I sent on October 19, 2012. The email expresses my interest in filing a patent application for Exome Plus (formerly referred to as the Accuracy Program). Because we had been receiving consumer inquiries, my opinion was that seeking a patent would provide a greater benefit to Personalis than maintaining the Exome Plus as a trade secret.

391. EX2093 is a true and correct copy of a Google Calendar invitation for the Personalis Accuracy Bi-Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Mark Pratt, Shujun Luo, and myself, among others. The meeting took place on Wednesday, October 24, 2012, from 3-4pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

392. On October 30th, 2012, we received from Agilent our first hybrid capture probe sets, ordered September 27th, 2012.

393. EX2100 is a true and correct copy of an email and PowerPoint presentation I received from Richard Chen on October 31, 2012. This PowerPoint was prepared for the Personalis Board of Directors Meeting. Slide 6 contains a review of “key goals & milestones” for Exome Plus (formerly referred to as the Accuracy Program), including custom pullout data. This PowerPoint further explains that Exome Plus will be part of a two-part commercial launch.

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G. Evidence of diligence in November 2012

394. My co-inventors and I were reasonably continuous and diligent in our pursuit of the Accuracy Program throughout November 2012. Evidence of our diligence includes, for example, EX2099, which is a true and correct copy of an email and attached PowerPoint presentation I sent on November 1, 2012. The PowerPoint presentation is my CEO Overview that I sent to Richard Chen, Carol Tillis, and Christian Haudenschild in advance of the November 1, 2012 Board of Directors meeting. The PowerPoint presentation discusses genome sequencing related to Exome Plus (formerly referred to as the Accuracy Program), including commercialization efforts.

395. EX2101 is a true and correct copy of a Google Calendar invitation for the Personalis Board of Director Meeting. The meeting took place on Thursday, November 1, 2012, from 9am-11am. During the Board of Directors meeting, we discussed updates on the Accuracy Program.

396. In November 2012, the Board approved expenditure of up to \$110,000 plus taxes and shipping to acquire an additional MiSeq DNA sequencing instrument. See November 1, 2012 Meeting Minutes at page 2.

397. EX2102 is a true and correct copy of an email and attached PowerPoint I received from Shujun Luo on November 1, 2012. The PowerPoint discusses lab

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updates for Exome Plus (formerly referred to as the Accuracy Program), including current workflow and project goals.

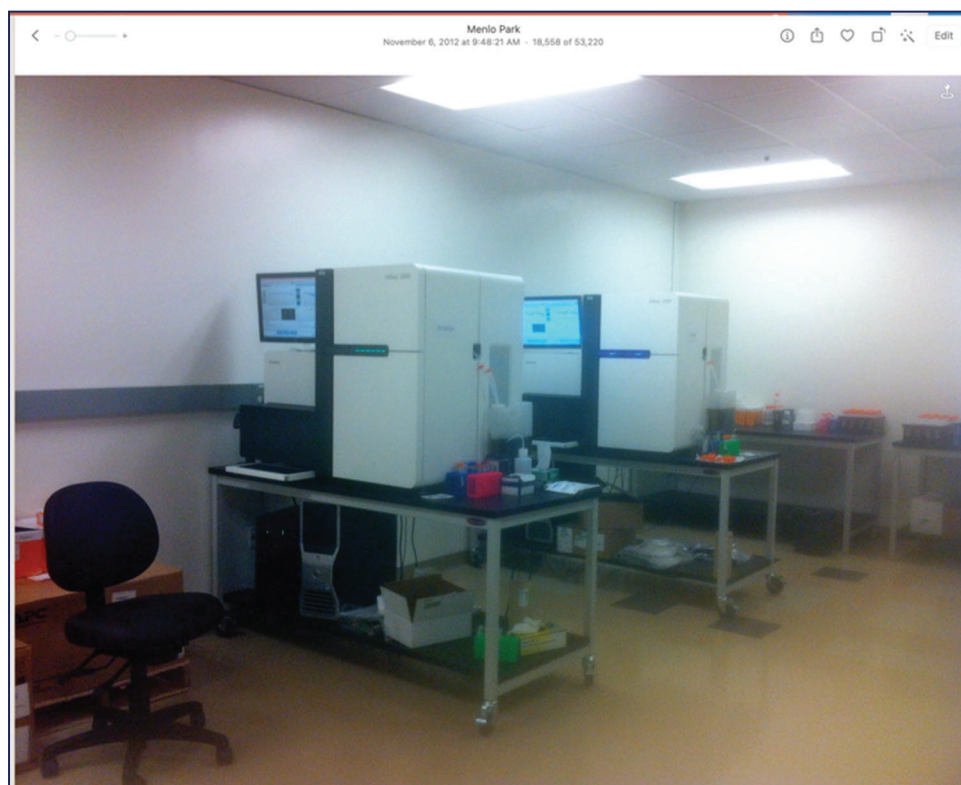
398. Exhibit 2123 is a Google Calendar invitation for the Personalis Monthly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. The meeting took place on Friday, November 2, 2012, from 4-6pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

399. On November 5th, 2012, I took this photograph of Shujun Luo standing in our lab with our MiSeq instrument and a device called a cBot, which was part of the HiSeq system.



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The same day, I also took this photo showing our two Illumina HiSeq-2000 instruments. This gave us a modest but sufficient DNA sequencing capability for the time:



The same day, I also took this photo of Shujun Luo at the molecular biology workbench in our new lab:

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400. EX2103 is a true and correct copy of a Google Calendar invitation for the Personalis Accuracy Bi-Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Mark Pratt, and myself, among others. The meeting took place on Wednesday, November 21, 2012, from 3-4pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

H. Evidence of diligence in December 2012

401. My co-inventors and I were reasonably continuous and diligent in our pursuit of the Accuracy Program throughout December 2012. Evidence of our diligence includes, for example, EX2104, which is a true and correct copy of a

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Google Calendar invitation for the Personalis Accuracy Bi-Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. The meeting took place on Friday, December 7, 2012, from 10:30am-12pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

402. EX2105 is a true and correct copy of an email and PowerPoint presentation I received from Richard Chen on December 12, 2012. This PowerPoint was prepared for the Personalis Board of Directors, and explains leveraging Personalis' proprietary content for the Exome Plus (formerly referred to as the Accuracy Program).

403. EX2106 is a true and correct copy of an email and attached PowerPoint presentation I sent on December 13, 2012. The PowerPoint presentation is my CEO Overview that I sent to Richard Chen, Carol Tillis, and Christian Haudenschild in advance of the December 2012 Board of Directors meeting. The PowerPoint presentation discusses genome sequencing updates related to Exome Plus (formerly referred to as the Accuracy Program).

404. Privileged communications with patent counsel regarding the pursuit of the provisional patent application that was eventually filed on January 17, 2023 occurred on the 18th, 21st, and 27th of December 2012. Personalis and its legal

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counsel diligently pursued drafting of the patent application that was eventually filed on January 17, 2013.

I. Evidence of diligence in January 2013

405. My co-inventors and I were reasonably continuous and diligent in our pursuit of the Accuracy Program from January 1, 2012 through the filing of the provisional patent application on January 17, 2012. Evidence of our diligence includes, for example, Exhibit 2117 is a true and correct copy of an email thread dated January 11, 2013. This email thread is between several Personalis employees and founders, including Richard Chen, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. This email explains Personalis' decision to rename Exome Plus to ACE Exome.

406. Exhibit 2119 is a true and correct copy of an email I sent to Richard Chen, Christian Haudenschild, and Carol Tillis on January 14, 2013. The email outlines my notes from the staff meeting that occurred earlier that same day. Specifically, I confirmed that Personalis would be changing the name of Exome Plus to ACE Exome.

407. EX2108 is a true and correct copy of a Google Calendar invitation for the Personalis Accuracy Bi-Weekly Team Meeting that was attended by several Personalis employees and founders, including Richard Chen, Hugo Lam, Sarah Garcia, Gemma Chandratillake, Mark Pratt, and myself, among others. The meeting

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took place on Wednesday, January 16, 2013, from 3-4pm. During the weekly team meeting, we discussed updates on the Accuracy Program.

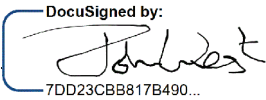
408. Privileged communications with patent counsel regarding the pursuit of the provisional patent application occurred on the 4th, 10th, 16th, 17th, and 18th of January 2023.

409. Based on at least the foregoing, my co-inventors and I were reasonably continuous in our diligence leading from conception of the invention by no later than May 8, 2012 through the filing of the provisional application on January 17, 2013.

V. CERTIFICATION

410. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 10/5/2023

By:  _____
7DD23CB817B490...
John West