UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS INC.,
Petitioner,

v.

PERSONALIS, INC.,
Patent Owner.

IPR2023-00224 (Patent 11,384,394)
IPR2023-00317 (Patent 11,408,033)

DECLARATION OF JOHN QUACKENBUSH, PH.D. IN SUPPORT OF PETITIONER'S REPLY TO PATENT OWNER RESPONSE

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I. Introduction

1. My name is John Quackenbush. I previously submitted declarations in support of Foresight Diagnostics Inc.'s Petitions for *inter partes* review of U.S. Patent Nos. 11,384,394 and 11,408,033.

2. I submit this declaration to respond to certain arguments raised in the declaration of Patent Owner Personalis's expert Dr. Furneaux. Ex2031. I also respond to some aspects of the declaration submitted by Mr. West regarding the alleged conception of the claimed inventions. Ex2032.

II. Response to Dr. Furneaux's Opinions Regarding Claim Construction

3. Patent Owner and Dr. Furneaux's response to the Petitions raise issues regarding the appropriate claim construction of the terms "whole genome sequencing" ('394 patent) and "capture probes" ('394 and '033 patents). I briefly summarize the disputes here.

a. For "whole genome sequencing" the parties dispute whether Leary's mate-pair whole genome sequencing technique satisfies the claim. In short, the contemporaneous literature described Leary (or analogous techniques) as "whole genome sequencing," thus in my opinion a POSA would have understood that Leary discloses WGS regardless of the precise countours of a formal claim construction for this term. Nevertheless, I understand that the Board has preliminarily construed

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"whole genome sequencing" to mean "a nontargeted approach to sequencing all or almost all of the genome." Under this framework, the question ultimately becomes whether Leary's technique – which is a nontargeted approach – sequences "almost all of the genome." (There is no dispute that sequencing "all" of the genome was not possible at the relevant time (and perhaps even today).) A POSA's understanding of "almost all" would have taken into account the techniques that the contemporaneous literature – including Personalis's patents – considered to be "whole genome sequencing," which included low coverage techniques that performed nontargeted sequencing at 50% or less (including 10%) sequence coverage. Accordingly, Leary's technique, which Dr. Furneaux asserts achieves between 53-90% sequence coverage, sequences what a POSA would have understood to be "almost all" of the genome.

b. For "capture probes," the parties dispute whether PCR primers fall within the scope of that term as it would have been understood in light of the specification. In light of the specification, the Board, in my opinion, was correct to construe the term to encompass, at a minimum "PCR primer capture probes and solution-based hybridization capture probes (e.g., biotinylated oligonucleotide baits)." Personalis disputes

this construction, nominally contending that capture probes include array-based capture probes on a solid support or solution-phase hybridization capture probes. In application, Personalis seeks to limit the term to "pulldown probes," which a POSA would have understood to encompass biotinylated oligonucleotide baits. Such baits are comprised of a nucleic acid linked to a biotin moiety. Because the specification is clear that biotin is a separate, optional component of a capture probe, e.g., a "label," in my view a POSA reading the Specification would not adopt Personalis's construction. Moreover, as detailed below, the testimony of Mr. West and the contemporaneous literature confirm that PCR primers satisfy the claim.

A. "whole genome sequencing"

4. I understand that it in its Institution Decision for the '394 patent, the Board preliminarily construed the term "whole genome sequencing" as used in claim element 1(b) of the '394 patent to mean, "a nontargeted approach to sequencing all or almost all of the genome." As explained in Section III, below, the grounds of unpatentability set forth in my initial declaration satisfy this construction.

5. As discussed further below, Dr. Furneaux's application of the preliminary construction adds potentially indeterminate mathematical endpoints to the term "whole genome sequencing" that are inconsistent with how the term was

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understood in the literature (and hence by a POSA) at the time of the priority date (regardless of whether May 8, 2012 or January 13, 2013 is used). The literature of the time demonstrates that a POSA would have understood that the term "whole genome sequencing" encompassed Leary's PARE technique.

6. The '394 patent introduces the term "whole genome sequencing," in the "Background of the Invention," purporting to define the invention (consistent with the intent of Personalis's "Accuracy Program") as techniques that improve known drawbacks associated with prior art "whole genome sequencing" methods. Ex1001, 1:23-25 ("Current methods for whole genome [] sequencing may be costly and fail to capture many biomedically important variants."). The patent does not expressly define the term "whole genome sequencing," let alone in a manner that clearly alters its meaning to refer to the allegedly "improved" techniques.

7. Accordingly, a POSA would understand that when the patent uses the term "whole genome sequencing," it is referring to the methods that existed at the time, which included the alleged shortcomings identified in the patent. I note this explicitly because aspects of Dr. Furneaux's testimony suggest that he applied an interpretation of "whole genome sequencing" that imports the patent's alleged improvements to sequencing that would not have been reflected in the meaning of the term at the priority date.

8. For example, Dr. Furneaux contends that "to cover the all the base pairs in the whole human genome using the mate pair approach in Leary, one would need to very accurately sequence about 64 million non-overlapping mate-pairs (i.e., 3.2 billion divided by 50)." Ex2031 ¶96. But there is no requirement in the claims that the whole-genome sequencing achieve an undefined standard of "very accurate," and at most, the patent requires that "[t]he accuracy of the sequencing reaction may be greater than about 70%." Ex1001, 7:18-14 ("The accuracy of the sequencing reaction may be greater than about 70%, 75%, 80%, 90%, 91% . . . ."). Dr. Furneaux further contends that "one would still need to contend with biases such as . . . G/C rich sequences." Ex2031 ¶96. But at his deposition, Dr. Furneaux confirmed that the claims do not require implementing the '394 patent's purported solution to G/C rich sequences. Ex1223, 103:15-104:20 (Q. And that's the one that's not reflected in the claims of the '394 patent; correct? A. Absolutely not. And yeah, why [] it isn't, you know, I couldn't say.).

1. Application of the preliminary construction.

9. The Board's construction includes the requirements that the "whole genome sequencing" assay sequence "all" or "almost all of the genome." This construction is satisfied by the cited prior art, because a POSA would have understood that "almost all" of the genome encompassed the shallow paired-end and mate pair sequencing techniques that were commonly used in the art. *See* Section

III. I clarify in this section some of the ambiguities injected by Dr. Furneuax's application of the Board's construction.

a) "All of the genome"

10. As Mr. West confirmed, sequencing of "all of the genome," to the extent possible at all, became possible only recently, well after the filing of the patent:

> Q. When did it first become possible to sequence a human genome consistent with approximately 3.2 billion base pairs without any gaps?
>
> A. In the last few years, ***quite a long time after we filed these patents*** or filed for the – filed the provisional filing. So – but I don't know the exact date. You could look it up.

Ex1222, 46:15-21; *id.* 37:17-24 ("It was well known at that time and is still mostly true that the – there are portions of the human genome which are difficult for current sequencing technologies and sequencing technologies of that time to capture . . . . And – and so those are not included in the reference sequence."). The '394 patent's usage of the term "whole genome sequencing" is consistent with this understanding, as it repeatedly recognizes that "whole genome sequencing" data has gaps, misses certain regions, and includes zero and low mean coverage regions.[1]

[1] In fact, Mr. West was correct regarding the relative dates of the patent filings and the completion of the genome. It was not until March 2022 that a "complete" genome sequence was announced (Nurk 2022;

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11. Even though no method was capable of sequencing "all of the genome," this endpoint of the Board's construction is still important because it must be known to apply the "almost all" component of the Board's construction. For example, Dr Furneaux testified to the following at deposition:

> Q. Your testimony was since your declaration, you've pondered the question further, including in light of Mr. West's experience and [Illumina's] experience, and determined that the threshold for almost all of the genome was 90 percent; correct?
>
> A. Coverage.
>
> Q. 90-percent coverage?
>
> A. Uh-huh.

Ex1223, 97:21-98:8.

12. In light of this testimony, Dr. Furneaux was shown the formula below. Ex1223, 106:12-17; Ex1210. To determine whether a given experiment sequenced "almost all of the genome," one must know the appropriate denominator to use.

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https://www.genome.gov/news/news-release/researchers-generate-the-first-complete-gapless-sequence-of-a-human-genome) and even then the Y chromosome was not completed until August 2023 (https://www.nih.gov/news-events/news-releases/researchers-assemble-first-complete-sequence-human-y-chromosome).

Sequence Coverage

"almost all of the genome"

$$90\% = \frac{\text{X basepairs}}{\text{Y basepairs}}$$

13. As Mr. West confirmed at deposition, the value for "all of the genome" that a POSA would have applied was the size of the known reference genome to which raw sequence reads are mapped in a sequencing assay. "Generally, the goal was to sequence as much as possible of the known reference sequence because the – you could only form a consensus sequence by aligning sequence reads to the reference." Ex1222, 38:3-6; *see also id.* 38:7-8 ("Any portion of the human genome, which was not in the official reference, couldn't be included.").

14. The ungapped length of the reference sequence at the time the '394 patent was filed, hg18, rounded to 2.9 Gb. Ex1209; Ex1222 45:6-9 ("[W]hen we say that the length of the human reference sequence at that time was about 2.85 billion bases, I believe that did not include any of – gaps."). These datapoints are consistent

with the ’394 patent itself, which uses a genome size of “2,861 Mbp,” (2.86 Gbp) as the size of the “DegappedGenome” in the few examples of laboratory preparation steps for sequencing experiments noted in its Specification. *See* ’394 patent, Table 13.

15. Accordingly, a POSA would have understood “all of the genome,” to mean the ~2.86 Gbp recognized in the degapped reference genome known at the priority date.

b) “Almost all of the genome”

(1) Dr. Furneaux’s 90% Opinion

16. I note that Dr. Furneaux added further confusion to his 90% opinion, testifying in response to the question “Did the 90-percent number change over time?” that “I think the Board is extremely insightful here – is that they are well aware that all of this is a moving target.” Ex1223, 94:21-25. Thus, it appears that Dr. Furneaux considers that both the threshold percentage for “almost all,” as well as the denominator “Y” to use in the equation referenced above, are “a moving target.” I understand that this is legally incorrect, as the meaning of a claim term is the meaning it would have had to a POSA at the time of the alleged invention.

17. Setting aside Dr. Furneaux’s testimony that his 90% opinion is a “moving target” in multiple respects, it is difficult to apply his understanding of the

term because he would not even identify what he believed to be the appropriate denominator.

18. In his declaration testimony, Dr. Furneaux readily divided 2.9 billion base pairs sequenced in Leary by the known length of the human genome (3.2 billion bases) to arrive at 91% sequence coverage. Ex2031 ¶97. In that analysis, he asserted that 2.9 billion bases was "far less than the 3.2 billion bp acknowledged to be present in the reference genome at this priority date." *Id.* I note first that Dr. Furneaux incorrectly called 3.2 billion base pairs the length of the known reference genome. No reference genome today, let alone in 2012-2013, lacked gaps. *See* Section II.A.1.a), above. As noted above and confirmed by the patent itself, the reference genome at the relevant time period was about 2.86 billion bases. *See id.*

19. However, Dr. Furneaux could not explain how to use his new 90% cutoff in practice. For example he suggested that the number of bases required to be sequenced in order to satisfy "almost all of the genome" could vary depending on the experiment:

> Q. And I just wanted to see again, are you able to tell me what numbers you would plug in for X and Y in this equation to get to the genome?
>
> A. So let's make sure that we're talking about the same thing. We're talking about an inspection assay that determines whether are residue is covered by a read.

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> Are we agreed on that?
>
> Q. I believe so.
>
> A. Okay. ***And so here you're referring to Y being the size of genome in base pairs.***
>
> Q. ***And what is Y?***
>
> A. ***What is Y?*** Well I'm sure there's going to be discussions about what Y may or may not be, ***and what's important is what the investigators who were carrying out the experiment might have thought it might be***.

Ex1223, 106:1-17. Dr. Furneaux further testified that he understood this number to be a moving target, and that it couldn't be understood from the Board's construction: "So the construct that the Board provided merely indicated nearly all, and what we're saying here is 90 percent corresponds to nearly all. ***There isn't anything in the Board's construct that indicates how one arrives at that number which, for our purposes, is to clarify what 'nearly all' means.***" *Id.*, 107:3-13.

20. In light of the discussion above, however, the record is clear that the appropriate denominator in such a calculation is 2.86 billion base pairs, the known length of the degapped reference genome. For example, Table 13 of the '394 patent purports to show Personalis's data using its "improved" techniques. The data for "whole genome" use a "DegappedGenome" length of 2,861 Mbp (2.86 billion base

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pairs), and report an "improved" whole genome sequencing assay which covers at most 98.7% of those bases, confirming that even Personalis's "improvements" did not achieve sequencing "all" of the genome. Table 13 further shows that the patent considers sequencing 95.3% of 2.8 billion bases to be "improved" whole genome sequencing.

75 76

TABLE 13

				Product Category			
				Whole Genome		Whole Exome	
				Product Type			
				Full Flowcell (PL 2.0) Personalis 92x		TruSeqExome (PL 2.0) B Personalis 54x	
		Set Size					
	~Price Point	Size	Unit	A	B	A	B
Bronze	NEMAR corrections						
Genome	NEMAR.DegappedGenome	1,102	kbp	765,476	64,324	25,409	3,170
	NEMAR.RefSeqExons	17,999	kbp	12,488	1,059	10,436	1,045
	NEMAR.RefSeqCodingExons	6,692	kbp	4,713	383	4,460	419
	NEMAR.RefSeqUTR	11,307	kbp	7,775	676	5,976	626
	NEMAR.PersonalisExome	7,394	kbp	5,029	435	4,356	446
	NEMAR.PersonalisVariants	4,050	kbp	2,171	360	376	72
	NEMAR.PersonalisNetContent	11,080	kbp	7,005	769	4,547	489
	Reference						
	DegappedGenome	2,861	Mbp	98.7%	51	3.7%	50
	RefSeqExons	70,467	kbp	98.7%	52	77.9%	49
	RefSeqCodingExons	33,366	kbp	99.0%	53	85.4%	49
	RefSeqUTR	37,101	kbp	98.4%	52	69.1%	50
	PersonalisExome	29,056	kbp	99.2%	53	81.3%	49
	PersonalisVariants	172	kbp	99.8%	49	83.0%	49
	PersonalisNetContent	29,095	kbp	99.3%	53	80.0%	49
	Content.RefSeqFirstCodingExons	2,389	kbp	99.1%	53	74.0%	47
	Content.GCgt70	1,639	kbp	99.0%	53	38.2%	48
	Content.NoMapPE0	903	kbp	71.0%	46	54.0%	38
	Content.Segmental_Duplications	2,046	kbp	89.1%	43	71.9%	38
	Content.HomopolymerFlank	136	kbp	97.2%	44	57.7%	41
	Content.STRgt50f50	453	kbp	94.0%	42	66.8%	34
	SNPs						
	DegappedGenome	2,861	Mbp	95.3%	0.34%	1.9%	1.65%
	RefSeqExons	70,467	kbp	95.8%	0.21%	61.9%	1.60%
	RefSeqCodingExons	33,366	kbp	95.0%	0.19%	69.7%	1.61%
	RefSeqUTR	37,101	kbp	96.3%	0.22%	57.2%	1.60%
	PersonalisExome	29,056	kbp	95.6%	0.21%	64.0%	1.50%
	PersonalisVariants	172	kbp	99.8%	0.02%	12.6%	0.31%
	PersonalisNetContent	29,095	kbp	97.0%	0.14%	44.1%	1.44%
	Content.RefSeqFirstCodingExons	2,389	kbp	92.8%	0.10%	60.5%	1.17%
	Content.GCgt70	1,639	kbp	91.2%	0.11%	24.3%	1.21%
	Content.NoMapPE0	903	kbp	65.4%	1.06%	46.3%	10.98%
	Content.Segmental_Duplications	2,046	kbp	83.6%	0.97%	56.2%	7.00%
	Content.HomopolymerFlank	136	kbp	81.8%	1.28%	23.1%	13.64%
	Content.STRgt50f50	453	kbp	76.6%	1.29%	59.1%	9.90%

(2) Personalis's contemporaneous patents set the cutoff no higher than 50%.

21. Dr. Furneaux's 90% cutoff is far higher sequence coverage than a POSA would have required to consider a particular sequencing assay to be "whole genome sequencing." Indeed, Personalis's contemporaneous patents define "whole

genome sequencing" as "untargeted sequencing," and do not impose a hard boundary on the required sequence coverage. Indeed, Personalis's contemporaneous patents reflect the knowledge and understanding of a POSA at that time, which recognized that even so-called "low coverage" whole genome sequencing techniques constituted "whole genome sequencing." While I understand these patents may not necessarily qualify as prior art, I understand that non-prior art evidence of what was known can be relied on for indicating the level of ordinary skill in the art, what certain terms would mean to one with ordinary skill in the art, and how one with ordinary skill in the art would have understood a prior art disclosure.

22. For example, in Personalis's U.S. Patent No. 11,456,058, which claims priority to August 30, 2013, the inventors (which include John West), repeatedly use the term "whole genome sequencing" as synonymous with "untargeted" sequencing, as distinguished form "targeted" sequencing like "exome sequencing." Ex1211 ('058 patent). For example:

- "Methods provided herein advantageously employ untargeted (e.g., whole genome) sequencing and target-specific sequencing to generate an output that indicates the presence or absence of one or more polymorphisms in the sample of the subject." *Id*., 1:45-49.
- "In another embodiment, the whole genome sequencing data comprises paired-end reads. In another embodiment, the whole genome sequencing

data comprises mate-pair reads. In another embodiment, the paired-end reads have insert-sizes of larger than about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4***,*** 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0, 15.0, 16.0, 17.0, 18.0, 19.0, 20.0, 30.0, 40.0, 50.0, 60.0, 70.0, 80.0, 90.0, or 100.0 kilobasepairs. In another embodiment, the ***mate-pair reads have insert-sizes of*** larger than about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, ***1.4***, **[**[2]] 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0, 15.0, 16.0, 17.0, 18.0, 19.0, 20.0, 30.0, 40.0, 50.0, 60.0, 70.0, 80.0, 90.0, or 100.0 ***kilobasepairs***." *Id.*, 3:37-49.

- "***Untargeted sequencing (i.e., whole genome sequencing)*** can determine the complete DNA sequence of the genome at one time. Untargeted sequencing (i.e., whole genome sequencing or the non-exonic portion of whole exome sequencing) can cover sequences of almost about 100 percent, or about 95%, of the sample's genome. ***In some cases, the untargeted sequencing (i.e., whole genome sequencing*** or non-exonic portion of the whole exome sequencing) can cover sequences of the whole genome of the nucleic acid sample of about or at least about 99.999%, 99.5%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80%, 79%, 78%, 77%, 76%, 75%, 74%, 73%, 72%, 71%, 70%, 69%, 68%, 67%, 66%, 65%, 64%, 63%, 62%, 61%, 60%, 59%, 58%, 57%, 56%, 55%, 54%, 53%, 52%, 51%, or 50%.

[2] As I explain further in Section III, Leary's whole-genome sequencing comprised mate-pair reads with insert lengths of 1,400 bp (1.4 kilobasepairs).

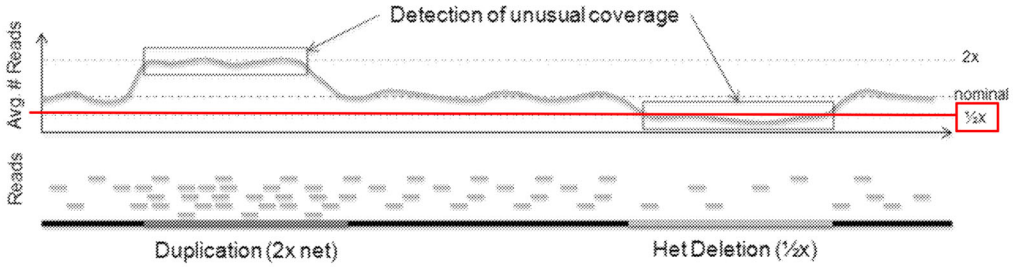
In some cases, the output can have a coverage of about or at least about 99.999%, 99.5%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80%, 79%, 78%, 77%, 76%, 75%, 74%, 73%, 72%, 71%, 70%, 69%, 68%, 67%, 66%, 65%, 64%, 63%, 62%, 61%, 60%, 59%, 58%, 57%, 56%, 55%, 54%, 53%, 52%, 51%, or 50% of the whole genome of the nucleic acid sample from a subject." *Id.* at 17:33-55.

- "The paired-end reads and/or mate-pair reads may sequence 100 basepairs (bp) reads on both ends of the insert. For example, when an untargeted sequencing data (e.g. whole genome sequencing data) is comprised of either paired-end reads with an insert size of larger than 1 kilobasepairs (kbp) or mate pairs with a separation of larger than 2 kbp, then even with low (˜1×) read depth, there may be at least about 10 molecules spanning any particular position on the genome, which may be sufficient to provide corroborating evidence of large CNVs detected by methods and systems presented herein. In another example, methods and systems of the present disclosure, such as the HMM method, can be used to detect a 50 kbp heterozygous deletion. When paired-end reads are used, about half of the paired-end molecules that span the detection breakpoints may have insert-sizes that are 50 kbp larger than normal. The insert-sizes may appear larger because they may be mapped to a reference with the sequence segment that is deleted in the sample. In some examples, when 1 kbp insert sizes are used, then 10 reads span the breakpoint, 5 of which can have anomalous insert size. Five reads may provide sufficient statistical power and information to generate accurate and/or reliable results. In some cases, if an insert-size of only about 300

basepairs is used, then there may be only about 3 reads that span the breakpoint on average, and half of that may be about 1 read, which may not provide sufficient statistical power and information to generate accurate and/or reliable results." *Id.* at 25:14-41.

- Figure 3 "illustrates a statistical model on sensitivity vs. coverage of genomic regions with single run whole genome sequencing data," *id.* 9:36-37, and depicts data confirming that ½x coverage "whole genome sequencing" was within the scope of the term. *See* Fig. 3 (annotated below).

Figure 3



23. In Personalis's U.S. Patent No. 11,584,968, which claims priority to 10/30/2014, the inventor Mr. West similarly defined "whole genome sequencing" to include "low coverage whole genome sequencing." For example, the '968 patent repeatedly states that its whole genome sequencing comprises "untargeted sequencing data (e.g., low coverage whole genome sequencing data) and one or more target-specific data." Ex1212 ('968 patent), 25:54-67; *see also id.*, 26:6-9 ("In some cases, the methods as disclosed herein comprise untargeted sequencing data

(e.g., a low coverage whole genome sequencing data)."); *id.*, 18-20 ("In some cases, the untargeted sequencing (e.g., whole genome sequencing) in the methods as disclosed herein . . . ."). The '968 patent cites on its face at page 4 "Pasaniuc, et al., Extremely low-coverage sequencing and imputation increases for genome-wide association studies," Ex1213, which describes "sequencing libraries appropriate for whole-genome sequencing" that are sequenced "at ultra-low coverage (0.1-0.5x[])," consistent with the patent's understanding that "whole-genome sequencing" refers to untargeted, as opposed to targeted (e.g., exome or specific sets of genes) sequencing.

24. Personalis's U.S. Patent No. 11,640,405, which claims priority to October 3, 2013, also used "whole genome sequencing" synonymously with "untargeted" sequencing.[3] For example, the '405 patent explains that "[t]he low coverage untargeted sequencing (i.e., single run whole genome sequencing data) can be fast and economical, and can deliver genome-wide polymorphism sensitivity in addition to the target-specific sequencing data. In addition, variants detected in the low coverage untargeted sequencing data can be used to identify known haplotype blocks and impute variants over the whole genome with or without targeted data." Ex1214, 13:21-25. Like the '058 patent, the '405 patent expressly considers 50%

[3] The inventors of the '405 patent include Gemma Chandratillake, Sarah Garcia, and Richard Chen, each of whom is named as an inventor or the '394 patent.

coverage whole genome sequencing to fall within the scope of "whole genome sequencing." *Id.*, 13:1-43; *see id.*, 13:31-44 ("In some cases, the untargeted sequencing (i.e., whole genome sequencing or non-exonic portion of the whole exome sequencing) can cover sequences of the whole genome of the nucleic acid sample of about or at least about 99.999%, 99.5%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80%, 79%, 78%, 77%, 76%, 75%, 74%, 73%, 72%, 71%, 70%, 69%, 68%, 67%, 66%, 65%, 64%, 63%, 62%, 61%, 60%, 59%, 58%, 57%, 56%, 55%, 54%, 53%, 52%, 51%, or 50%.").

(3) Extrinsic evidence cited by Dr. Furneuax sets the cutoff as low as 10%.

25. Over several paragraphs of his declaration, Dr. Furneaux argues in effect, that because certain prior art literature did not expressly cite Leary in non-exhaustive lists of whole-genome sequencing studies, that its technique did not constitute whole genome sequencing. The logic of that argument does not follow, and in fact a careful review of the references he cites confirms (a) that Leary's technique was understood to be whole genome sequencing; and (b) that the cutoff for "almost all of the genome" would need to be around 10% in order to encompass methods considered to be whole genome sequencing as of the priority date.

26. First, references, such as Forshew (Ex1030) and Diehn (Ex1112) (filed March 15, 2013) affirmatively describe Leary as a whole genome sequencing paper. Ex1030, 10 ("Previously proposed methods for personalized monitoring of tumor dynamics relied on . . . identification of rearrangements using whole genome sequencing (18 [Leary], 19 [McBride])."); Ex1112, [0003] ("Other studies have proposed identifying patient-specific chromosomal rearrangements in tumors via whole genome sequencing (WGS), followed by breakpoint qPCR from cfDNA (Leary et al. (2010) Sci. Transl. Med. 2:20ra14; McBride et al. (2010) Genes Chrom. Cancer 49:1062-1069)").

27. Dr. Furneaux notes that "Meyerson (EX1031) has a table that summarizes 'whole-genome sequencing studies of cancer.'" Ex2031 ¶106. He states that "Leary is cited as reference 99 in Meyerson, but it is not included in the list of whole genome sequencing studies in Table 1." *Id.* Meyerson's Table 1 is reproduced below:

Table 1 | **Whole-genome sequencing studies of cancer**

Study	Method	Cancer type	Number of samples sequenced	Aberration type	Refs
Ley *et al.*, 2008	Deep single-end whole-genome sequencing	AML	1	Point mutations, insertions, deletions	10
Campbell *et al.*, 2008	Shallow paired-end whole-genome sequencing	Lung	2	Deletions, amplifications, tandem duplications, interchromosomal rearrangements	22
Stephens *et al.*, 2009	Shallow paired-end whole-genome sequencing	Breast	24	Deletions, amplifications, tandem duplications, interchromosomal rearrangements, inversions	39
Pleasance *et al.*, 2010	Deep paired-end whole-genome sequencing	Melanoma	1	Point mutations, insertions, deletions, amplifications, interchromosomal rearrangements	12
Pleasance *et al.*, 2010	Deep paired-end whole-genome sequencing	Small-cell lung	1	Point mutations, insertions, deletions, amplifications, interchromosomal rearrangements	13
Mardis *et al.*, 2009	Deep paired-end whole-genome sequencing	AML	1	Point mutations, insertions, deletions, amplifications, interchromosomal rearrangements	11
Shah *et al.*, 2009	Deep paired-end whole-genome sequencing	Breast	1	Point mutations, insertions, deletions, amplifications, interchromosomal rearrangements	15
Ding *et al.*, 2010	Deep paired-end whole-genome sequencing	Breast	1	Point mutations, insertions, deletions, amplifications, interchromosomal rearrangements, inversions	35
Lee *et al.*, 2010	Deep paired-end whole-genome sequencing	Lung	1	Point mutations, insertions, deletions, amplifications, interchromosomal rearrangements, inversions	14

AML, acute myelogenous leukaemia.

28. Meyerson's list does not purport to be exhaustive, and Dr. Furneaux does not dispute in his declaration that the listed studies were understood at the time to constitute whole genome sequencing studies. Indeed, as a review article published in 2010, Meyerson is an informative snapshot into what those skilled in the art thought at the time. Importantly, Meyerson cites Campbell 2008 and Stephens 2009, each shallow paired end whole-genome sequencing studies, in its list of "Whole-genome sequencing studies."

29. Notably, Campbell 2008 used the same whole-genome sequencing method as McBride 2010, which Dr. Furneaux agrees used a "similar paired-end rearrangement screen" to Leary. Ex1015, 3 ("Samples of genomic DNA were extracted from fresh-frozen primary tumor material and studied by massively parallel, paired-end sequencing (Campbell, et al., 2008)."). Thus, Meyerson's

inclusion of Campbell 2008 in its Table 1 is reflective of the understanding in the art that similar techniques, including Leary's, constituted whole-genome sequencing.

30. Dr. Furneaux makes similar arguments with respect to Newman (Ex2152), contending that because a paragraph that mentions "whole genome sequencing" does not footnote to Leary (which is cited elsewhere) that it must mean that Leary's method is not whole genome sequencing. Ex2031 ¶107. I have excerpted the relevant part of Dr. Furneaux's declaration below:

> IPR2023-00546 that challenge two more of Personalis' patents. Newman referenced several whole genome sequencing references as follows:
>
> > Following therapy, ctDNA concentrations typically drop, thus requiring even lower detection thresholds. Previously published methods employing amplicon[8,10,11], whole exome[12], or ***whole genome[9,32,33,24] sequencing*** would not be sensitive enough to detect ctDNA in most patients with NSCLC, even at 10-fold or greater sequencing costs (Fig. 1d and Supplementary Fig. 8).
>
> EX2152 (Newman) at page 7. Leary is not included in the list of exemplary whole genome sequencing references by Newman. However, Leary is cited elsewhere in Newman as reference 5. *See* Ex2152 (Newman) at page 11.

31. The paragraph of Newman that Dr. Furneaux cites is plainly discussing studies focused on measurements on ctDNA, and the part he bolded cites four studies regarding the whole genome sequencing of ctDNA. Ex2152, 7. The whole genome sequencing in Leary is performed on DNA derived from tissue. If the footnotes in

the above-referenced paragraph truly included all of the "whole genome sequencing" references cited in Newman, surely they would have cited Dawson (Ex1070, Newman's footnote 11), which is indisputably a whole genome sequencing reference. Ex1070, 1199 ("We used . . . whole-genome sequencing to identify somatic genomic alterations . . . .").

32. To briefly summarize the ctDNA ("circulating tumor DNA") whole genome sequencing studies in Newman relied upon by Dr. Furneaux (Dr. Furneaux does not dispute the status of these studies as whole genome sequencing):

- Leary 2012 (Reference 9), is titled "Detection of Chromosomal Alterations in the Circulation of Cancer Patients with Whole-Genome Sequencing." Ex2152, 11.

- Chan 2013 (Reference 32) (Ex1008), is titled "Cancer genome scanning in plasma . . . ." Ex2152, 12.

- Heitzer 2013 (Reference 33) (Ex1214), is titled "Tumor associated copy number changes in the circulation of patients with prostate cancer identified through whole-genome sequencing." Ex2152, 12. Heitzer explains that "[p]reviously it had been shown that whole-genome sequencing with a shallow sequencing depth of about 0.1x is sufficient for a robust and reliable analysis of copy number changes from single cells." Ex1214, 2. Heitzer outlines its method as follows: "We performed whole-genome sequencing from plasma at a shallow sequencing depth to establish a genome-wide copy number profile of the tumor at low costs within 2 days." *Id.*, 1. In

summarizing its methods in Figure 2, Heitzer confirms that its "whole genome plasma sequencing is performed with a shallow sequencing depth of approximately 0.1x." *Id.*, 7.

- Fan 2008 (Reference 24), is titled "Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood," is a reference regarding the whole genome sequencing of circulating DNA in plasma, given that the target DNA is circulating fetal DNA.

(4) The application of "almost all" must include the art-recognized whole genome sequencing techniques.

33. These references confirm, consistent with Personalis's own contemporaneous patents, that a POSA would have considered low coverage, non-targeted sequencing methods to be whole genome sequencing. Thus, the application of the "almost all" part of the Board's construction necessarily must account for this understanding, and include techniques such as Pasniuc and Heitzer (0.1x coverage), and at a minimum must include the 50% coverage techniques expressly acknowledged to be whole genome sequencing by Personalis's patents.

2. Express construction of the term "whole genome sequencing" is not required.

34. Dr. Furneaux's application of the Board's preliminary construction – notably his testimony that the amount of the genome required to be sequenced to constitute "almost all" of the genome is a "moving target," as well as his unwillingness to identify a denominator to be used in such calculations – adds

uncertainty to the term "whole genome sequencing" that could depart from a POSA's contemporaneous understanding of the term's plain meaning.

35. The Leary method discussed in my initial declaration was repeatedly described as "whole genome sequencing" in the contemporaneous literature, reflecting the understanding of the concept among practitioner's in the art, so it is not clear that further words need to be used to define "whole genome sequencing" in the claims of the '394 patent. To the extent they do, a POSA would have understood the plain meaning of "whole genome sequencing" (in the context of the human genome for which there was a reference sequence) to be: "**a non-targeted approach to generating sequencing reads and mapping those reads back to a reference genome (rather than a genome subset).**"

36. This distinguishes whole genome sequencing techniques from, for example, whole exome sequencing, which was understood to (a) target exonic sequences during library preparation; and to (b) to map reads back to only the known areas of the genome that encode for protein. *See* '394 patent at 1:23-36 (distinguishing whole exome and whole genome sequencing, and noting "commercially available exome enrichment kits (e.g., Illumina's TruSeq exome enrichment and Agilent's SureSelect exome enrichment)."); Institution Decision at 22 ("In considering the scope of 'whole genome sequencing' we take particular note of the Specification's distinction between whole genome sequencing and targeted

sequencing of the exome or other sub-genomic regions (e.g., Ex. 1001, 5:38-59, 24:35-58), as well as the Specification's acknowledgement that whole genome sequencing may encompass 'low mean coverage regions' and 'zero mean coverage regions,' (*id.* at 24:59-62, 28:33-42).").

B. "capture probes"

37. The Board preliminarily construed the term "capture probes" to "encompass, at a minimum, PCR primer capture probes and solution-based hybridization capture probes (e.g., biotinylated oligonucleotide baits)." '394 Institution Decision at 28-29; '033 Institution Decision at 24.[4] At deposition, the inventor Mr. West confirmed, consistent with the specification of the patents, that PCR primers constitute capture probes:

> Q. ***Did you ever try to use PCR primers to capture DNA for sequencing?***
>
> A. So in my career, ***yes, I had certainly done that***.

[4] Dr. Furneaux takes issue with the use of the term "PCR primer capture probes" as a way of mapping the structures of the prior art to the claims. As Dr. Furneaux conceded at deposition, the literature need not describe a particular structure as a "capture probe" for it to constitute a "capture probe" within the meaning of the claims. Ex1223, 161:25-162:10 (Q…[Y]ou cite this Gellert reference, Exhibit 2027 – I'm sorry – as an example where a single nucleotide can function as a capture probe; is that correct? A. Uh-huh. Q. And so throughout this reference – and I'm happy to search – the Gellert reference doesn't use the term "capture probe." Is that fair? A. Oh, that would be very fair.).

Ex2122, 95:15-18. *See also id.*, 97:4-21 (Q…As of 2012, it was known that PCR would be perfectly adequate for capturing those two loci for subsequent sequencing; correct? A. So I would say that the PCR could be used for certain loci. . . . But if you wanted to conduct two PCR reactions for two different genomic loci, certainly you could do that."). This is consistent with the contemporaneous literature, discussed in Section II.B.3, which consistently referred to PCR as a technique for capturing genomic loci for sequencing.

1. The preliminary construction comports with the intrinsic evidence.

38. As described in my initial declaration, the specification associates a "capture probe" to a nucleic acid structure that "typically . . . comprises a nucleic acid binding site," and optionally includes additional features, such as "linkers" and "labels." Ex1020 ¶¶100-106. According to the specification, "linkers" and "labels" are thus not part of the "capture probe." '394 patent, 31:7-12 ("Typically, the capture probe comprises a nucleic acid binding site. The capture probe ***may*** further comprise one or more linkers. The capture probes ***may*** further comprise one or more labels.").

39. This structural definition is important, as Personalis argues that the claimed "capture probes" are synonymous with "pulldown probes." Ex2031, ¶¶61-67. A POSA would have understood a "pulldown probe" to refer to a "biotinylated

oligonucleotide bait," a specific structure. Notably, the term "pulldown," refers to a "pulldown" assay:

> One of the most widely used techniques for studying interacting proteins is the pull-down or the co-immunoprecipitation assay. In the classical pull-down assay, the protein of interest or bait is selectively isolated from cell or tissue extracts. The physiological binding partners of the bait protein, or the prey proteins, co-purify with the bait protein.

Ex1215 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3654178/). In the pulldown probes relevant here, the protein-ligand interaction at issue is typically that between streptavidin and biotin. The specification is explicit that biotin and streptavidin are considered "linkers" or "labels," '394 patent, 14:22-46, 23:23-36, which are optional and not necessary components of "capture probes." Thus, molecules that include a nucleic acid binding site but lack any type of additional chemical moiety (label or linker), such as biotin, must fall within the scope of a "capture probe" as set forth in the Specification. This includes PCR primers, which are nucleic acids that hybridize to a target (i.e., contain a nucleic acid binding site), but which do not necessarily comprise linkers and/or labels.

40. Dr. Furneaux contends that the "specification treats capture probes and PCR primers as different types of nucleic acids." Ex2031 ¶59. In fact, the Specification does not treat such structures as mutually exclusive. For example, in support of that argument he cites the '394 patent at column 23 lines 23-26, which

states: "The methods disclosed herein may comprise one or more labels. The one or more labels may be attached to one or more ***capture probes, nucleic acid molecules***, beads, ***primers***, or a combination thereof." '394 patent, 23:23-26. There is no dispute that "nucleic acid molecules"include "capture probes" and "primers," confirming that the lists throughout the '394 patent's specification are not intended to be mutually exclusive. Hence, it is unremarkable that "capture probes" appear in the Specification in lists that also include "primers."

41. In my initial declarations, I also explained that dependent claims in each patent that recite "wherein the plurality of capture probes further comprise barcodes" required the scope of "capture probes" to include PCR primers. I am not aware of an example of a biotinylated oligonucleotide bait capture probe that has been barcoded (as I explain in my initial declarations, it would not make sense to do so). On the contrary, PCR primers are ubiquitously barcoded. Ex1020, ¶¶104-106. At his deposition, Mr. West confirmed that for biotinylated baits, "the bar codes are not part of the capture [prob]es. They're part of the molecule that's being sequenced." Ex1222, 169:16-170:4; *see also id.*, 170:1-4 ("Q. Right. But the barcodes are sequenced? A. Yes, they are part of the molecule. They're not part of the capture probe."). Moreover, the only example of a barcoded capture probe Dr. Furneaux identified in his declaration is not a biotinylated oligonucleotide, but instead a "zip-

code array" that has far more in common with a PCR primer structure than with a biotinylated oligonucleotide bait. Ex2031 ¶70.

2. Personalis's proposed construction contradicts its patents and the extrinsic evidence.

42. Personalis proposes construing "capture probe" as "a nucleic acid sequence that hybridizes to target DNA, either in solution or on a solid support, so that one can physically capture and isolate the ***target DNA***." Ex2031 ¶57.

a) Personalis's proposed construction contradicts the claim language and the specification.

43. The claim language and the specification does not require the "capture probe" structure to "physically capture" DNA. The relevant claim limitations require only "contacting" a nucleic acid sample with "capture probes." '394 patent, Claim 1(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"); '033 patent, Claim 1(b) ("contacting said nucleic acid sample with said plurality of capture probes produced in (a)").

44. The specification describes multiple ways to create subsets of nucleic acids using capture probes, and physical separation is only one example. As the Board correctly observed, "the Specification suggests that physical separation is an independent method of producing a subset." '394 Institution Decision at 25; '033 Institution Decision at 20. The specification is quite clear that "separation" is a

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distinct step from contacting with "capture probes." It explains that "[t]he one or more subsets of nucleic acid molecules may be produced by contacting a nucleic acid sample with one or more beads, capture probes, labels, or a combination thereof." '394 patent, 32:12-15. "***Alternatively, or additionally,***" it continues, "the one or more subsets of nucleic acid molecules are produced ***by separating***," at least one nucleic acid molecule from another nucleic acid molecule." *Id.*, 32:15-18.

45. Consistent with this, the specification defines subsets of molecules based on their capture-probe-hybridization status: "methods disclosed herein may comprise producing two or more subsets of nucleic acids by contacting the nucleic acid sample with one or more capture probes to produce a first subset of nucleic acid molecules comprising one or more capture probe hybridized nucleic acid molecules and a second subset of nucleic acid molecules comprising one or more capture probe fere nucleic acid molecules." *Id.* 32:26-33.

46. Elsewhere, the specification describes what Personalis now appears to refer to as "capture" as performing an "elution reaction"

> The methods disclosed herein may comprise conducting one or more elution reactions on one or more nucleic acid molecules in a sample. ***The elution reactions may comprise contacting a sample with one or more beads or bead sets***. The elution reaction may comprise separating bead bound nucleic acid molecules from bead free nucleic acid molecules. ***The elution reaction may comprise separating capture***

> ***probe hybridized nucleic acid molecules from capture probe free nucleic acid molecules.***

Id., 37:5-18.

47. Thus, it is plain from the specification that physical separation and/or isolation refer to a distinct step that is not a necessary component of the step of "contacting" a nucleic acid sample with capture probes. None of the challenged claims require this distinct, additional step.

48. Dr. Furneaux also contends that "[i]f one were to assume that PCR amplification were synonymous with capture . . . then such capture would require two molecules. In contrast, only ***one*** capture molecule is required to physically pulldown one target DNA molecule." Ex2031 ¶66. But this is not true, as the pulldown step involves the interaction of streptavidin and biotin, which the specification notes are not required components of the capture probe. But for capture to occur in this manner, Dr. Furneaux confirmed that this pulldown process also required at least two molecules – the biotin linked to the nucleic acid probe, and the streptavidin on the magnetic bead. Ex1223, 148:15-149:8 (testifying that capture occurs when "streptavidin on the magnetic beads binds to the biotin on the capture[] probe," "one has washed away all of the molecules that do not have the probe," and that this "process requires at least the streptavidin molecule and at least the biotin molecule.").

b) The extrinsic evidence does not support Personalis's requirement of capturing native "target DNA."

49. Personalis's proposed construction also deviates from the extrinsic evidence from which it purports to be derived. For example, Dr. Furneaux adapts language from Mertes to arrive at his construction of "capture probes." I note below the passage of Mertes on which he purports to base his construction:

> amplification techniques. Mertes (EX1006) explains "hybrid capture" techniques as follows:
>
> > 'Hybrid capture': wherein ***nucleic acid strands derived from the input sample are hybridized specifically to preprepared DNA fragments*** complementary to the targeted regions of interest, ***either in solution or on a solid support, so that one can physically capture and isolate the sequences of interest***.
>
> EX1006 (Mertes) at page 375.[4] Mamanova and Mertes provide appropriate

Ex2031, ¶57. In his proposed construction, Dr. Furneaux changes "sequences of interest" to "target DNA." *See id.*

50. The reason for this subtle change is to support his argument that "hybrid capture" techniques involve isolating unmodified native DNA. Ex2031, ¶74 ("Perhaps most importantly, capture probes are uniquely different from PCR in that capture probes physically isolate native DNA."). But this is not true. Solution-phase hybridization capture baits are frequently used in experiments where the target DNA has been PCR amplified and modified with sequencing adaptors before capture.

Ex1033, 91 ("High-Throughput, Targeted Deep Sequencing: Overview," "Pooling and Hybrid Capture"). Alternatively, as Gnirke observes in language pasted into Dr. Furneaux's declaration, "*The 'catch' is pulled down with streptavidin-coated magenetic beads*, PCR amplified with universal primers and analyzed on a next-generation sequencing instrument." Ex2031, ¶62. Thus, the molecules ultimately sequenced are not "native DNA," even under the construct set forth by Dr. Furneaux.

51. In fact, as I discussed in my initial declaration, both techniques – biotinylated oligonucleotide baits and PCR primer capture probes – are used to preserve sequence information and generate a sufficient quantity of nucleic acids for subsequent sequencing experiments. Ex1020 ¶¶66-78.

c) Dr. Furneaux's arguments regarding differences between PCR primers and pulldown probes are beside the point.

52. Dr. Furneaux points to certain pros and cons of "enrichment by PCR" and "enrichment by hybrid capture" discussed in Mertes as alleged evidence that the two techniques are "very different." Ex2031, ¶¶71-74. In fact, the sections he cites confirm that the techniques are different approaches of achieving the same goal: enrichment of target loci for sequencing. As I explained in my initial declaration, a POSA would readily be able to evaluate the pros and cons of these (and other) enrichment techniques depending on the needs of their experiment. Ex1020 ('394) ¶¶66-69.

53. Notably, Dr. Furneaux points to statements in Mertes and Mamanova that show differences in various parameters between PCR, MIPs, on-array hybrid capture, and in-solution hybrid capture. He concludes that based on these data, "[a] POSA would have understood that capture probes and PCR primers are different techniques." Ex2031 ¶74. Even though they are different techniques, both involve "capture probes," and both perform the function of "enrichment." Curiously, Dr. Furneaux's proposed construction of "capture probes" includes array-based hybrid capture on a solid support. *Id.* ¶57. Just as PCR primers and solution phase hybridization capture probes have different pros and cons, so too do on-array hybrid capture probes and solution phase hybrid capture probes. *See id.* ¶¶71-73. Despite those differences, Dr. Furneaux presumably still considers both to be "capture probes." For the same reasons, the identified differences do not exclude PCR primers from the scope of the claimed "capture probes."

3. The literature and Mr. West confirm that PCR primers perform the function of capturing DNA loci for sequencing.

54. As quoted above, Mr. West twice testified that PCR primers perform the function of capturing DNA loci for sequencing. Ex1222, 95:15-97:21.

55. This understanding was reflected in the contemporaneous knowledge of a POSA as well. For example, Forshew expressly described its use of PCR as a

capture technique: "[A]ll primer sets were used together to capture the starting molecules present in the template." Ex1030, 3.

56. Additionally, on his "Enseqlopedia.com" blog, James Hadfield, Head of Genomics at the Cancer Research UK Cambridge Institute,[5] which Dr. Furneaux testified was "one of the most sophisticated sequencing laboratories in the world at that time," published in 2011 that PCR is a capture technology:

> Fluidigm's Access Array, RainDance's new ThunderStorm, Halo Genomics, MIPs, traditional multiplex ***PCR assays*** are all competition from the in-house kits of Illumina and Life Technologies. ***The major differences with all the platforms are the way in which multiple loci are captured and amplified. Microfluidics, emulsion PCR and oligo-probes are the different 'capture' mechanisms***. All rely on PCR for the amplification and to add the sequencing platform adapters and barcodes. The cost of the RainDance instrument is very high, AccessArray is medium and the probe based systems can require almost nothing additional over what is already in your wet lab. AccessArray is the only system where the user has complete flexibility over what goes in the panel, if you want to change something just order a new pair of primers. RainDance, Halo and other platforms, as well as Life and Illumina's offerings, all require you to design a panel and order quite a lot to become cost effective.

[5] https://enseqlopedia.com/about-me/

Ex1216 (https://enseqlopedia.com/2011/10/amplicon-ngs-battles-begin-in-earnest/).

57. Similarly, a 2012 editorial described the developing market on "NGS with Sequence Capture," noting that "[t]here are two basic approaches to sequence capture: PCR-based and hybridization-based, the latter of which can be done either in solution or on the surface of an oligonucleotide microarray." Ex1217 (https://www.biocompare.com/Editorial-Articles/124486-Maximize-Your-NGS-with-Sequence-Capture/); *see also id.* (**"PCR-based capture tools**[:] Agilent and Life technologies also offer PCR-based enrichment solutions."); *id.* ("For those doing more traditional PCR-based capture, RainDance Technologies and Fluidigm have devised automated solutions to simplify the process.").

III. Response to Dr. Furneaux's Opinions Regarding the '394 Patent

A. Ground 1

1. Step 1(b): "whole genome sequencing"

a) Leary's method constitutes whole-genome sequencing under the appropriate understanding of the term.

58. As explained above, Leary's technique was repeatedly recognized in the art – explicitly and implicitly – to constitute whole genome sequencing.

59. ***First***, Leary's technique was a non-targeted approach. Leary's library preparation involved randomly shearing genomic DNA, and the "[s]equence data were mapped to the human genome reference sequence (hg18)," which was a

reference genome with a degapped length of 2.86 Gbp. Ex1002, 5 (SOLiD library preparation and sequencing).

60. Dr. Furneaux cites out of context my discussion of a passage of Chan that "explains that approaches like those of Leary and McBride have a 'targeted nature,' and thus may provide only a partial glimpse of the Tumor genome ***in the plasma of cancer patients***.'" Ex2031, ¶88 (emphasis added). I have emphasized the part of the quote that refers to "the plasma of cancer patients," because it is critical to understanding that this passage of Chan is comparing its whole genome sequencing of plasma to Leary's follow-up analysis, which involved PCR-based capture followed by targeted resequencing. Chan's reference to "targeted" sequencing in Leary is not a reference to Leary's initial polymorphism discovery using its PARE whole genome sequencing assay, which was performed on tissue DNA, not the plasma. Leary's WGS is nontargeted because it results in "[s]equence data [that] were mapped to the human genome" reference, without restriction to preselected loci (cf. whole-exome sequencing). Ex1002, 5; Ex1031, 687.

61. I note that the board correctly rejected this same argument in its Institution Decision:

> Finally, Patent Owner argues that "Chan expresses uncertainty as to whether" a targeted sequencing approach based on Chan and Leary

"would work." Prelim. Resp 52-53. In support, Patent Owner relies on the Chan's statement that:

> These data suggest that for an accurate measurement of the total tumor load in a cancer patient, the use of a genomewide shotgun approach might provide a more representative picture, compared with the more traditional approach of targeting specific tumor associated mutations. For the latter approach, *if only a subset of the tumor cells possesses the targeted mutations, one might miss important information regarding imminent relapse or disease progression caused by tumor cells* not possessing the targeted mutations, or one might miss the emergence of a treatment-resistant clone.

Id. at 52 (citing Ex. 1008, 222). The cited passage compares the "genomewide shotgun approach" employed by Chan, to "the more traditional approach of targeting specific tumor-associated mutations." Ex. 1008, 222. ***As we read this passage, Chan's caution about "potentially miss[ing] important information," refers to the latter, and thus, is not pertinent to the whole-genome sequencing approach used by Chan (and Leary, under our present construction) and relied on by Petitioner.***

'394 Institution Decision at 39-40.

62. Moreover, Personalis attempted to advance this distortion at my deposition, and I repeatedly explained why its interpretation of Chan is incorrect, consistent with the Board's analysis above. Ex2018 at 58-63; *see id.*, 61:15-22

(explaining with respect to Chan's mention of targeted approaches, "I can only infer that Chan was referring to the subsequent analysis, which if we review either Leary or McBride is carried out using capture probes, in the case of Leary, PCR probes directed towards specific alterations.").

63. ***Second***, Dr. Furneaux puzzlingly contends that Leary is "at most a physical mapping approach that did not report the actual sequence of the polymorphism." Ex2031, ¶89. Leary plainly determined the sequences of polymorphisms, even if they were not reported. Leary clearly determined the relevant sequences, as it reports: "Mate-pair tag sequences associated with a candidate rearrangement ***were used as target sequences for primer design using Primer3***." Ex1002, 6; *id.* at 5 (describing alignment of reads to reference: "[s]equence data were mapped to the human genome" reference).[6]

64. ***Third,*** Leary expressly discloses sequencing "almost all of the genome." Dr. Furneaux expressly states, "Leary's sequence coverage was only 0.9x," Ex2031, ¶151, which constitutes 90% and satisfies his current opinion regarding "almost all of the genome." Dr. Furneaux's characterizations of Leary

[6] It should also be noted that the claims do not require that the sequencing information of claim element 1(b) ("whole genome sequencing") does not actually need to be used in subsequent steps.

elsewhere in his declaration also confirm that its various embodiments constituted whole genome sequencing.

65. Dr. Furneaux states that "to cover the all of the base pairs in the whole human genome using the mate pair approach in Leary, one would need to very accurately sequence about 64 million non-overlapping mate-pairs (i.e., 3.2 billion divided by 50)." Ex2031, ¶96. He then provides a calculation that, "if we were to make the very unlikely assumption that there were no overlapping mate-pairs, the maximum number of mate-paired tags matching the human genome in Table 2 of Leary is 59,019,031, which is for the Co84 normal sample." *Id.*, ¶97. He asserts that "[t]his accounts for only 2.9 billion bp." *Id.* Under Dr. Furneaux's new 90% opinion, this amount of sequence coverage constitutes "almost all" of the genome regardless of whether 3.2 billion base pairs is (incorrectly) used as the denominator (91%) or if 2.86 billion base pairs is used as the denominator (100%).

66. Even accepting for the sake of argument Dr. Furneaux's math that Leary sequenced 1.71 Gb of the genome, Ex2031, ¶98, such sequence coverage (1.71 Gbp/2.86 Gbp = 60%)[7] was still sufficient to constitute "almost all of the genome" as it would have been understood by a POSA. *See* Section II.A.1.b).

[7] If the incorrect 3.2 Gbp denominator is used, then it would be about 53%.

b) A POSA would have been motivated to increase the sequencing coverage of Leary's WGS step according to the needs of their experiment.

67. Even though Leary's initial whole genome sequencing assay satisfies the properly construed claim, increasing Leary's sequencing coverage and depth would have involved no more than routine skill in the art. As I explained in my initial declaration, a POSA would have been able to do so by "running additional sequencing assays: 'it is very easy to increase the coverage or sequence depth if you later decide you need more data. Provided you still have your original sample, you can just sequence more, and combine the sequencing output from a few different flow cells.'" Ex1020, ¶65; *see also id.* ¶¶203-205.

(1) Increasing sequencing coverage would have involved no more than routine skill in the art.

68. Leary's mate-pair technique provided high physical coverage, indicating that the sequence reads were broadly distributed across the genome in a nontargeted manner. A POSA would have known how to modify the mate-pair sample preparation to adjust the physical and sequence coverage depending on the needs of the experiment. This was well known in the art by October 2010, when Meyerson described this routine optimization process in its section headed **"Whole-genome sequencing**." Ex1031, 687-688. Meyerson explained:

> Physical coverage is important for detecting rearrangements and this detection is aided by analysis of 'paired reads.' In standard shotgun

> library methods, the fragments of DNA are typically 200-400 bases long, and second-generation sequencing technologies currently yield 50-100 base reads from each end of a fragment (known as paired reads). The expected distance between the paired reads is used to uniquely place the reads on the reference genome and unexpected read pairing can be used to detect structural anomalies.
>
> ***The distance between the paired reads can be increased to thousands of bases by the creation of jumping libraries, which can be constructed by generating large circular fragments of DNA. This leads to higher physical coverage of the genome with less sequence coverage and, consequently, lower cost. For example, with 3 kb spacing between pairs, the physical coverage of the genome is 10 times higher than with 300 bp inserts, so equivalent physical coverage can be obtained with 10 times less sequence coverage*** (FIG. 1). Although powerful for the detection of structural rearrangements, the jumping library approach has two main limitations. First, with less total sequence, the coverage at any given position is lower, therefore the sensitivity to observe base changes such as point mutations is correspondingly lower. Second, the jumping library approach requires large quantities of high-quality input DNA, which may not be possible with all clinical cancer samples, especially those derived from FFPE specimens.

Ex1031, 688. In addition to further confirming that Leary's rearrangement screen was whole genome sequencing (given the inclusion of even lower coverage

techniques in the section headed "Whole Genome Sequencing"), Meyerson thus confirms that a POSA would have been readily able to increase sequence coverage, for example to increase "sensitivity to observe base changes such as point mutations," by decreasing the distance between mate pairs. *Id.* This is confirmed in Personalis's '058 patent, which describes essentially this approach. Specifically, it describes whole-genome sequencing with "mate pairs with a separation of larger than 2kbp," so that "even with low (~1x) read depth, there may be at least about 10 molecules spanning any particular position on the genome, which may be sufficient to provide corroborating evidence of large CNVs detected by methods and systems herein." Ex1212 ('058 patent) at 25:14-41. This passage further explains that "[i]n some examples, when 1 kbp insert sizes are used, then 10 reads span the breakpoint, 5 of which can have anomalous insert size. . . . In some cases, if an insert-size of only about 300 basepairs is used, then there may be only about 3 reads that span the breakpoint on average…." *Id.*

(2) The articles Dr. Furneaux cites encourage and promote WGS methods.

69. Dr. Furneaux asserts that a POSA would not have been motivated to increase Leary's sequencing coverage because of an allegedly large data burden and because of alleged expense in the 2012-2013 timeframe. Ex2031 ¶¶109-127. A brief review confirms that, far from discouraging the use of WGS methods, the articles he

cites affirmatively encourage its use and explain why a POSA would have been motivated to use such methods going forward. Meyerson notes that WGS "is allowing substantial advances in cancer genomics," Ex1031, 686, describes "[t]he major potential of whole-genome sequencing for cancer," Ex1031, 687, and observes that "the mountains of genomic data" are far from a drawback, but rather "likely to potentiate accurate genome-based diagnosis for an ever wider set of patients with cancer." *Id.*, 694.

70. Mertes observes that "whole-genome sequencing[,] which is becoming ever more affordable," is an "alternative" to "targeted enrichment" approaches. Ex1006, 374 ("Looking to the future, whole-genome sequencing will continue to become cheaper, simpler, and faster.").

71. Mamanova explained that "whole-genome sequencing of complex organisms will become routine." Ex1007, 111.

72. Shendure predicted – in 2008 – "that next-generation sequencing technologies will become as widespread, commoditized and routine, as microarray technology has become over the past decade." Ex1013, 1143.

73. Ross established that POSAs in 2011 believed "[t]he technologic advantages offered by NGS will eventually reduce the cost of sequencing and decrease the turnaround times that will support unprecedented analytic depths." Ex1014, 537.

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74. Forshew explains that "[w]hole-genome sequencing of tumor material ***was used*** to identify tumor mutations" in the first step of its study. Ex1030, 9.

75. Anderson notes that "[t]o meet the expectations associated with these emerging technologies, diagnostic laboratories may be anticipated to offer more comprehensive sequence analysis than ever before, ***encompassing the entire genome*** instead of single genes." Ex1004, 59. While noting that "the most successful ***initial*** clinical applications of next-generation seqeuencing ***may be*** through sequencing targeted subsets of the genome," in no way does discourage the use of WGS.

76. The Quackenbush papers Dr. Furneaux cites similarly confirm that "exponential decrease in sequencing costs has led to the ability to perform WGS studies" widely, Ex2019, 6, and that "cancer care" would "shift[] toward personalized intervention based on" NGS of the tumor genome. Ex2020, 580. Ex2158 merely notes that "whole-exome sequencing presents an alternative to whole-genome sequencing." Ex2158, 2648. The use of the phrase "alternative" indicates that both options are acceptable.

77. Dr. Furneaux's cited passages from Pryzabl and Newman discuss detection of ctDNA in plasma, confirm Leary is non-targeted, and do not disparage WGS. Ex2021, 2688, *see also* Ex2152, 2.

78. Blighe, a 300+ page thesis, concludes that "the method for detecting genomic variation that offers the highest resolution is next generation sequencing." Ex2155, 258.

79. Sims repeatedly describes the benefits of WGS, and notes that "[i]n WGS, reasonable specificity can be obtained with an average depth of as little as 0.1x." Ex2022, 124

80. Gnirke expressly contemplates that its targeted-enrichment techniques will be useful in applications including "resequencing targets, such as genomic regions implicated by whole-genome association scans…." Ex1005, 182.

81. Liao says nothing that would discourage the use of WGS in cancer, in fact utilizes WGS in its studies of prenatal diagnostics. Personalis quotes Liao's observation that targeted sequencing may be more logical on its applications (even though WGS worked), but fails to acknowledge that Liao's reasoning is that "the prime focus of interest was chr21," Ex1009, 99 a sensible approach given Liao's goal of "measuring small proportional increments of chromosome 21 (chr21) DNA in maternal plasma of pregnancies carrying trisomy 21 (T21) fetuses." Ex1009, 92-93.

82. Dr. Furneaux's suggestion that the literature "consistently describe[s] whole genome sequencing as being undesirable," Ex2031, ¶110, simply misreads the literature and does not accurately reflect the mood in the field at the time, which

reflected uniform excitement about whole genome sequencing. As I noted in my initial declaration, in 2008, Ley nicely summarized this fact by explaining that its approach was possible because "Whole-genome sequencing is now possible at a reasonable cost and timeframe to use this approach for the unbiased discovery of tumor-specific somatic mutations that alter the protein-coding genes." Ex1012, 66; Ex1020, ¶79. While cost and data storage issues presented challenges and constraints, they did not discourage the use of whole genome sequencing, particularly given that those skilled in the art were well aware that costs were consistently dropping and that data storage was becoming rapidly more facile.[8] *See* Ex1002, 5 (Leary reporting, in 2010: "the cost of massively parallel sequencing, which has decreased substantially over the last 2 years, continues to spiral downwards.").

[8] Nothing in the claims requires a particular application, let alone commercial viability. For example, certain methods suggested in the patent are recognized to be "10-fold to 100-fold more expensive per base than bulk sequencing and [] often not commercially viable for the entire content regions." '394 patent, 72:26-64.

2. Step 1(c): "capture probes"

a) Leary teaches the claimed capture probes under the Board's correct construction.

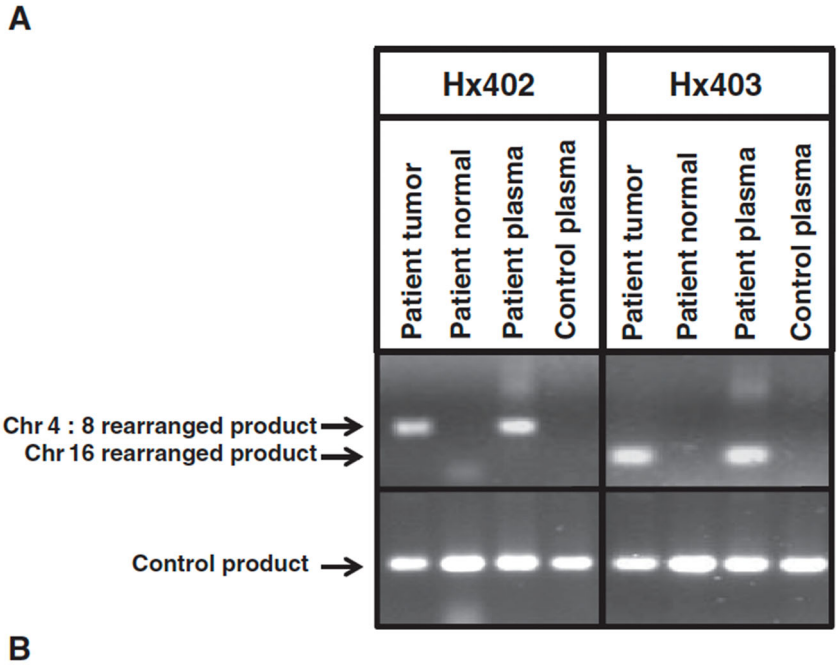
83. Dr. Furneaux does not dispute that, if the Board adopts its preliminary construction, Leary's PCR primers constitute the "capture probes" required by the claim.

b) Leary teaches the claimed capture probes under Personalis's construction.

84. Personalis contends that "capture probe" should be construed to mean "a nucleic acid sequence that hybridizes to target DNA, either in solution or on a solid support, so that one can physically capture and isolate the target DNA." Ex2031 ¶57. PCR primers satisfy Personalis's construction of "capture probe," because DNA captured with PCR can be physically isolated, for example using gel electrophoresis and well-known physical separation and elution techniques.

85. Dr. Furneaux argues that PCR primers are not capable of capturing and isolating target DNA. This is incorrect. For example, in his declaration, in arguing that the labelled probes used in a Southern blot can be considered capture probes, Dr. Furneaux contends that "capture" can occur by physically separating the nucleic acid from a nitrocellulose filter, and then eluting it with common laboratory techniques. Ex2031, ¶65.

86. Similar techniques can be used to physically separate and isolate DNA that has been captured using PCR. For example, PCR products are commonly purified through the use of gel electrophoresis, a ubiquitous laboratory technique that separates nucleic acids on the basis of size. Ex1223, 159:10-15 (Q. One of the techniques known for separating DNA based on size is gel electrophoresis; correct? A. Absolutely correct, yeah. It goes gel electrophoresis or acrylamide electrophoresis if they're smaller DNAs."). This technique is demonstrated in, for example, Leary's Figure 4 (reproduced below), which shows the localization of different sized nucleic acids on the gel. Ex1002, Figure 4. As Dr. Furneaux testified, "if you can find and visualize the fragment of a particular size on a gel, then you can physically remove it from the gel." 159:22-25.



87. To physically collect a desired product from such a gel, one simply would have needed to cut out the part of the gel with the desired nucleic acid band, and separate the DNA from the gel using standard techniques. Ex1223 (Furneuax), 160:22-161:3 (Q. And so by the ’80s, if you had an electrophoresis gel with a clean DNA band, it would be relatively facile to extract that DNA; correct? A. The extract process is facile.”).

88. Additionally, because the use of PCR primers creates an excess of molecules with the sequence of interest, the sequence information can be captured even without physical separation, as such sequences will create the dominant signal output on a sequencing machine.

3. Step 1(e): “using said plurality of capture probes to generate an additional subset . . . .”

89. Dr. Furneaux contends that “Leary fails to disclose a plurality of probes that would meet limitation 1(e).” Ex2031 ¶142.

90. His argument appears to be that since Leary’s Figure 4 monitors “a single amplicon produced from a single primer pair to measure the personalized biomarker,” that there is not a “plurality of capture probes.” Ex2031, ¶146. Thus, it appears that Dr. Furneaux reads the phrase “plurality of capture probes” to require a “plurality of capture probes with different nucleic acid sequences that bind to

different targets," although he does not explicitly explain how he understands the claim term.

91. I understand that in patent law, a "plurality" means "at least two." Even accepting Dr. Furneaux's argument that Leary is limited to the use of PCR primer capture probes that generate a single amplicon as a biomarker, such usage involves a plurality of capture probes. This is so because PCR primers are well-known in the art to be used in solution at molar excess, and thus far more than a single capture probe molecule will be used in any given PCR capture assay. *See* Ex1020, ¶72.

92. Moreover, Leary expressly motivates tracking multiple PCR amplicon biomarkers in the same patient. For example, Leary explains that clonal evolution of cancer cells could result in rearranged sequences – which serve as biomarkers – disappearing during the progression of a patient's cancer. Ex1002, 5 ("Although somatic alterations in oncogenes and tumor suppressor genes persist throughout the clonal evolution of a tumor, it is conceivable that some rearranged sequences could be lost during tumor progression."). Leary explains that a POSA would have readily mitigated this risk through "[t]he identification of several PARE biomarkers, each specific for different chromosomal regions . . . as it is unlikely that all such markers would be lost in any particular patient." *Id.* Thus, Leary expressly describes the use of a plurality of capture probes even under Dr. Furneaux's mistaken interpretation.

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B. Ground 2

93. Dr. Furneaux sets forth internally inconsistent criticisms of Ley that would not have dissuaded a POSA from following its teachings.

94. In paragraph 158 of his declaration, Dr. Furneaux argues that "Ley teaches sequencing less than the whole genome is preferable because it would be 'faster, cheaper, and more efficient' for finding polymorphisms." Ex2031, ¶158 (citing Ex1012, 71). The next sentence states, "[a]lthough this approach," meaning the transcriptome approach, "will undoubtedly be an important adjunct to whole-genome sequencing, there are several advantages to the approach we used," i.e., whole genome sequencing. Ex1012, 71. Thus, Ley absolutely does not teach that "sequencing less than the whole genome is preferable."

95. In paragraph 159 of his declaration, Dr. Furneaux then argues that Ley's "method i[s] not 'feasible' without performing whole genome sequencing two times," and that "[a] POSA would have been dissuaded from selecting a method that performs whole genome sequencing twice for reasons discussed above regarding data burden and expense constraints." Ex2031, ¶159. As I explain in Section III.A.1.b)(2), those alleged "constraints" would not have dissuaded a POSA from using whole genome sequencing like Ley's. Indeed, Ley observed in 2008 that its whole-genome sequencing was "now possible at a reasonable cost and timeframe." Ex1012, 66. As explained in my initial declaration and above, a POSA as of the

priority date would have further understood that such costs were continuing to decline at a rapid rate.

96. Dr. Furneaux also argues that "the facilities available to Ley at The Genome Center at Washington University were not available to the POSA in the 2012-2013 timeframe." Ex2031, ¶161. This is true, but not for the reasons Dr. Furneaux suggests. By 2012-2013, the facilities available to the POSA at many institutions would have been significantly improved as compared to the technology available to Ley in 2008. Moreover, Dr. Furneaux fails to identify anything unique about the facilities at Washington University that are linked to the sequencing performed. Ley used the Illumina and Roche/454 sequencing platforms. These were widely available in the 2012/2013 timeframe, especially given that sequencing services could be contracted out to third party companies. *See* Ex2032 (West Declaration), ¶328 (discussing board approval of "up to $157,000 for third party sequencing of genomes of the 17-person, 3-generation CEPH 1463 family, and Craig Venter.").

C. Ground 3

97. Dr. Furneaux argues that "Chan's 'shotgun sequencing of plasma DNA . . . does not constitute sequencing all or almost all of the patient's genome because the fragmented DNA circulating in the plasma does not include the entire genome." Ex2031, ¶168. But as discussed above, the contemporaneous literature, such as

Newman, characterized Chan's sequencing of plasma as whole genome sequencing, which Dr. Furneaux did not dispute. *See* Section II.A.1.b)(3).

98. Moreover, Chan discloses performing whole genome sequencing on matched tumor tissue from hepatocellular carcinoma (HCC) and normal buffy coat DNA. Ex. 1008 at 211 ("Four hepatocellular carcinoma patients . . . were recruited. DNA was extracted from tumor tissues, and the preoperative and postoperative plasma samples of these patients were analysed with shotgun MPS."). This sequencing was generated using "MPS" or "massively parallel sequencing," and that the "tumor DNA and buffy coat DNA" was sequenced "to mean depths of 29.5-fold . . . and 43-fold . . . haploid genome coverage, respectively." Ex. 1008 at 218. This was non-targeted whole-genome sequencing to "explore[] the ***genomewide*** detection of tumor-derived SNVs in the plasma of the 4 HCC patients." Chan reported that for DNA obtained from sources other than plasma samples, i.e., the tumor and buffy coat DNA samples, "Sequencing libraries of the genomic DNA samples were constructed with the Paired-End Sample Preparation Kit (Illumina)," which involved shearing genomic DNA into 200-bp fragments." *Id.* The prepared DNA libraries were then sequenced "by 51 X 2 cycles or 76 X 2 cycles of sequencing on a HiSeq 2000 system (Illumina) with the TruSeq SBS Kit (v2)." A POSA would have been motivated to use this sequencing protocol in instances where high depth

of coverage was desired, such as to track SNPs, in light of Chan's demonstrated success in implementing it using off-the-shelf sample preparation kits from Illumina.

99. I also find it necessary to respond to the mischaracterizations in paragraph 173 of Dr. Furneaux's declaration, which I reproduce below.

> 173. The claimed invention recites a specific method that first conducts whole genome sequencing (which neither Leary, Chan, or Liao teach), and then uses capture probes ***after*** whole genome sequencing on a second sample. Chan does not teach using capture probes ***after*** whole genome sequencing, and further does not teach a second sample. Dr. Quackenbush asserts that Chan's supposed use of solution-phase hybridization capture is conducted ***before*** the sequencing—not after like claimed. EX1020 (Quackenbush Declaration IPR2023-00224) ¶238 ("The catch is then pulled down or fished out using beads that bind the biotin that was incorporated into the baits, and the catch can then be PCR amplified ***before*** analysis with Next-Generation Sequencing.").

100. As I explained in my initial declaration, Ground 3 argues that "Chan expressly motivates first conducting whole-genome sequencing," which could be accomplished by using Chan's method "as well as" those of "prior art protocols like Ley (Ex. 1012), Leary (Ex. 1002), and McBride (Ex. 1015), each of which performed an initial whole-genome sequencing step on a tumor sample," before "then using that information to target specific mutations identified through whole-genome sequencing at subsequent timepoints with capture probes, followed by sequencing

of the captured nucleic acids." Ex1020, ¶235. Thus, Chan clearly teaches using capture probes after whole genome sequencing, and that is exactly what I proposed in Ground 3. After identifying polymorphisms of interest, the combination of Leary, Chan, and Liao renders obvious using, e.g., Agilent's SureSelect product, *id.* ¶239, to enrich target DNA from subsequent samples before further sequencing. Dr. Furneaux's characterization of my testimony "that Chan's supposed use of solution-phase hybridization capture is conducted before the sequencing—not after like claim," respectfully appears to be confused. Ex2031, ¶173. The use of solution-phase hybridization capture in the proposed composition occurs after whole-genome sequencing, and before the sequencing of the catch obtained by using capture probes designed with the benefit of the whole-genome sequencing data. *See* Ex1020, ¶¶236-241.

IV. Response to Dr. Furneaux's Opinions Regarding the '033 Patent

A. Ground 1

1. Step 1(c): "generated from said nucleic acid sample"

101. Dr. Furneaux argues that Forshew fails to anticipate element 1(c) because "its sequencing assay is conducted on molecules that result from PCR amplification, rather than on molecules captured by contacting capture probes with the nucleic acid sample." Ex2031 ¶198. To the extent this argument can be understood, it appears that Dr. Furneaux requires the direct sequencing of a "nucleic

acid molecule" that has not been modified in any way. For example, in its Institution Decision, the Board described this argument as follows:

> According to Patent Owner, "Forshew does not disclose this step because it does not disclose performing a sequencing assay on a subset of molecules that are generated from step (b). Specifically, the sequencing assay disclosed in Forshew is conducted—not on molecules that were captured by contacting the capture probes to the nucleic acid sample— but on molecules that result from the PCR amplification reactions." Prelim. Resp. 29.
>
> Patent Owner's argument is unavailing on the present record because claim step 1c, recites that the sequencing step is conducted on "nucleic acid molecules *generated from* said nucleic acid sample in step (b). ***We presently understand the plain meaning of "generated from" to be permissive of additional steps, including the PCR amplification taught by Forshew***. Although Patent Owner criticizes as conclusory essentially the same interpretation from Petitioner's expert, we understand Dr. Quackenbush's testimony to support that one of ordinary skill in the art would similarly apply the plain and ordinary meaning to this element. See Prelim. Resp. 2930; Ex. 1020 ¶127.

'033 Institution Decision, 27-28. I agree with the Board's analysis.

102. Such intermediate steps are entirely consistent with the claim, which recites "comprising," and thus allows additional steps to be performed. Moreover, although Dr. Furneaux does not explicitly say so, his argument appears to be

premised on re-defining the term "generated" in a narrow way – although he does not precisely articulate what it requires – that is inconsistent with how a POSA would understand it. For example, Dr. Furneuax does not seem to require the narrow construction of "generate" he applies here when the same term is used multiple times in claim 1 of the '394 patent. He is correct not to apply a narrow reading in that case, because the reading he applies to the '033 patent is not supported by the specification. Indeed, most of the times the word "generated" is used in the specification are in the context of producing a biomedical report "generated from data or results." The other usages support applying the plain meaning of the term, which would allow additional steps and modifications. '033 patent, 13:35-40 ("The electronic storage location may include a pool or collection of sequence information and analyzed ***sequence information generated from the nucleic acid sample***."); *id.*, 63:16-17 ("A library may be ***produced or generated from*** any of the methods, kits, or systems disclosed herein."). *See also* Ex1033 (Wagle) ("Massively parallel sequencing libraries (Illumina) that contain barcoded universal primers were ***generated with*** the use of genomic DNA from formalin-fixed, paraffin-embedded tumor material. After preamplification and DNA quantification, equimolar ***pools were generated*** consisting of 12 barcoded tumor DNAs.").

103. Personalis's argument about "generated from" is inconsistent with how sequencing would be performed on nucleic acids generated using any type of capture

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probe. Indeed, even with biotinylated oligonucleotide baits, the nucleic acid is modified as compared to its native form before it is sequenced, including to append the required sequencing adaptors and/or for the sequencing platform to be used. Ex1222, 168:21-23 ("The barcodes are generally added to the – during the library prep process prior to the hybrid capture."); 174:22-24 ("So the claims of the '033 patent and the '394 patent do not call for sequencing the original molecules from the sample"). And in almost all cases, PCR amplification is used either before or after capture with such baits. For example, Gnirke describes a process in which "[t]he 'catch' is pulled down with streptavidin-coated magnetic beads," and then "PCR amplified with universal primers and analyzed on a next-generation sequencing instrument." Ex1005, 183. Wagle describes amplifying, barcoding, and adding sequencing adaptors to libraries of target DNA, before pooling them together for hybrid capture and subsequent sequencing. Ex1033, 91. Thus, Dr. Furneaux's suggestion that the claimed methods require sequencing "native" DNA – which may be possible in some circumstances with Sanger sequencing – is inconsistent with the understanding of a POSA, and potentially inoperable with NGS methods, which uniformly required the use of sequencing adaptors.

B. Grounds 2 and 3

104. Dr. Furneaux argues that "[a] POSA would not have been motivated to replace Forshew's PCR-based amplification with capture probes with a reasonable

expectation of success because capture probes do not amplify DNA," and "[c]apture probes only capture the amount of DNA that is already present in the sample. Ex2031, ¶208. From this premise, he then argues that "[t]he 3.6 *micro*gram amounts of DNA required for Wagle's capture probes is at least 100 times more . . . than the 0.9-19.7 *nano*gram amounts of DNA present in Forshew's plasma samples." *Id.* He raises analogous arguments in Ground 3. *See id.*, ¶226.

105. ***First***, it is important to note that Dr. Furneaux's characterizations regarding the "amount of DNA present in Forshew's plasma samples," are not consistent with the reference. It appears that Dr. Furneaux conflates Forshew's report of "plasma volume per amplification reaction" with the amount of plasma Forshew collected for its experiments. *See* Ex2031, ¶¶205-207. Forshew used very small sample volumes in part because a goal of its method was to show that it could work on samples containing "even single copies of ctDNA." Ex1030, 1. Forshew's sample collection notes that "[a]liquots (1 ml) of plasma were centrifuged in a benchtop microfuge . . . . The supernatant was transferred to sterile 1.5 -ml tubes and stored." *Id.*, 10. An aliquot refers to a subdivided sample, typically into equal parts. *See* Ex1223, 166:3-14. Forshew's reference to "aliquot**s**" suggests that at least two 1 ml plasma samples were available per patient. Moreover, obtaining additional plasma would have involved nothing more than a routine blood draw.

106. ***Second***, Dr. Furneaux ignores that Wagle's DNA was PCR amplified and pooled before being exposed to its hybridization capture probes. In its "Methods" section, Wagle explains under the heading "High-Throughput, Targeted Deep Sequencing: Overview":

> Massively parallel sequencing libraries (Illumina) that contain barcoded universal primers were generated with the use of genomic DNA from formalin-fixed, paraffin-embedded tumor material. After preamplification and DNA quantification, equimolar pools were generated consisting of 12 barcoded tumor DNAs. These DNA pools were subjected to solution-phase hybrid capture with biotinylated RNA baits targeting all exons from 137 actionable cancer genes. Each hybrid capture reaction was sequenced . . . .

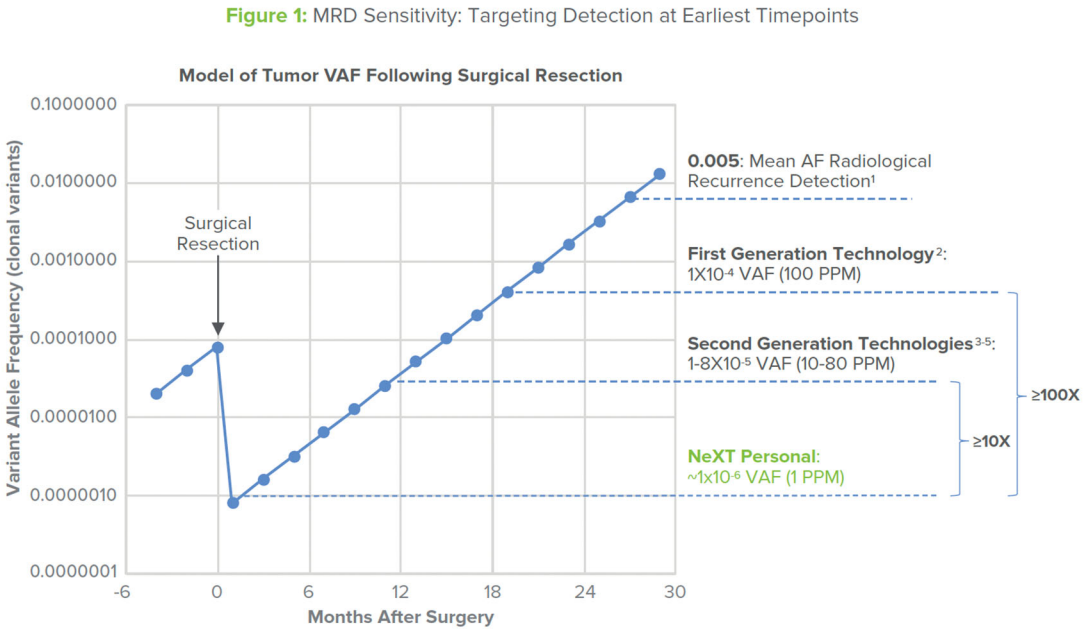
Ex1033, 91.

107. In its section titled "Pooling and Hybrid Capture," Wagle notes that "DNA libraries were pooled by mixing 300 ng of each library," and then "[t]his entire amount (3,600 ng DNA in 4 μL) was used for hybrid selection." *Id.* In other words, Wagle amplified using PCR and then pooled together multiple different samples to yield the 3,600 ng of DNA it used for hybrid capture.

V. Response to Dr. Furneaux's Arguments Regarding Secondary Considerations

1. Dr. Furneaux's arguments regarding the "sensitivity" of Next Personal are irrelevant and inaccurate.

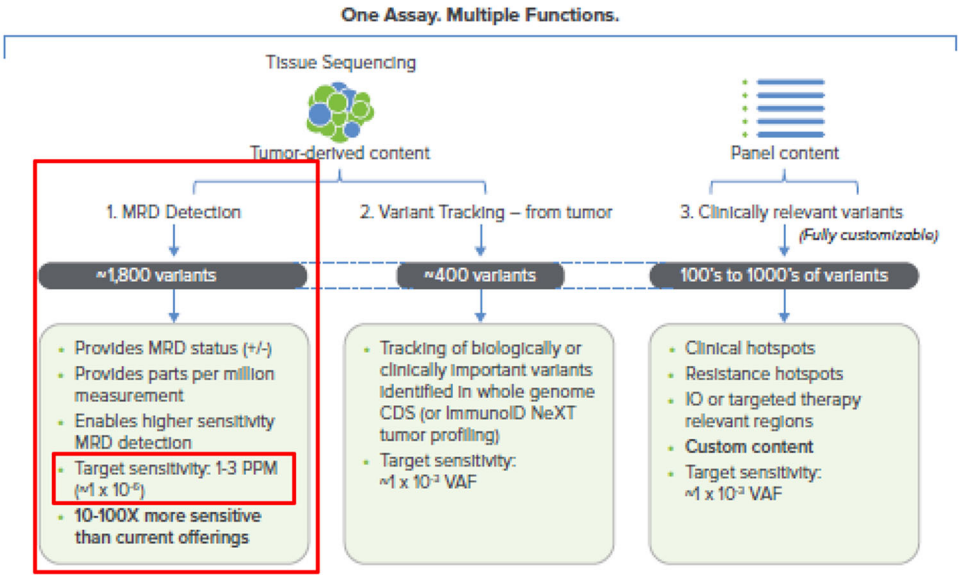
108. Citing the figure excerpted below (Ex2012, 15), Dr. Furneaux argues that "Personalis' assay can detect tumor in DNA in blood plasma at levels of about one part per million (or 0.0001%)." Ex2031, ¶180, ¶ 230.



109. At deposition, Dr. Furneaux was asked if he had "an understanding of if that sensitivity is for detecting any one specific variant as opposed to any one of the 1800 variants" monitored in the assay. Ex1223, 56:20-22. Dr. Furneaux testified that he "hadn't thought about that at all," and that his "perception here is simply what the overall sensitivity is across the board." *Id.* 56:23-25. The reported 1 ppm sensitivity in Personalis's document does, in fact, refer to the sensitivity for detecting

any one of the 1,800 variants included in the panel, rather than any one particular mutation. *See* Ex2012, 16.

Figure 2: NeXT Personal Assay Features: Advanced, higher sensitivity, personalized, tumor-informed liquid biopsy for MRD & Variant Tracking



110. Personalis's marketing documents report a sensitivity for detecting any one particular variant of $1x10^{-3}$ VAF ("Variant Allele Fraction"), or 1,000 ppm. Ex2012, 16-17, 21; *see id.*, 17 ("Target sensitivity for individual variant detection is 0.1% VAF."); Ex1223, 61:15-17 (Q. And what I said was target sensitivity for individual variant detection is 0.1 percent VAF; correct? A. Correct.).

111. Dr. Furneaux compares the 1 ppm sensitivity for detecting any one of 1,800 variants in Personalis's MRD test to what he calls "the best sensitivity from plasma DNA in the Leary reference," which he contends "was about 0.3%," thus declaring Leary's sensitivity "several hundred times less sensitive than the claimed

method." Ex2031, ¶¶180, 230. But an apples-to-apples comparison requires comparing Personalis's 1,000 ppm sensitivity for detecting any particular variant with Leary's 0.3% VAF sensitivity, meaning that, at best, Personalis's sensitivity in 2023 is about 3 times greater than Leary's in 2010.

112. Importantly, I note that the claims of the '394 and '033 patents do not recite any particular sensitivity requirements.

2. Dr. Furneaux's arguments about skepticism are confusing and distort the record.

113. Dr. Furneaux's arguments regarding alleged "skepticism" essentially rehash the arguments he makes about the alleged costs and data burden of NGS experiments. Ex2031, ¶¶181-183, 231-233. These arguments fly in the face of uniform excitement about WGS methods in the prior art, as well as the successful performance of such methods demonstrated by the numerous references I have cited in my two declarations.

VI. Response to Mr. West's Conception Testimony

114. Personalis contends that every claim of both the '394 and '033 patents was conceived by no later than May 8, 2012. I have reviewed the declarations of named co-inventor John West (the West Declaration) and former Personalis Board member Jonathan MacQuitty as well as the exhibits cited in the West Declaration to

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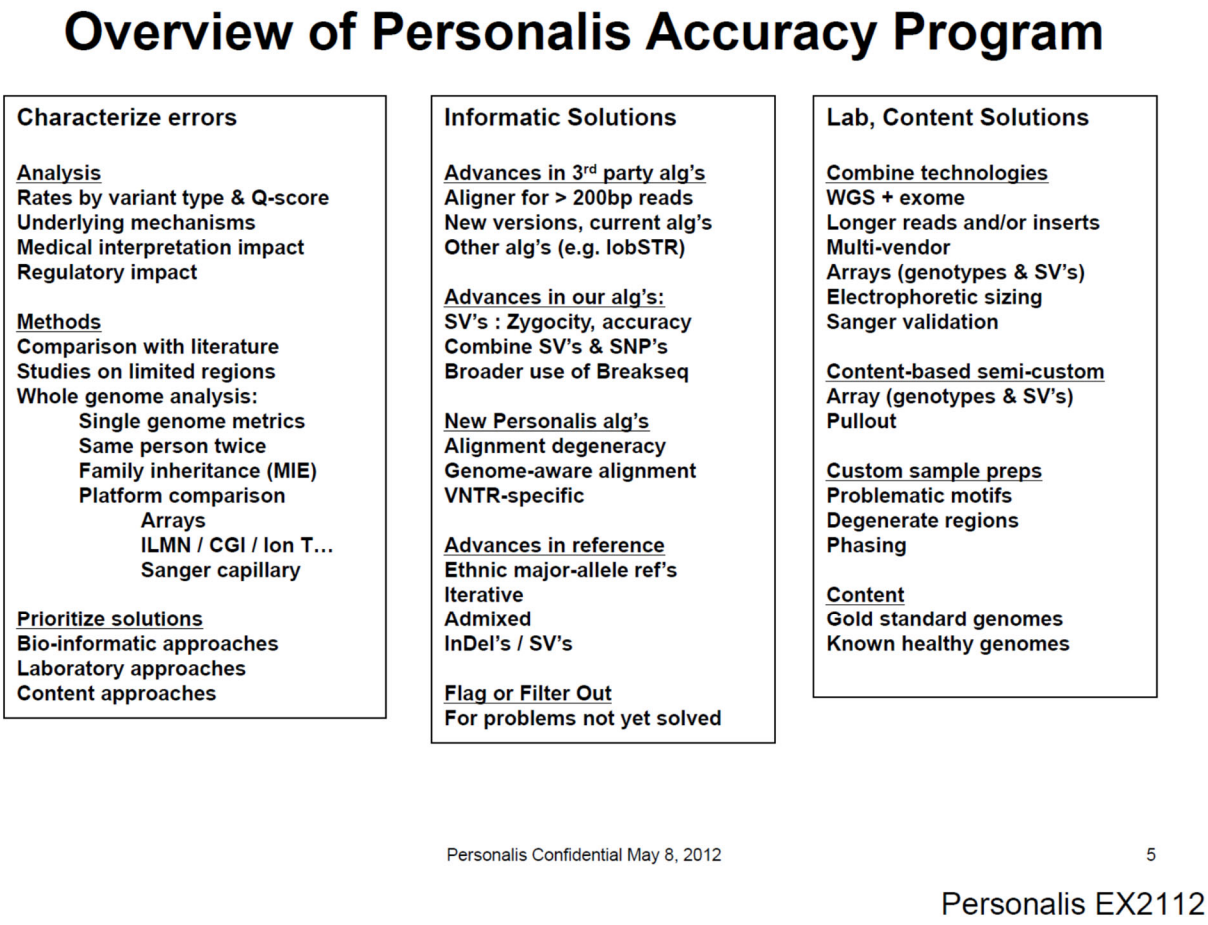
support the claimed May 8, 2012 conception date (namely, Exs2030, 2036-2045, 2089, 2102, 2109, 2112, 2114-2115).

115. I understand that Personalis must prove conception with corroborating evidence showing that the inventor disclosed to others a "completed thought expressed in such clear terms as to enable those skilled in the art to make the invention."

116. Personalis relies heavily on Exhibit 2112, which on its face is a "CEO Overview" presentation for a Personalis Board of Directors meeting dated May 8, 2012. I disagree that this Exhibit, in combination with the other evidence Personalis has submitted in support of its claimed May 8, 2012 conception date, demonstrates the disclosure of a "completed thought expressed in such clear terms as to enable those skilled in the art to make the invention." Given Personalis's heavy reliance on Exhibit 2112 in its attempts to corroborate the conception of multiple claim elements by the date of this presentation, I focus on Exhibit 2112 here. However, in reaching my opinion, I have considered the totality of the evidence Personalis has submitted on the issue of conception.

117. Slide 5 of Exhibit 2112 is key to Personalis's position on conception. I reproduce Slide 5 below from Exhibit 2112 below.



Personalis EX2112

118. In my opinion, a POSA reviewing Slide 5 in the context of Exhibit 2112, and in light of the overall record on conception, would have the following understandings.

119. As a general matter, a POSA would understand that the "Accuracy Program" referred to Personalis's efforts to improve the accuracy of whole exome or whole genome sequencing. A POSA would not have understood that program to refer to efforts to develop a minimum residual disease ("MRD") test such as NeXT Personalis, which Personalis asserts is covered by the claims of the '394 and '033

patents. (In fact, I understand that Personalis contends that NeXT Presonal "embodies" and is "co-extensive" with claim 1 (the sole independent claim) of each patent.) This is further borne out by the fact that Personalis's first product was its "Exome Plus" product, released in February 2013. Personalis did not release its NeXT Personalis MRD test until 2021- nine years after this presentation. In fact, MRD is not mentioned anywhere in the presentation and "cancer" appears only once in passing reference on slide 4 with no detail about any assays or products.

120. A POSA would understand that the initial step or phase of Personalis's program for more accurate whole exome or whole genome sequencing, as reflected in the left-hand column of Slide 5, was to "characterize errors" in existing sequencing technology as of this time in 2012. Thus, a POSA would understand the reference to "Characterize errors" in the heading for the left-hand column to refer to Personalis's proposed efforts to characterize errors in existing sequencing technology. These efforts included several ways to "analy[z]e" sequencing errors and several "methods" Personalis proposed to use to characterize sequencing errors. One such method involved performing "whole genome sequencing" on the "same person twice." A POSA would understand that performing WGS on the same person twice was a method for characterizing sequencing errors because divergent results would indicate an error in the sequencing. This is also reflected in Ex2046, slide 14:

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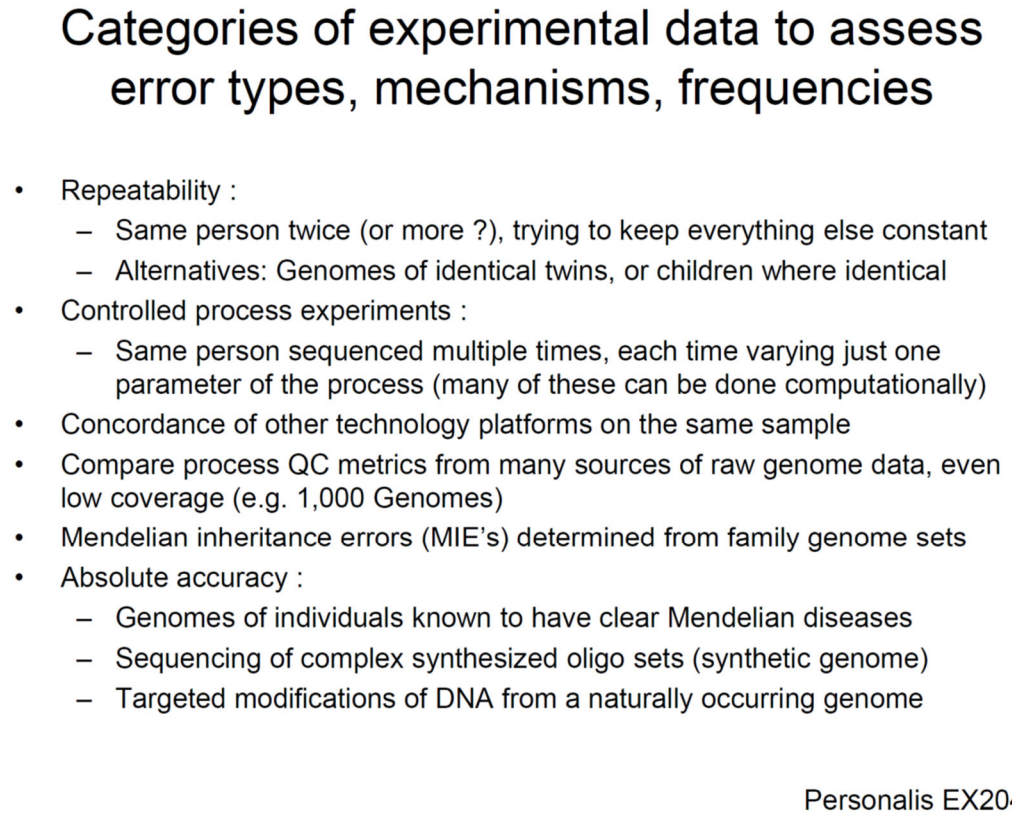

"Repeatability" is referred to here as a type of experimental data to assess sequencing errors, including sequencing the "Same person twice (or more?), trying to keep everything else constant." A POSA would understand this to involve sequencing the ***same sample*** twice or more, thereby keeping "everything else constant," in order to determine whether the sequence results were "repeatable." As Mr. West explained at his deposition:

> Q. So if you're sequencing the same person twice and you're getting different results, then that told you in 2012, "Oh, there must be a problem with sequencing, and let's see how we can address that as part of our accuracy in sequencing program"; right?

> A. Yes, that was one of the methods we used to identify errors, and then to identify the underlying mechanism was a separate step. [Ex1222, 122:17-24]

121. A POSA reading Exhibit 2112 (or Ex2046) in the context of the overall record would ***not*** understand the reference to WGS on "same person twice" to refer to any type of diagnostic assay tracking polymorphisms in a single individual over time, e.g., by sequencing different samples from the individual taken at different time points. In my opinion, a POSA would find no such disclosure of that concept here or in any of the other exhibits Personalis has submitted in an attempt to corroborate a May 8, 2012 conception date.

122. At the bottom of the "characterize error" column in Ex2112 is an item labeled "Prioritize solutions." A POSA would understand this to refer to a step of prioritizing solutions to the "errors" that Personalis's proposed analyses and methods would characterize. The solutions Personalis contemplated for addressing the errors it identified in 2012 sequencing technology consisted of bioinformatics approaches, laboratory approaches, and content approaches.

123. The middle column of Slide 5 is titled, "Informatic Solutions." A POSA would understand that this column related to the "bioinformatics approaches" referenced at the bottom of the "Characterize errors" column. In other words, a POSA would understand that this column referred to several bioinformatic solutions

Personalis contemplated for improving the accuracy of sequencing in light of the "errors" it identified as impacting 2012 sequencing technology. Again, a POSA would *not* understand these "Informatic Solutions" to relate to an MRD test, or any other type of diagnostic assay tracking polymorphisms in a single individual over time, e.g., by sequencing different samples from the individual taken at different time points. A POSA would also find that the "Informatic Solutions" referenced here are listed at a very high level of generality without describing any meaningful, much less novel or innovative, details, and further that these high-level references to purported "Informatic Solutions" are not claimed in the '394 or '033 patents.

124. The right-hand column of Slide 5 is titled, "Lab, Content Solutions." A POSA would understand that this column was intended to flesh out the "laboratory approaches" and "content approaches" referenced at the bottom of the "Characterize errors" column. In other words, a POSA would understand that this column identified several lab and content solutions Personalis contemplated for improving the accuracy of sequencing in light of the "errors" it identified as impacting 2012 sequencing technology. Again, a POSA would *not* understand these "Lab" and "Content Solutions" to relate to an MRD test, or any other type of diagnostic assay tracking polymorphisms in a single individual over time, e.g., by sequencing different samples from the individual taken at different time points. A POSA would again find that the "Lab, Content Solutions" referenced here are listed at a very high

level of generality without describing any meaningful, much less novel or innovative, details. Given the lack of detail, a POSA would literally have to invent the method on their own and would not be convinced that Personalis possessed any distinctive intellectual property as of this date.

125. Under the subheading "Content-based semi-custom" in the "Lab, Content Solutions" column is a reference to "Pullout." A POSA would understand this to be a vague reference to probes that include a chemical moiety- usually biotin—to perform hybrid capture. A POSA would understand "semi-custom" to refer to the fact that these types of probes were available as off the shelf products from, e.g., Agilent Technologies (SureSelect), and that some customization of these off-the-shelf probes was available (hence "semi-custom"). However, a POSA reviewing Slide 5 in light of the overall record on conception would have insufficient information to determine how, specifically, Personalis intended to use the "Pullout," other than that their purpose was to provide a laboratory solution to improve the accuracy of 2012 sequencing technology in some way.

126. In my opinion, a POSA would find a number of claim elements of the '394 and '033 not disclosed in Exhibit 2112 or elsewhere in Personalis's conception exhibits. These missing elements include at least:

- Step 1(a) of the '033 patent: capture probes hybridizing to polymorphisms in sequences encoding genes with known biomedically interpretable variants, based on or extracted from databases of polymorphisms

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- Steps 1(b) and (c) of the ’033 patent, which use the capture probe set of step 1(a).
- Step 1(d) of the ’033 patent and steps (e)-(f) of the ’394 patent: contacting multiple samples from the same individual taken at different time points with capture probes.
- Steps (c) and (d) of the ’394 patent, which Personalis interprets to cover contacting a sample with a set of capture probes hybridizing to polymorphisms identified during an initial WGS step and sequencing the results. *See* EX1011, 3-4 (Personalis’s district court infringement claim chart for ’394 patent, claim 1).

127. In his declaration, Mr. West attempts to backfill some of these missing elements with reference to a February 2012 paper from Mike Snyder’s group at Stanford, which is referenced at Slide 3 of Exhibit 2112. I have reviewed that paper. In my opinion, a POSA would have regarded the Snyder paper as involving a very different research project, by a separate research group, as compared to the “Accuracy Program” that the group at Personalis was envisioning. The title of the Snyder Paper is, “Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes.” It was not a paper on improving the accuracy of 2012 sequencing technology. Notably, there is no reference to the Snyder Paper on Slide 5 of Exhibit 2112. While Mr. West describes the Snyder Paper as “seminal” on Slide 3, nothing in Exhibit 2112 explains how, if at all, the Snyder Paper is related to, or could be combined with, the Accuracy Program Personalis was contemplating.

128. For the foregoing reasons, I disagree that a POSA who reviewed Personalis’s conception exhibits, including Exhibit 2112, would find that the

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Personalis inventors disclosed to others a "completed thought" corresponding to any of the claims of the '394 or '033 patents, much less one "expressed in such clear terms as to enable those skilled in the art to make the invention." A POSA would have found, at most, an incipient research project for improving the accuracy of sequencing technology that would involve the use of an undefined combination of various conventional techniques (e.g., aligners, unspecified algorithms, arrays, electrophoretic sizing, Sanger validation, pullout, sample preps, etc.), many of which the document admits were available as "3rd party algs.". In my view, Personalis's conception exhibits do not even evidence sufficient conception, under the governing legal standard, of Personalis's Accuracy Program, let alone conception of the claims of the '033 and '394 patents, which Personalis contends both in these proceedings and in the co-pending district court proceedings cover MRD tests.

VII. Conclusion

I hereby 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: December 22, 2023 By: _____
John Quackenbush, Ph.D.