

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

Foresight Diagnostics Inc.,
Petitioner,

v.

Personalis, Inc.,
Patent Owner.

IPR2023-00224 (U.S. Patent No. 11,384,394)
IPR2023-00317 (U.S. Patent No. 11,408,033)

March 19, 2024



Summary of Key Issues

- **Trial confirmed** the Board's analysis in the Institution Decisions
- PCR primers are “**capture probes**” as claimed in the Personalis patents
- Leary used **whole-genome sequencing**
- Personalis **failed to prove prior invention**
- Personalis's subsidiary arguments are **meritless**

Overview of Grounds

'394 Patent



- Ground 1 – **Leary**
- Ground 2 – **Leary + Ley**
- Ground 3 – **Leary + Chan + Liao**

'033 Patent



- Ground 1 – **Forshew**
- Ground 2 – **Forshew + Wagle**
- Ground 3 – **Wagle + Chan**

Roadmap

- **Global Issues**
- IPR2023-00224 ('394 Patent)
- IPR2023-00317 ('033 Patent)

- **Global Issues**
 - **Claim Construction: “capture probes”**
 - Personalis Failed to Prove Prior Invention
 - No Credible Evidence of Secondary Considerations

Claim Construction: “capture probes”

Board's Preliminary Construction Is Correct

In view of the above, we preliminarily conclude that one of ordinary skill reading the '394 patent would understand that there is no discernable physical distinction between capture probes and amplification primers, and that Patent Owner's functional distinction—hybridizing to target DNA so as to form subsets of molecules that are/are not hybridized—is a commonly desired trait for polynucleotides used in hybridization-based methods including PCR. Considering the argument and evidence presently of record, we agree with Petitioner that the claimed “capture probes” encompass, at a minimum,¹⁴ PCR primer capture probes and solution-based hybridization capture probes (e.g., biotinylated oligonucleotide baits).

-224 Institution Decision at 28-29
-317 Institution Decision at 24



Claims Are Interpreted In Light Of The Specification

[R]equiring that any definition of claim language in the specification be express, is inconsistent with our rulings that the specification is “the single best guide to the meaning of a disputed term,” and that the specification “acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication.”

Properly viewed, **the “ordinary meaning” of a claim term is its meaning to the ordinary artisan after reading the entire patent.**

Phillips v. AWH Corp., 415 F.3d 1303, 1320-21 (Fed. Cir. 2005) (en banc)

Specification Sets Forth Expansive View Of Capture Probes

Capture Probes

The methods disclosed herein may comprise one or more capture probes, a plurality of capture probes, or one or more capture probe sets. 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. The one or more linkers may attach the one or more labels to the nucleic acid binding site.

The one or more capture probe may comprise a nucleic acid binding site that hybridizes to at least a portion of the one or more nucleic acid molecules or variant or derivative thereof in the sample or subset of nucleic acid molecules.

The capture probes may comprise one or more nucleotides. The capture probes may comprise 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 20 or more, 30 or more, 40 or more, 50 or more, 60 or more, 70 or more, 80 or more, 90 or more, 100 or more, 125 or more, 150 or more, 175 or more, 200 or more, 250 or more, 300 or more, 350 or more, 400 or more, 500 or more, 600 or more, 700 or more, 800 or more, 900 or more, or 1000 or more nucleotides. The

Only requirements for “capture probes”:

- One or more nucleotides
- That hybridize to one or more nucleic acids

PCR Primers Capture DNA Through Hybridization

Dr. Quackenbush

“PCR ‘primers’ or ‘probes’ [] are short oligonucleotides that are complementary to a small portion of the DNA templates . . . [They] hybridize (i.e., bind through base pairing interactions) to the DNA template strand at a particular target region of interest (specified by the order of bases) to capture that specific sequence for replication.”

-224 EX1020 at ¶72

-317 EX1020 at ¶74

Forsheaw



Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA
Tim Forsheaw *et al.*
Sci Transl Med 4, 136ra68 (2012);
DOI: 10.1126/scitranslmed.3003726

Editor's Summary

Deep Sequencing Tumor DNA in Plasma

Five liters of circulating blood contain millions of copies of the genome, broken into short fragments; in cancer patients, a small fraction is circulating tumor DNA (ctDNA). An even smaller number harbor mutations that affect cancer outcome. Looking for diagnostic answers in circulating DNA is a challenge, but Forsheaw, Murtaza, and colleagues have risen to the occasion by developing a tagged-amplicon deep sequencing (TAM-Seq) method that can amplify and sequence large genomic regions from even single copies of ctDNA. By sequencing such large regions, the authors were able to identify low-level mutations in the plasma of patients with high-grade serous ovarian carcinomas.

Forsheaw *et al.* designed primers to amplify 5995 bases that covered select regions of cancer-related genes, including *TP53*, *EGFR*, *BRAF*, and *KRAS*. In plasma obtained from 38 patients with high levels of ctDNA, the authors were able to identify mutations in *TP53* at allelic frequencies of 2% to 65%. In plasma samples from one patient, they also identified a *de novo* mutation in *EGFR* that had not been detected 15 months prior in the tumor mass itself. Finally, the TAM-Seq approach was used to sequence ctDNA in plasma samples collected from two women with ovarian cancer and one woman with breast cancer at different time points, tracking as many as 10 mutations in parallel. Forsheaw and coauthors showed that levels of mutant alleles reflected the clinical course of the disease and its treatment—for example, stabilized disease was associated with low allelic frequency, whereas patients at relapse exhibited a rise in frequency.

Through several experiments, the authors were able to show that TAM-Seq is a viable method for sequencing large regions of ctDNA. Although this provides a new way to noninvasively identify gene mutations in our blood, TAM-Seq will need to achieve a more sensitive detection limit (<2% allelic frequency) to identify mutations in the plasma of patients with less advanced cancers. Nevertheless, once optimized, this “liquid biopsy” approach will be amenable to personalized genomics, where the level and type of mutations in ctDNA would inform clinical decision-making on an individual basis.

sciencetranslmed.org on May 31, 2012

fication process: a limited-cycle preamplification step where all primer sets were used together to capture the starting molecules present in the template, followed by individual amplification to purify and select

EX1030 at 3

PCR Primers Capture DNA Through Hybridization

Amplicon NGS battles begin in earnest

Archive

Select Month

A short while ago I posted about the [recent exome sequencing comparisons](#) in [Genome Research](#). In that post I did ask whether we really need to target

Categories

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

Maximize Your NGS with Sequence Capture

November 06, 2012

Post Share 0 0 0 0

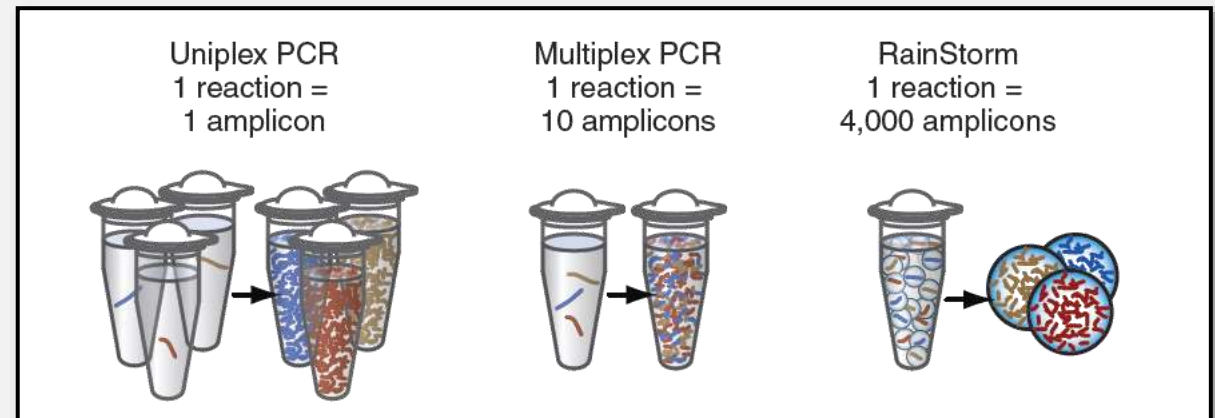
There are two basic approaches to sequence capture: **PCR-based and hybridization-based**, the latter of which can be done either in solution or on the surface of an oligonucleotide microarray. In practice, says Baiju Parikh, marketing manager for sequencing solutions at Roche Applied Science, few researchers use the array-based method any more, and none of the major manufacturers still offers such tools off-the-shelf

"[C]onsiderable effort has been devoted to develop 'target enrichment' methods, in which **genomic regions are selectively captured** from a DNA sample before sequencing."

*Listing **PCR**; MIPs; in-solution hybrid capture; and on-array hybrid capture*

EX1007 at 111-112

Figure 1 | Approaches to target enrichment.



PCR Primers Capture DNA Through Hybridization



Mr. West
Named Inventor

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.**



PCR Primers and Baits Are Two Types of Capture Mechanisms

Dr. Quackenbush

Ex. 1006 (Mertes 2011) at 380. Thus, in assays where a POSA sought to analyze many sequences of interest, solution-based hybrid capture would have been an ideal enrichment strategy. On the other hand, in assays where a POSA intended to analyze relatively few sequences of interest, then a PCR approach would have been particularly well-suited. For intermediate numbers of potential targets, either technique might serve equally well. However, these parameters would not have been considered as strict limitations, and the techniques can and were used on a relatively interchangeable basis in many experimental protocols, and could also be used together as complements to one another. *See Ex. 1006* (Mertes 2011) (Table 1)

-224 EX1020 at ¶69

-317 EX1020 at ¶71

Forsheaw



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stem.sciencemag.org on May 31, 2012

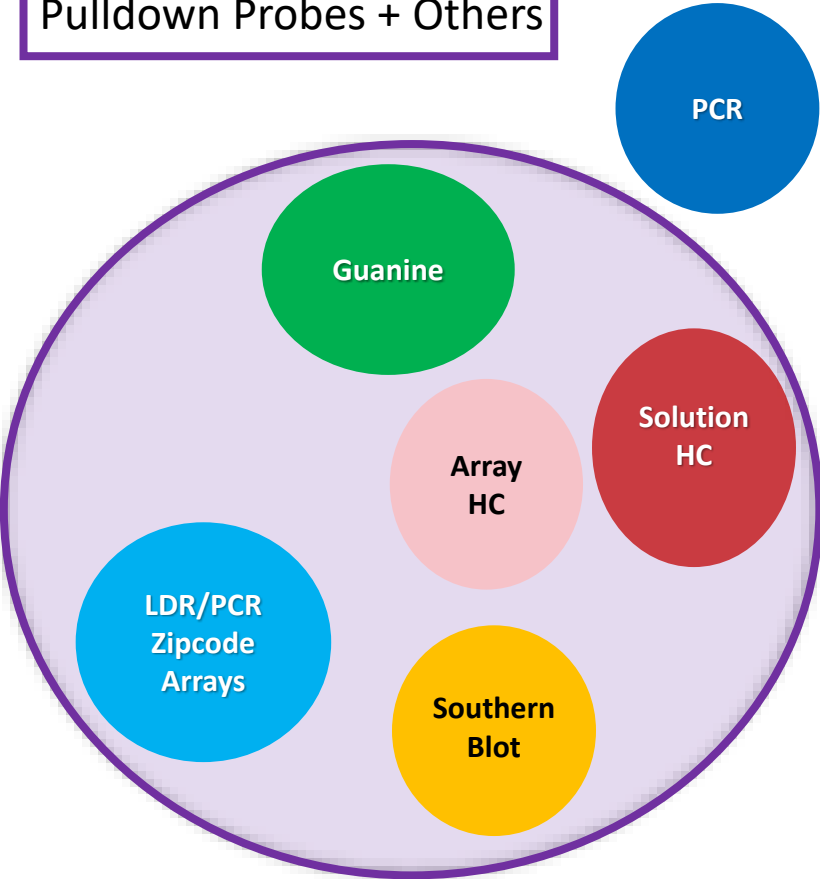
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Forsheaw EX1030, 3

Personalis's Inconsistent Positions On Scope Of "Capture Probes"

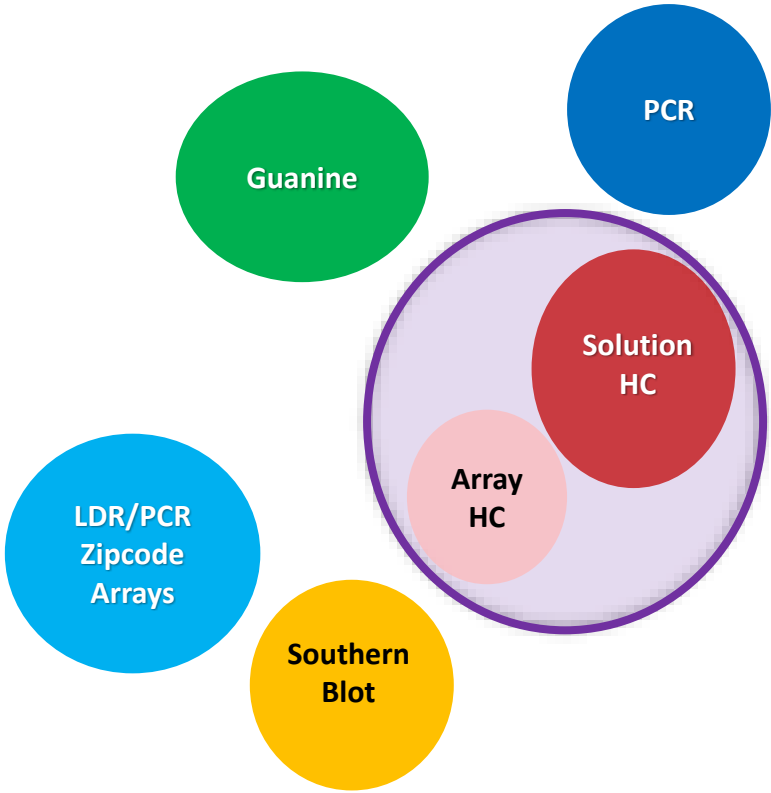
Personalis POR/Expert

Capture Probes =
Pulldown Probes + Others



Personalis Sur-Reply

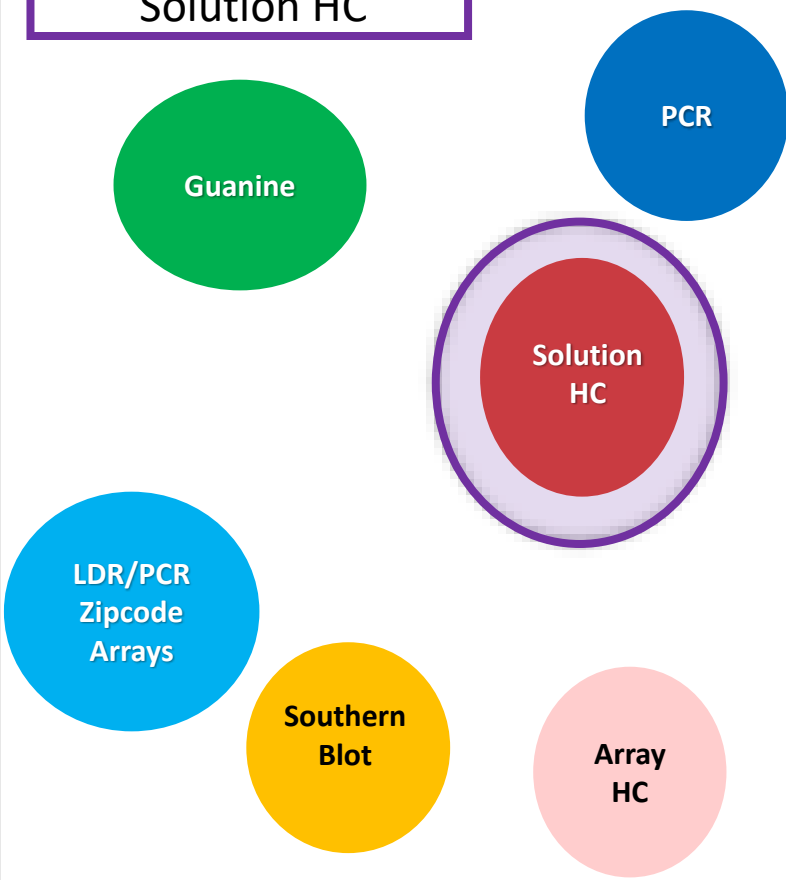
Capture probes =
Solution HC and Array HC



-224 Sur-Reply at 2
-317 Sur-Reply at 10

Personalis Inventor

Capture probes =
Solution HC

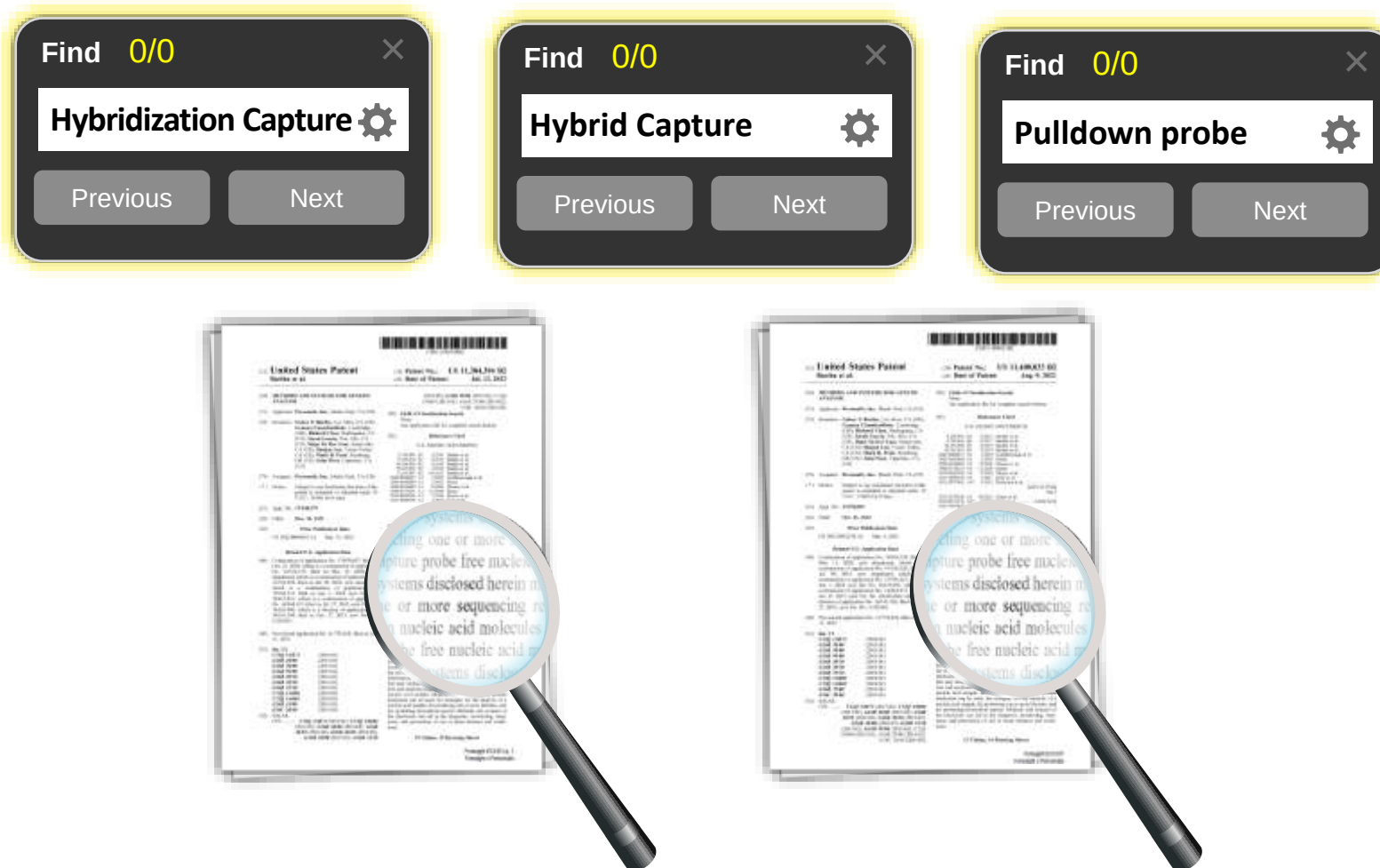


EX1222 at 88:18-89:3

Personalis's Shifting Positions Ignore The Intrinsic Record

Personalis POR Argument: “capture probes” is synonymous with “pulldown probes”

Personalis Sur-Reply Argument: “capture probes” refer exclusively to “hybridization capture”



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

“Capture Probe” Is Not Exclusive To “Hybridization Capture”



Sur-Reply



Dr. Furneaux
Expert Witness



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

-224 Sur-Reply at 2
-317 Sur-Reply at 10

Disregards own evidence that “capture probes” include:

- Single guanine residues (published in 1962)
 - EX2031 ¶169 ; EX2027
- Southern Blot probes (published in 1975)
 - EX2031 ¶165; EX3003
- “Zip-Code” PCR/ligase detection reaction arrays (published in 1999)
 - EX2031 ¶170, EX2028

Not used for the “hybridization capture” technique

Personalis's Lawyers Consider Arrays To Be Pullout Probes, But Mr. West Does Not



Mr. West
Named Inventor



- Q. Let's put aside, well, first of all, whether or not the purpose was for subsequent sequencing steps, you are aware that arrays included probes that were used to capture DNA molecules, right?
- A. **I don't think that that's what we were talking about when we referred to "pull out" here**, and so you can propose many different circumstances that have nothing to do with what we were doing.

Dependent Claims To Barcoded Capture Probes Support Board's Construction

'394 Patent

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

'033 Patent

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

- **No dispute** that barcoded PCR primers are ubiquitous
- **No evidence** of any barcoded pulldown probe/hybrid capture bait
- Personalis inventor **contradicted** his declaration at his deposition

Hybridization Capture Baits Are Not Barcoded

West Declaration

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



West Deposition

Q. **[T]he barcodes are not part of the capture probes.** They're part of the molecule that's being sequenced; correct?

A. Yes, **that's correct.**

EX1222 at 169:12-25

Chemical Modifications Required For Pulling Are Optional

Sur-Reply

Mr. West explained that a pulldown probe includes **any chemical modification that allows the capture probe to be pulled**. EX1222 83:18-84:12



Mr. West

“Most commonly that’s done by adding a chemical element onto the capture probe with what is called ‘biotin.’ And biotin binds to another chemical called ‘streptavidin.’ And streptavidin, then, is often on magnetic beads.”

Specification

Capture Probes

The methods disclosed herein may comprise one or more capture probes, a plurality of capture probes, or one or more capture probe sets. 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.** The one or more linkers may attach the one or more labels to the nucleic acid binding site.

Detectable labels also include any useful linker molecule **(such as biotin, avidin, streptavidin,** HRP, protein A, protein

EX1001 at 31:7-12; EX1001 at 14:33-42; -224 Reply at 11, 317 Reply at 14-15

“Pulldown Probes” Are A Subset Of “Capture Probes”



Dr. Quackenbush
Expert Witness



**Harvard
University**

Ex1215: <https://www.ncbi.nlm.nih.gov/patents/US2014017911> 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.

EX1225 ¶48

PCR Primers And Oligo Baits Are Different Nucleic Acids That Satisfy The Claimed Capture Probes (As Are Guanylic Acid, Zipcode Arrays, Mips, Southern Blot Probes)

3. Leary's PCR primers are not capture probes

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

Entire section of Sur-Reply predicated on Personalis's re-modified construction that "capture probes" refers exclusively to hybridization capture baits.

EX2188 123:22-124:16; *id.* 120:1-123:21. There was no motivation to complicate Leary's workflow with capture probes because a POSA would still need to perform PCR. Further, Leary uses PCR as its detection method (not as an enrichment technique for subsequent sequencing), POR 30-31, and Foresight has no reply regarding how Leary's workflow could be modified to use capture probes as a detection method.

- Foresight has **never** argued that PCR primers are hybrid capture baits
- PCR primers and hybrid capture baits are both capture probes
- '394 Ground 1 does **not** call for replacing Leary's PCR primers with hybrid capture baits
- '033 Ground 1 does **not** call for replacing Forshew's PCR primers with hybrid capture baits

“PCR Primer Capture Probes”



Dr. Furneaux
Expert Witness



Q. So I just want to understand, in your declaration you 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**. This is 1962.

The Claims Require Contacting, Not Physically Separating, Target DNA

'394 Step 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

Foresight argues that Forshe's PCR primers are capture probes because amplicons can be physically isolated in subsequent assay procedures. Reply 18-19. Forshe's PCR primers operate via a fundamentally different "core reaction principle" from capture probes. EX1006 375. PCR can only copy DNA to preserve sequence information—it cannot physically isolate the target DNA molecules. POR

Sur-Reply at 15

Not Claimed

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. The elution reaction may comprise separating a first subset of nucleic acid molecules from a second subset of nucleic acid molecules, wherein the first subset of nucleic acid molecules differ from the second subset on nucleic acid molecules by mean size, mean GC content, genomic regions, or a combination thereof.

EX1001 at 37:5-18; -224 Reply at 13, -317 Reply at 16; EX1225 ¶46-47

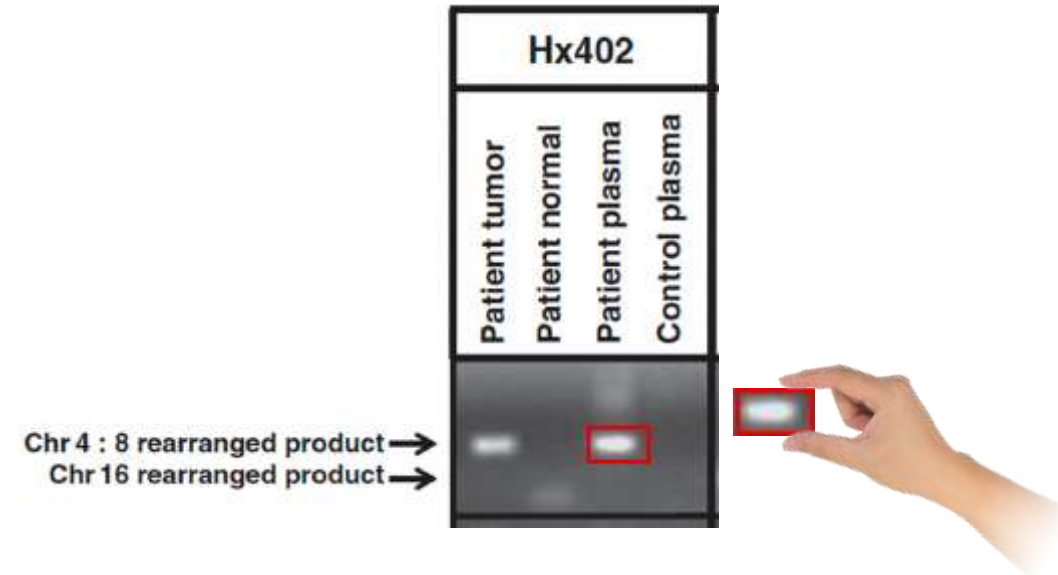
Dr. Furneaux Admitted that PCR Primers Can Physically Isolate Target DNA

'394 Step 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

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-224 Sur-Reply at 8
-317 Sur-Reply at 15

Not Claimed



EX1223 at 160:22-161:3; EX1002 at Figure 4
-224 Reply at 15, -317 Reply at 18-19; EX1225 ¶84-88

“Core Reaction Principles”

Sur-Reply at 14

Foresight truncates a portion of Mr. West’s transcript to assert that PCR primers qualify as “capture probes,” which is a noun. Reply 17-18. Foresight slipped the verb “capture” into the tail end of a question. Mr. West appropriately

Sur-Reply at 13 (preceding paragraph)

as “capture probes.” Instead, Foresight identifies three instances where the words “PCR” and “capture” were used in the same sentence. Reply 18. Two instances come from the same laboratory—the author of EX1216 was a co-author of Forshew (EX1030). EX2188 16:1-17:14. More importantly, EX1216 places the word “capture” in scare quotes, which indicates that “capture” was used in a nonstandard manner. EX2178 7-55 (“scare quotes”); EX2188 32:9-33:8, 49:1-50:9 (“the scare

Mr. West

1st Question:

“Did you ever try to use PCR primers to capture DNA for sequencing?”

1st Answer:

“So in my career, yes, I had certainly done that.”

2nd Question:

“As of 2012, it was known that PCR would be perfectly adequate for capturing [] two loci for subsequent sequencing; correct?”

2nd Answer:

“So I would say that PCR could be used for certain loci.”

Mr. West readily agreed with alleged “nonstandard” usage

EX1222 at 95:15-95:20; 97:5-13

- **Global Issues**
 - Claim Construction: “capture probes”
 - **Personalis Failed to Prove Prior Invention**
 - No Credible Evidence of Secondary Considerations

Undisputed Inventorship Disproves May 8th, 2012 Conception Date

Undisputed Inventorship Disproves May 8th, 2012 Conception Date

Undisputed Facts

- Personalis maintains that Gabor Bartha and Shujun Luo are properly named as inventors
- Personalis maintains that both patents are entitled to a conception date ***no later than May 8, 2012***
- Bartha did no work for Personalis before May 1, 2012
- Luo did no work for Personalis before June 18, 2012

Mr. West

“I would say that the -- of **all the pieces that came together to form the basis for the '033 and '394 patent, probably the last of those elements to come together was from a paper** that was -- I believe it's an exhibit here -- that was published by Mike Snyder's group at Stanford.

The publication came out in March of 2012, and our group had seen a preview copy of it at least a month earlier. We worked very closely with Mike since he was a cofounder of the company.”

EX1222 at 48:19-49:3, -224 Reply at 20, n.4; -317 Reply at 9

Undisputed Inventorship Disproves May 8th, 2012 Conception Date

- Personalis has **no response** to facts that:
 - Mr. West's May 8th presentation was drafted **before** the meeting
 - Dr. Bartha was **not** listed as a participant at Personalis May 3/4 meetings (EX2037-EX2040)
 - **No evidence** Dr. Bartha made any contributions to conception between May 1st, when he joined Personalis, and May 8th
 - Mr. West testified that the pieces allegedly came together in **March 2012**

Undisputed Inventorship Disproves May 8th, 2012 Conception Date

- **Undisputed** that:
 - Dr. Luo did not join Personalis until June 18th, 2012
 - Mr. West contends that every claim of the '394/'033 patents was conceived no later than May 8th, 2012
 - Mr. West only identifies Dr. Luo as involved in reduction to practice
 - Yet, Personalis maintains that Dr. Luo is a properly named inventor

An Inventor Must Contribute To Conception

“Conception is the touchstone of inventorship, the completion of the mental part invention.”

Burroughs Wellcome Co. v. Barr Lab'ys, Inc.,
40 F.3d 1223, 1227–28 (Fed. Cir. 1994)

A person **must contribute to the conception** of the claimed invention **to qualify as a joint inventor.**

Vanderbilt Univ. v. ICOS Corp.,
601 F.3d 1297, 1303 (Fed. Cir. 2010)



An Inventor Must Contribute To Conception



“[L]ogic dictates that the **earliest date of conception** among a claim invented by joint inventors is the **date that the last of the joint inventors began to work on creating the invention.**”

4 Annotated Patent Digest § 26:122

“Since [joint inventor] did not become involved with the project until late November 1984, **only activities which occurred after that time may be relied upon** by [inventive entity] to establish joint conception and reduction to practice on their behalf.”

Samson v. Crittenden, 14 U.S.P.Q.2d 1810 (B.P.A.I. 1989)



Mr. West's Declaration Did Not Describe Dr. Luo's "Contribution" As Conception

Conception Section

3. '394 Patent Claim 3

264. Claim 3 of the '394 patent recites:

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

265. By no later than May 8, 2012, the Accuracy Program at Personalis included one or more polymorphisms comprising one or more insertions, deletions, structural variant junctions, variable length tandem repeats, single nucleotide mutations, or a combination thereof. Conception of this claim is reflected by, for example the above discussion of claim 1. For example, as discussed above for claim 1, Slide 5 of my May 8, 2012 CEO Overview Board of Director Presentation, includes identifying biomedically interpretable variants that were identified by the "analysis" of "whole genome sequencing," which included identifying "SV's" (structural variants), "SNP's" (single nucleotide polymorphisms), "InDel's" (insertions/deletions) and "VNTRs" (Variable Number Tandem Repeats, also referred to as "Variable Length Tandem Repeats" or just "Short Tandem Repeats" (STRs)) having "medical interpretation impact." Each of the "SV's" (structural variants), "SNP's" (single nucleotide polymorphisms), "InDel's" (insertions/deletions) and "VNTR's" are a type of polymorphism.

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

Diligence (RTP) Section

D. Evidence of diligence in August 2012

369. EX2075 and EX2076 are true and correct copies of an email thread and attachment I received and responded to on August 8, 2012. Shujun Luo created the attached PowerPoint Presentation, which discusses lab options and data for the Accuracy Program. This showed that Shujun had identified a DNA sequencing chemistry which could provide enough reads in regions of certain difficult VNTR's (variable length tandem repeats) that the lobSTR algorithm could correctly call them. One such example was the Huntington's disease locus in the HTT gene, which I had examined in my own genome data in 2010 and found no coverage. Shujun also provided data on our ability to sequence through difficult motifs, particularly long homopolymers.

Personalis's Sur-Reply Excuse For Inclusion Of Luo Is Factually And Legally Defective

Sur-Reply

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

Fatal Flaws

- Claims recite “variable length tandem repeats” (VLTRs), but Ms. Luo allegedly improved VNTRs
- Even if VLTRs and VNTRs were synonymous, conception occurred before Ms. Luo’s help reducing to practice
- If Ms. Luo contributed to conception, priority date would be August 2012

Personalis's Cited District Court Conclusions of Law Are Inapposite

Ethicon, Inc. v. U.S. Surgical Corp., 937 F.Supp. 1015 (1996)

 KeyCite Yellow Flag - Negative Treatment
Distinguished by Infineon Technologies AG v. Feinics AmaTech Teoranta,
Patent Tr. & App. Bd., September 1, 2023

937 F.Supp. 1015

United States District Court, D. Connecticut.

ETHICON, INC. and Inbae Yoon, M.D., Plaintiffs,

v.

UNITED STATES SURGICAL
CORPORATION, Defendant,

and

Young Jae Choi, Intervenor–Defendant.

No. 5:89CV00386 (RNC).

|

Sept. 9, 1996.

III. Conclusions of Law

[5] 1. A patent is valid only if all true inventors are named.

See  *Jamesbury Corp. v. United States*, 207 Ct.Cl. 516, 518 F.2d 1384, 1395 (1975) (inclusion of more or less than true inventors renders patent void).  *Amax Fly Ash Corp. v. United States*, 206 Ct.Cl. 756, 514 F.2d 1041, 1050 (1975) (same).

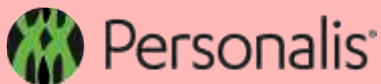
[24] 24. If a prior invention of one inventor is modified as a result of the collaborative effort of joint inventors, the modified invention may become a joint invention. See *General Motors Corp. v. Toyota Motor Co.*, 667 F.2d 504, 506–07 (6th Cir.1981), *cert. denied*, 456 U.S. 937, 102 S.Ct. 1994, 72 L.Ed.2d 457 (1982).

Does not support entitlement of “modified invention” to priority date of the “prior ‘invention’”

Mr. West: Alleged VNTR “Invention” Conceived By May 8th

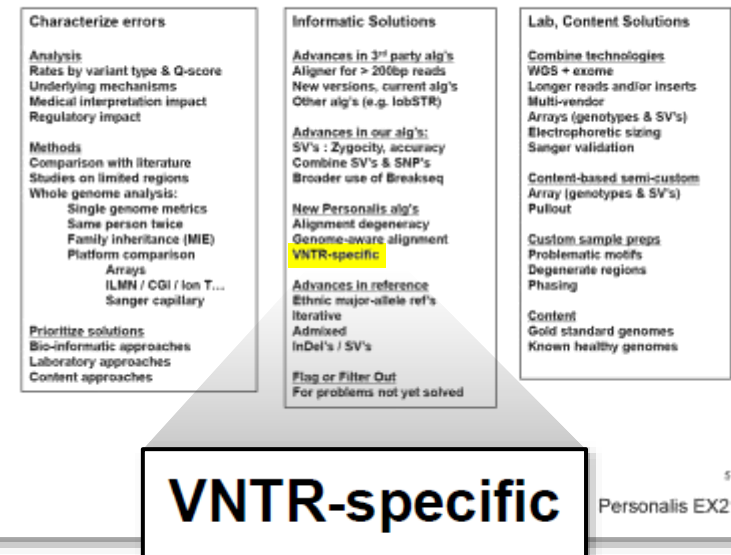


Mr. West
Named Inventor



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

Overview of Personalis Accuracy Program



EX2032 ¶¶142-143 ('033 patent);

¶¶264-266 ('394 patent); EX2112 at 5 DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Claims 3 and 4 Do Not Recite Dr. Luo's Alleged "Improvement" To Prior Conception

'394 Claim 3 / '033 Claim 4: "wherein the one or more polymorphisms comprise one or more insertions, deletions, structural variant junctions, **variable length tandem repeats**, single nucleotide mutations, or a combination thereof.

Sur-Reply

claim 3. EX2032 ¶¶264-266. In August of 2012, Ms. Luo improved the "variable length tandem repeat" aspect of claim 3 by "identif[ying] a DNA sequencing chemistry which could provide enough reads in regions of certain difficult VNTR's (variable length tandem repeats) that the lobSTR algorithm could correctly call them." *Id.* ¶369; EX2075 1, 7, 27. Thus, claim 3 was conceived by May 8, and

- Claims contain nothing beyond bare recitation of types of polymorphisms
- Thus, no claim to any alleged "improvements" by Dr. Luo
- No evidence that "variable length tandem repeats" ("VLTRs") is the same as VNTRs ("Variable **Number** Tandem Repeats")

Alleged “Improvement” To “VNTRs”, Not To Claimed Variable Length Tandem Repeats (“VLTRs”)

’394 Claim 3 / ’033 Claim 4: “wherein the one or more polymorphisms comprise one or more insertions, deletions, structural variant junctions, ***variable length tandem repeats***, single nucleotide mutations, or a combination thereof.

Col. 27, lines 48-67

The methods disclosed herein may comprise nucleic acid samples or subsets of nucleic acid molecules comprising one or more genomic regions, wherein at least one of the one or more genomic regions comprises a genomic region feature comprising a polymorphism or a portion thereof. Generally, a polymorphism refers to a mutation in a genotype. A polymorphism may comprise one or more base changes, an insertion, a repeat, or a deletion of one or more bases. Copy number variants (CNVs), transversions and other rearrangements are also forms of genetic variation. Polymorphic markers include restriction fragment length polymorphisms, **variable number of tandem repeats (VNTR’s)**, hypervariable regions, minisatellites, dinucleotide repeats, trinucleotide repeats, tetranucleotide repeats, simple sequence repeats, and insertion elements such as Alu. The allelic form occurring most frequently in a selected population is sometimes referred to as the wildtype form. Diploid organisms may be homozygous or heterozygous for allelic forms. A diallelic polymorphism has two forms. A triallelic polymorphism has three forms. Single nucleotide polymorphisms (SNPs) are a

Col. 28, lines 1-12

not called out as “VNTR’s”)

form of polymorphisms. In some aspects of the disclosure, one or more polymorphisms comprise one or more single nucleotide variations, inDels, small insertions, small deletions, structural variant junctions, **variable length tandem repeats**, flanking sequences, or a combination thereof. The one or more polymorphisms may be located within a coding and/or non-coding region. The one or more polymorphisms may be located within, around, or near a gene, exon, intron, splice site, untranslated region, or a combination thereof. The one or more polymorphisms may be may span at least a portion of a gene, exon, intron, untranslated region.

Personalis's conception documents fail to corroborate Mr. West's self-interested testimony

Personalis's Burden To Swear Behind



It is no answer that Apator's evidence is “unrebutted,” as Apator repeatedly points out. This criticism misunderstands Apator's burden of proof under § 102(g), which requires that [Patent Owner] prove [the inventor] did conceive of his meter prior to [reference's] effective filing date, not that Kamstrup prove Mr. Drachmann did not. *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375-76 (Fed. Cir. 2016) (“[I]n the context of establishing conception and reduction to practice for the purposes of establishing a priority date, ... a patent challenger has the burden of producing evidence to support a conclusion of unpatentability under § 102 or § 103, but *a patentee bears the burden of establishing that its claimed invention is entitled to an earlier priority date than an asserted prior art reference.*”) (emphasis added).

Apator Miitors ApS v. Kamstrup A/S, 887 F.3d 1293, 1297 (Fed. Cir. 2018)

Though not required, Foresight presented evidence affirmatively disproving Personalis's conception story.

Personalis's Key Evidence Of Conception

Overview of Personalis Accuracy Program

Characterize errors

Analysis

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

Methods

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

Prioritize solutions

Bio-informatic approaches
Laboratory approaches
Content approaches

Informatic Solutions

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

Advances in our alg's:

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

New Personalis alg's

Alignment degeneracy
Genome-aware alignment
VNTR-specific

Advances in reference

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

Flag or Filter Out

For problems not yet solved

Lab, Content Solutions

Combine technologies

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

Content-based semi-custom

Array (genotypes & SV's)
Pullout

Custom sample preps

Problematic motifs
Degenerate regions
Phasing

Content

Gold standard genomes
Known healthy genomes

Personalis Confidential May 8, 2012

5

Personalis EX2112

Dr. Quackenbush's Testimony Is Highly Relevant

Sur-Reply

Foresight submits immaterial testimony about what it believes *a POSA* would have understood by reviewing Slide 5 of EX2112. Reply 22-23. “For conception,

-224 Sur-Reply at 23; -317 Sur-Reply at 6



The Law

Conception “must be proven by evidence showing what the inventor has disclosed to others and what that disclosure means to one of ordinary skill in the art.”

In re Jolley, 308 F.3d 1317, 1321 (Fed. Cir. 2002)

Dr. Quackenbush's Uncontested Testimony Disproves Personalis's Conception Story



Dr. Quackenbush
Expert Witness



Harvard
University

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.

Dr. Quackenbush's Uncontested Testimony Disproves Personalis's Conception Story



Dr. Quackenbush
Expert Witness



**Harvard
University**

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.

Dr. Quackenbush's Uncontested Testimony Disproves Personalis's Conception Story



Dr. Quackenbush
Expert Witness



**Harvard
University**

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
- 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).

Dr. Quackenbush's Uncontested Testimony Disproves Personalis's Conception Story



Dr. Quackenbush
Expert Witness



**Harvard
University**

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.

Before POR, Personalis Tried To Elicit Testimony From Dr. Quackenbush In Support Of Its Meritless Swear-Behind Theory



Dr. Quackenbush
Expert Witness



Personalis Swear-Behind Question

Q. Now, let me ask the same question as of **May 2012**. Would a person of -- let me ask the same question. I'll change the date.

Assume a person of ordinary skill in the art understood whole-genome sequencing, how to identify mutations in whole-genome sequencing data, how to use capture probes, and how to sequence DNA molecules that are identified using capture probes.

Would that person of ordinary skill in the art have had a reasonable expectation of being able to successfully perform the methods of the claims of the '394 patent in May of 2012?

Invented in Prior Art, Not at Personalis

A. So in 2010, **in February of 2010**, Rebecca Leary and her colleagues at Johns Hopkins **published** this analysis where they performed what eventually turned into Claim 1 of the '394 patent and that she demonstrated she could successfully do all of this work.

Before POR, Personalis Tried To Elicit Testimony From Dr. Quackenbush In Support Of Its Meritless Swear-Behind Theory



Dr. Quackenbush
Expert Witness



Harvard
University

Personalis Swear-Behind Question

Q. Let's start with the '033 patent. How much experimentation would it have taken for a person of ordinary skill in the art in **May of 2012** to practice all the steps of the claims of the '033 patent in view of the state of the prior art at that time? And I'm not asking about what Leary could do and if Leary could replicate Leary or Forshew could replicate Forshew. I'm asking about the claims of the '033 patent.

How much experimentation would it have taken for a person of ordinary skill in the art in May of 2012 to practice all the steps of the claims in view of the state of the prior art at that time?

Invented in Prior Art, Not at Personalis

A. Forshew in **2012** -- I don't know the date, but prior to the publication of his paper clearly carried out an analysis that encompasses all the steps of the '033 patent.

Summary of Missing Elements – '394 Patent

1. A method for analyzing nucleic acid samples isolated from an individual, comprising...

(c) generating a second subset of nucleic acid molecules from a second nucleic acid sample of said individual **by contacting said second nucleic acid sample with a plurality of capture probes, wherein said plurality of capture probes hybridize to one or more polymorphisms** which are based on or extracted from one or more databases of polymorphisms, **observed in a population of one or more samples**, or a combination thereof, wherein said first sample or said second sample is obtained from said subject at a first time point;

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

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

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

Summary of Missing Elements – '033 Patent

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

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

Mr. West's Testimony Is Based On A Meeting That Never Happened



Mr. West
Named Inventor



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

Q. So that statement you made in paragraph 372 was not, in fact, based on your own independent recollection of events in August, 2012; correct?

A. We didn't have that board meeting. So obviously it couldn't be, no.

Personalis *Failed* To Prove Constructive Reduction To Practice

Foresight Did Not Concede Provisional Support

31. The '394 patent (Ex. 1001) is titled "Methods and Systems for Genetic Analysis." Ex. 1001, Code (54). The patent claims priority to "[p]rovisional application No. 61/753,828, filed on Jan. 17, 2013." *Id.*, Code (60). I have considered January 17, 2013 to be the relevant date for assessing prior art invalidity in my analysis.¹

¹ I am not aware of any evidence suggesting that Patent Owner is entitled to an earlier priority date. Even if Patent Owner were to establish entitlement to a priority date as early as January 17, 2012, one-year prior to the filing of the provisional application, my analysis would not materially change, and the '394 patent's claims would still be unpatentable at least as set forth in Grounds 1 and 2.

- No dispute that all cited references predate the January 17, 2013 provisional filing date
- No dispute that Personalis did not raise prior invention theory until *after* IPR was instituted
- Personalis's suggestion that Foresight conceded the provisional priority date is false

Foresight Did Not Concede Provisional Support

PETITION FOR INTER-PARTES REVIEW OF U.S. PATENT NO. 11,384,394

The '394 patent purports to disclose “systems and methods for sample processing and data analysis,” which can include sampling of a “nucleic acid sample and subsequent sequencing. Some or all of the nucleic acid sample may be sequenced to provide sequence information.” Ex. 1001, Abstract. The patent conclusorily states that such systems and methods can be used to “aid in the diagnosis, monitoring, treatment, and prevention of one or more diseases and conditions,” including for “monitoring the health of a fetus,” assessing “transplant tolerance,” and “suggest[ing]” therapies such as “anti-cancer therapies.” *See id.*, Abstract, 54:1-26, 60:2-16. However, the specification provides no data or working examples of any clinical application of the alleged invention in those or any other fields, let alone any data or working example supporting the claims as issued. Instead, the specification’s “Examples” are generally directed to nucleic acid library preparation steps whereby genomic DNA is divided into various “subsets” prior to sequencing. *See id.* (Examples).

- **Global Issues**
 - Claim Construction: “capture probes”
 - Personalis *Failed* to Prove Prior Invention
 - **No Credible Evidence of Secondary Considerations**

February 27, 2024 Director's Guidance



This document is scheduled to be published in the Federal Register on 02/27/2024 and available online at <https://federalregister.gov/d/2024-03967>, and on <https://pgrinfo.gov>

3510-16-P

DEPARTMENT OF COMMERCE

Patent and Trademark Office

[Docket No. PTO-P-2023-0053]

Updated Guidance for Making a Proper Determination of Obviousness

AGENCY: United States Patent and Trademark Office, Department of Commerce.

ACTION: Notice.

SUMMARY: The United States Patent and Trademark Office (USPTO or Office) is publishing this updated guidance to provide a review of the flexible approach to determining obviousness that is required by *KSR Int'l Co. v. Teleflex Inc.* (*KSR*). The focus of this document is on post-*KSR* precedential cases of the United States Court of Appeals for the Federal Circuit (Federal Circuit), to provide further clarification for decision-makers on how the Supreme Court's directives should be applied. While highlighting the requirement for a flexible approach to the obviousness determination, this updated guidance also emphasizes the need for a reasoned explanation when reaching a conclusion that a claimed invention would have been obvious. This updated guidance, together with the direction provided in the Manual of Patent Examining Procedure (MPEP), serves as operable guidance for USPTO personnel when applying the law of obviousness.

DATES: This guidance is effective on [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER].

Without diminishing the need to consider all relevant evidence when making a determination about obviousness, the Federal Circuit has made it clear that an expert's conclusory opinion about a matter relevant to the obviousness inquiry may be unavailing unless accompanied by factual support. See, for example, *Ethicon*, 844 F.3d at 1352 (concluding in the context of an ex parte appeal that the Board properly gave little weight to conclusory expert testimony regarding objective indicia); *Quanergy Sys., Inc. v. Velodyne Lidar USA, Inc.*, 24 F.4th 1406, 1417 (Fed. Cir. 2022) (agreeing with the Board, in the context of an inter partes review proceeding, that the proffered expert testimony was “incomplete, unspecific, and ultimately conclusory” and therefore not entitled to controlling weight). Consistently, in the context of proceedings before the

Personalis's Incorporation By Reference of Dr. Furneaux's Conclusive Testimony Does Not Establish Nexus



Dr. Furneaux
Expert Witness



Q. And the **only difference** between the chart at page 120 of your declaration and this snippet from Exhibit 2012 **is the statement that Personalis reserves the right** and so on; correct?

A: ...So if I can just be clear here, what you're saying is: The only difference between what one sees in the left and the right is the statement that Personalis reserves the right to rely on expert testimony and analysis and to amend this chart as necessary.

Q. Correct.

A. **It seems like a very reasonable statement to me.**

POPR

Exemplary chart of Personalis' NeXT PersonalTM test practicing claim 1 of U.S. Patent No. 11,384,394 (the "'394 Patent'")

Personalis reserves the right to rely upon expert testimony and/or analysis and to amend this chart as necessary

'394 Patent Claim Language	NeXT Personal TM Test
1. A method for analyzing nucleic acid samples isolated from an individual, comprising:	The Next Personal test performs a method for analyzing samples isolated from an individual. Delivering Industry-Leading Sensitivity to Detect Residual Disease at the Earliest Timepoints NeXT Personal, an advanced personalized, and tumor-informed liquid biopsy assay, is designed to detect nucleic acid residual disease (NRD) and cancer recurrence at the earliest timepoints — prior to, during or after treatment — in patients previously diagnosed with cancer. While circulating tumor-derived DNA (ctDNA) is an emerging biomarker for many cancers, the limited sensitivity of current detection methods reduces its utility for diagnosing NRD within a variety of clinical applications. Standard-of-care (SOC) radiological-based techniques, including CT, PET, and MRI scans, also tends to fail in their ability to detect residual disease during or after surgery or systemic therapy due to the inherent tumor volume required. Therefore, sensitive detection and quantification of NRD remains a key challenge, particularly in early-stage cancers, where timely detection of small metastatic lesions may avoid treatment that prevents progression to advanced metastatic, incurable disease. To address these challenges, NeXT Personal was developed to deliver industry-leading NRD sensitivity in the range of 1:1 parts per million (PPM) representing a 10,000x increase over other available methods (Figure 1), while requiring only a single tube of blood (serum, plasma) or ctDNA, and time of 15 minutes.
(a) generating a first subset of nucleic acid molecules from a first nucleic acid sample obtained from said individual;	The NeXT Personal test generates a first subset of nucleic acid molecules from a first nucleic acid sample obtained from a tumor biopsy obtained from an individual.

Source: Exh. 1 - Personalis NeXT Personal Brochure, p.1

Furneaux Declaration/POR

'394 Patent Claim Language	Personalis' NeXT Personal TM assay
1. A method for analyzing nucleic acid samples isolated from an individual, comprising:	The Next Personal test performs a method for analyzing samples isolated from an individual. Delivering Industry-Leading Sensitivity to Detect Residual Disease at the Earliest Timepoints NeXT Personal, an advanced personalized, and tumor-informed liquid biopsy assay, is designed to detect nucleic acid residual disease (NRD) and cancer recurrence at the earliest timepoints — prior to, during or after treatment — in patients previously diagnosed with cancer. While circulating tumor-derived DNA (ctDNA) is an emerging biomarker for many cancers, the limited sensitivity of current detection methods reduces its utility for diagnosing NRD within a variety of clinical applications. Standard-of-care (SOC) radiological-based techniques, including CT, PET, and MRI scans, also tends to fail in their ability to detect residual disease during or after surgery or systemic therapy due to the inherent tumor volume required. Therefore, sensitive detection and quantification of NRD remains a key challenge, particularly in early-stage cancers, where timely detection of small metastatic lesions may avoid treatment that prevents progression to advanced metastatic, incurable disease. To address these challenges, NeXT Personal was developed to deliver industry-leading NRD sensitivity in the range of 1:1 parts per million (PPM) representing a 10,000x increase over other available methods (Figure 1), while requiring only a single tube of blood (serum, plasma) or ctDNA, and time of 15 minutes.
	EX2012 (Personalis NeXT Personal Brochure) at page 15.

Sensitivity Not Recited In Any Challenged Claim

'394 Patent, Claim 1

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

'033 Patent, Claim 1

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

Personalis Does Not Dispute That It Overstated The Sensitivity of Its Assay in the POR

- POR asserted that NeXT Personal was praiseworthy based on its sensitivity of “one part per million (or 0.0001%).” -224 POR at 82.
- Personalis compared this sensitivity to Leary’s reported 0.3% sensitivity for detecting **single variant**
- Personalis’s 0.0001% figure was for detecting **any one** of **1,800** variants
- Personalis’s sensitivity for **single variant**: 0.1% (1,000 ppm)

Table 1		
Key NeXT Personal Specifications		
General	Cancer Stage	All
		Solid tumors
		ng
		mL (1 tube) / 4 mL
		Tumor-informed
	Front-End Tissue Sequencing	WGS
		100X
		Targeted panel
		100,000X (raw)
		MRD
		2- Tumor variant tracking
		Customer-specified variant tracking
		100
		1 PPM
		99.9%
Tumor Variant Tracking		Variant capacity
		400
		Source of variants
		Coding regions only
		Analytical Sensitivity
		0.1% VAF
Panel Variant Tracking		Variant capacity
		1,000's
		Source of variants
		Custom / Customer specified
		Analytical Sensitivity
		0.1% VAF

Dr. Furneaux's Unfamiliarity With Personalis is Inconsistent With Alleged Praise



Dr. Furneaux
Expert Witness



Q. And before that first contact **in January 2023,**
what did you know about Personalis?

A. Well, embarrassingly, **not very much at all.**

'394 Patent (IPR2023-00224)

The '394 Patent

- **Ground 1**
 - Capture Probes
 - WGS
 - Second Sample
 - Resequencing
- Ground 2
- Ground 3

Limitations Disputed By Personalis

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

The '394 Patent

- **Ground 1**
 - **Capture Probes**
 - WGS
 - Second Sample
 - Resequencing
- Ground 2
- Ground 3

PCR Primers Satisfy Personalis's Construction

Leary's PCR Primers Meet Personalis's Proposed Construction

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS INC.,
Petitioner,

v.

PERSONALIS, INC.
Patent Owner,

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

PATENT OWNER RESPONSE



Foresight's exhibits consistently demonstrate that a POSA would have understood the plain meaning of "capture probes" to be *"a nucleic acid sequence that hybridizes to target DNA, either in solution or on a solid support, so that one can physically capture and isolate the target DNA."* Foresight's Mamanova exhibit

- **Undisputed:** PCR primers are nucleic acid sequences that hybridize to target DNA in solution
- Trial evidence establishes that one can physically capture and isolate target DNA using PCR primers

Mr. West Confirmed That PCR Captures Target DNA



Mr. West
Named Inventor



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***, and when I worked at Applied Biosystems, we commercialized thousands of PCR primers specifically for that purpose using the old Sanger sequencing.

Mr. West Confirmed That PCR Captures Target DNA



Mr. West
Named Inventor



Q. Let's say that you were only interested in a small handful of genomic loci. Let's say two. **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.** There're also other areas that -- where PCR does not work well. So the answer is, no, that would not be true for all loci. There are places where, if PCR did work, you could conduct two reactions. You might conduct them separately so they didn't interfere with each other. **But if you wanted to conduct two PCR reactions for two different genomic loci, certainly you could do that.**

It is “Facile” to Capture Nucleic Acids From a Gel



Dr. Furneaux
Expert Witness



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.**

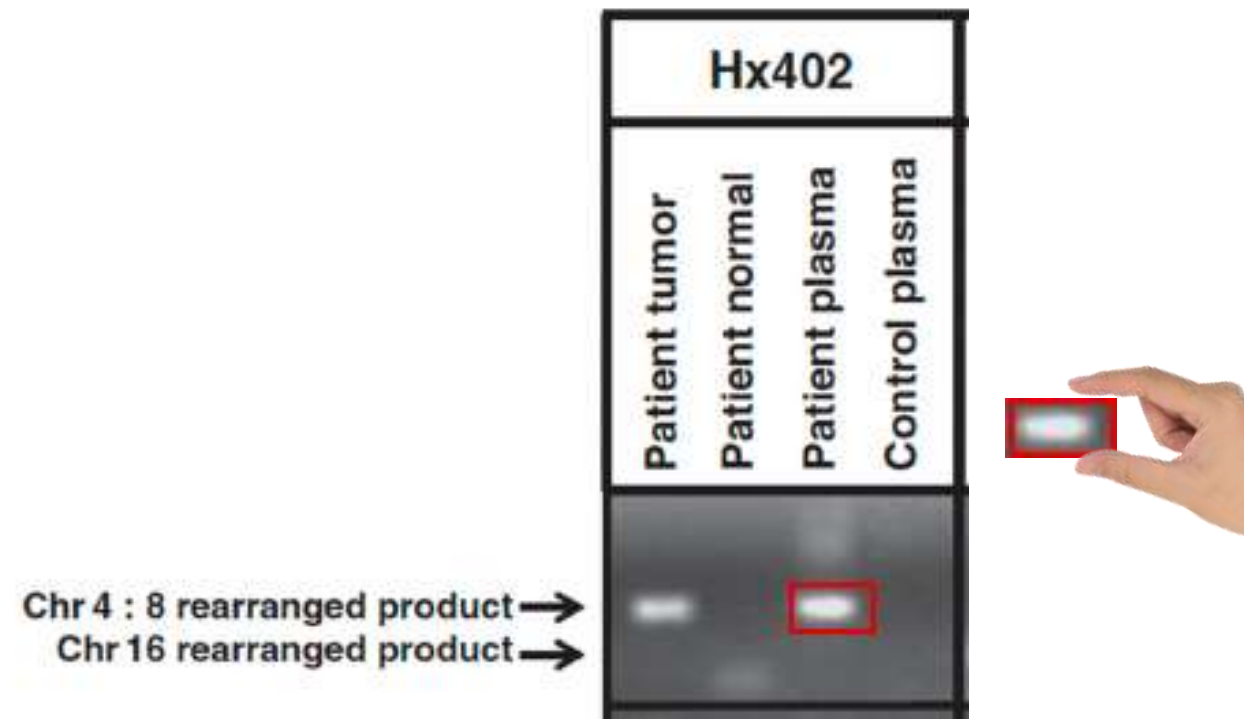
Leary's PCR Primers Physically Capture DNA

Dr. Furneaux

Q. And **if you can find and visualize the fragment** of a particular size on a gel, then **you can physically remove it** from the gel?

A. Uh-huh. **Absolutely.**

Leary (EX1002)



The '394 Patent

- **Ground 1**
 - Capture Probes
 - **WGS**
 - Second Sample
 - Resequencing
- Ground 2
- Ground 3

Claim Construction: “whole genome sequencing”

Board's Preliminary Construction



In light of the evidence and argument presently of record, we preliminarily interpret “whole genome sequencing,” as used in claim step 1(b), to mean “a non-targeted approach to sequencing all or almost all of a genome.” The panel may reconsider on the more complete record developed

Institution Decision at 22

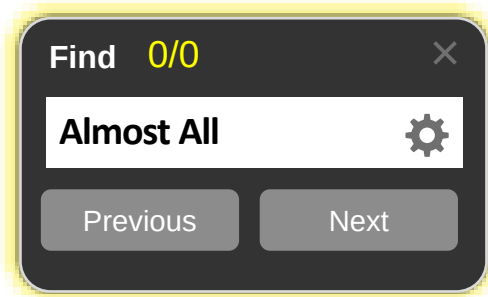
Express Construction Is Not Required

The Board is required to construe “only those terms ... that are in controversy, and only to the extent necessary to resolve the controversy.”

Realtime Data, LLC v. Iancu, 912 F.3d 1368, 1375 (Fed. Cir. 2019);
quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).



“Almost All” Injected By Personalis’s POPR; NOT the Intrinsic Record



- Distinction is **WGS vs. targeted** (e.g. exon) sequencing
- Specification does not describe WGS in terms of amount of genome sequenced
- Specification acknowledges gaps in WGS

The genomic region features may comprise one or more low mean coverage regions from whole genome sequencing (WGS), **zero mean coverage regions from WGS**, validated compressions, or a combination thereof. The genomic region

Personalis's Shifting Positions On "Almost All" Of The Genome

POR/Furneaux Declaration October 2023

91% is **insufficient**, **easy** to calculate

This accounts for only **2.9 billion bp** (59 million times 50-base pairs), **which is far less than the 3.2 billion** bp acknowledged to be present in the reference genome at this priority date. Thus, in this highest-case scenario, approx. **9%** of the human genome is still missing from this analysis.

Furneaux Deposition December 2023

90% is **sufficient**

Q. All right. And did you provide a guide point or endpoint for what "almost all" is?

A. I'm happy to provide that now. Sorry, I was being a bit obtuse there. **That magic number is not presently in the declaration.**

* * *

A. So in my mind, the "almost all" part of that statement would be that **if you are less than 90 percent, it ain't a whole genome.**

Reply at 2-3; EX1223 at 87:21-25; 92:20-93:2

Sur-Reply February 2024

90% is **sufficient**, but **difficult** to calculate

Foresight attempts to reduce sequence coverage to a "straightforward formula" of "X basepairs/Y basepairs." Reply 2-3. this equation cannot be used unless the X basepairs are randomly distributed across the entire genome in a non-targeted manner.

WGS Should Reflect Academic Consensus



Dr. Furneaux
Expert Witness



Q. [S]ince filing your declaration, you've done further analysis and determined an endpoint for what constitutes “almost all of a genome.” Is that your testimony?

A. My testimony is that I've thought earnestly about this question and looked at various sources of information so that I can form a consensus in my mind. **But importantly, I think it should also reflect a consensus of academic findings in the field and also what other experts would regard as “almost all.”**

Contemporary Consensus: Leary Used WGS



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). In this respect, we find it pertinent that Leary’s PARE studies began with sheared genomic DNA, and presumably resulted in non-targeted, randomly-distributed sequencing reads throughout the genome.¹⁰ We also find it pertinent that Forshew, a contemporary of Leary, described the mate-paired technique as employed in Leary’s PARE approach as whole genome sequencing. Ex. 1030, 10.

Contemporary Consensus: Leary Used WGS

Sur-Reply

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

2013 Patent Filing (Diehn, Alizadeh)

[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). While sensitive, such methods require optimization of molecular assays for each patient, limiting their widespread clinical application. More recently, several groups have reported amplicon-based deep sequencing methods to detect cfDNA mutations in up to 6 recurrently mutated genes (Forsheew et al. (2012) Sci. Transl. Med. 4:136ra168; Narayan et al. (2012) Cancer Res. 72:3492-3498; Kinde et al. (2011) Proc. Natl Acad. Sci. USA 108:9530-9535). While powerful, these approaches are limited by the number of mutations that can be interrogated (Rachlin et al. (2005) BMC Genomics 6:102) and the inability to detect genomic fusions.

EX1112, [0003]; EX1225, ¶26; Reply at 4

Contemporary Consensus: Leary Used WGS

Sur-Reply

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

Forshew

Previously proposed methods for personalized monitoring of tumor dynamics relied on expensive custom-designed probes (3) or identification of rearrangements using whole-genome sequencing (18, 19).

18. R. J. Leary, I. Kinde, F. Diehl, K. Schmidt, C. Clouser, C. Duncan, A. Antipova, C. Lee, K. McKernan, F. M. De La Vega, K. W. Kinzler, B. Vogelstein, L. A. Diaz Jr., V. E. Velculescu, Development of personalized tumor biomarkers using massively parallel sequencing. *Sci. Transl. Med.* **2**, 20ra14 (2010).
19. D. J. McBride, A. K. Orpana, C. Sotiriou, H. Joensuu, P. J. Stephens, L. J. Mudie, E. Hämäläinen, L. A. Stebbings, L. C. Andersson, A. M. Flanagan, V. Durbecq, M. Ignatiadis, O. Kallioniemi, C. A. Heckman, K. Alitalo, H. Edgren, P. A. Futreal, M. R. Stratton, P. J. Campbell, Use of cancer-specific genomic rearrangements to quantify disease burden in plasma from patients with solid tumors. *Genes Chromosomes Cancer* **49**, 1062–1069 (2010).

Contemporary Consensus: Leary Used WGS



Meyerson EX1031

Table 1 Whole-genome sequencing studies of cancer				
Study	Method	Cancer type	Number of samples	Findings
Ley et al., 2008	Deep single-end whole-genome sequencing	AML	1	
Campbell et al., 2008	Shallow paired-end whole-genome sequencing	Lung	2	Deletions, amplifications, tandem duplications, interchromosomal rearrangements
Stephens et al., 2009	Shallow paired-end whole-genome sequencing	Breast	24	Deletions, amplifications, tandem duplications, interchromosomal rearrangements, inversions
Plesance et al., 2010	Deep paired-end	Melanoma	1	Point mutations, insertions, deletions, amplifications, inversions

Whole-genome sequencing studies

Campbell et al., 2008

Shallow paired-end whole-genome sequencing

AML, acute myelogenous leukaemia.



Dr. Quackenbush
Expert Witness

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

Contemporary Consensus: Leary Used WGS

Leary

Description of the approach

The PARE (personalized analysis of rearranged ends) approach, shown schematically in Fig. 1, requires the identification of patient-specific rearrangements in tumor samples. To determine the feasibility of identifying such alterations using next-generation sequencing approaches, we initially analyzed four tumor samples (two colon and two breast tumors) and their matched normal tissue samples using the Applied Biosystems SOLiD System (Table 1). Genomic DNA from each sample was purified, sheared, and used to generate libraries with mate-paired tags ~1.4 kb apart. Libraries were digitally

EX1002 at 1

Personalis '058 Patent

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, 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 embodi-

EX1211 at 3:37-49; EX1225 ¶¶ 22,68

Does Leary Use WGS?

Meyerson
(2010)

YES



EX1031

Forsheew
(2012)

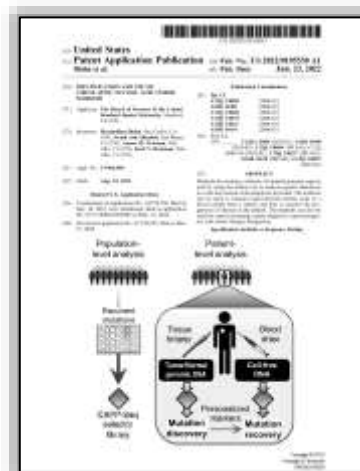
YES



EX1030

Foresight's
Founders
(2013)

YES



EX1112

Personalis
Patents
(2013-14)

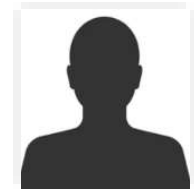
YES



EX1211
EX1212
EX1214

Dr. Furneaux
(2023)

NO



Dr. Furneaux
Expert Witness



Petitioner's Construction Captures Contemporaneous Understanding

In light of Personalis's abuse of the Board's construction, to the extent express construction is required, Petitioner believes that the plain meaning of WGS was (and remains) **"a non-targeted approach to generating sequencing reads and mapping those reads back to a reference genome (rather than a genome subset)."** This distinguishes WGS from techniques, like exome sequencing, that targeted subgenomic intervals during library preparation and then mapped reads back only to those regions. Ex1225 ¶¶34-36; DI22.

- Consistent with intrinsic evidence and extrinsic evidence
- Does not require additional calculations

Leary Discloses And Renders Obvious A Non-Targeted Approach To Sequencing All Or Almost All Of The Genome

Leary's WGS Was Non-Targeted



Dr. Quackenbush
Expert Witness



**Harvard
University**

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

Personalis’s mischaracterization already rejected in Institution Decision

Contemporaneous Personalis Patents: WGS Includes 50% Coverage

Personalis '058 Patent (2013)

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%.

Personalis '405 Patent (2013)

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%.

Contemporaneous Personalis Patents: WGS Includes 50% Coverage

Personalis '968 Patent (2014)

haplotypes, SNV, CNV or one or more polymorphisms. In some cases, the methods as disclosed herein comprise **untargeted sequencing data (e.g., a low coverage whole genome sequencing data)** that may have a sensitivity, specificity,

Personalis '405 Patent (2013)

supplement to target-specific sequencing data. Non-limiting examples of the low coverage untargeted sequencing data include low coverage whole genome sequencing data or the untargeted portion of the target-specific sequencing data. This low coverage genome data can be analyzed to assess copy number variation or other types of polymorphism of the sequence in the sample. The 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

Low-Coverage WGS is a Species of WGS

Pasniuc (Cited by '968 Patent)

a high throughput sample preparation for roughly \$100 per sample (see URLs), and we have recently demonstrated that **sequencing libraries appropriate for whole-genome sequencing** can be produced for approximately \$15 per sample on a scale of thousands of samples¹¹. Below, we show that by **sequencing such libraries at ultra-low coverage (0.1–0.5x,** at an effective sequencing cost of \$10–\$100 per sample) followed by genotype calling using 1000 Genomes Project reference panels², the effective sample size per unit cost of this approach is several times greater than for the standard GWAS study design using SNP arrays. This gap will increase if sequencing costs continue to drop more quickly than genotyping costs.

Dr. Furneaux Affirmatively Cited Reference With 10% Coverage As WGS

Dr. Furneaux

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 exome¹², or whole genome^{9,32,33,34} 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

Heitzer (Reference 33)

time-consuming. Previously 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 [39].

Figure 2 Outline of our whole-genome plasma analysis strategy. After blood draw, plasma preparation, and DNA-isolation we start our analysis, which is two-fold: first (left side of the panel), an Illumina shotgun library is prepared (time required, approximately 24 h). Single-read whole genome plasma sequencing is performed with a shallow sequencing depth of approximately 0.1x (approximately 12 h). After alignment

Each of Dr. Furneaux's Calculations Confirms Leary Met the Threshold for "Almost All"



Dr. Furneaux
Expert Witness



"[T]he matepaired analysis for Co84 normal covers, in a best-case scenario, only about 1.71 Gb." [1.71 Gb/2.86 Gb=]

EX2031 ¶¶99-100

60%

"This accounts for only 2.9 billion bp (59 million times 50-base pairs), which is far less than the 3.2 billion bp acknowledged to be present in the reference genome at this priority date. Thus, in this highest-case scenario, approx. 9% of the human genome is still missing from this analysis."

EX2031 ¶¶98

91%

"Leary's sequence coverage was only 0.9x...."

EX2031 ¶¶151

90%

Leary Rendered Obvious Additional Sequencing



Dr. Quackenbush
Expert Witness



**Harvard
University**

Complete Genomics. Ex. 1027 at 78. Sequencing to even greater depth when required by an experiment also would have been routine, as it would require only 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 different flow cells.” Ex. 1028 at 2.

Leary Rendered Obvious Additional Sequencing



Dr. Quackenbush
Expert Witness



**Harvard
University**

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:

Whole-genome sequencing.

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^{4,13}. 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

Mate-Pair Inserts Are Sequenced in Different Fragments

Sur-Reply

Leary's PARE approach intentionally sequences only the 25-bp mate-paired tags at the ends of the original fragments, while the 1,400 bases in the middle of the fragments are intentionally discarded. EX1002 1; EX2031 ¶¶93-96. This approach

Personalis '058 Patent

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, 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 embodi-

Personalis's own patents consider 100,000 "discarded" base pairs in the middle of fragments to be WGS

Personalis's Cost And Data Burden Arguments Are Meritless

Leary (EX1002)

Moreover, the cost of massively parallel sequencing, which has decreased substantially over the last 2 years, continues to spiral downwards. Finally, there are clinical settings where the fraction of any

Dr. Quackenbush (EX1020)

D. Personalized Cancer Testing and Monitoring

79. Once NGS techniques became available, those skilled in the art immediately sought to leverage them to develop methods to discover, monitor, and track mutations in cancer patients. For example, a 2008 *Nature* paper by Timothy

Ley (EX1012)

Acute myeloid leukaemia is a highly malignant haematopoietic tumour that affects about 13,000 adults in the United States each year. The treatment of this disease has changed little in the past two decades, because most of the genetic events that initiate the disease remain undiscovered. Whole-genome sequencing is now possible at a reasonable cost and timeframe to use this approach for the unbiased discovery of tumour-specific somatic mutations that alter the protein-coding genes. Here

No Dispute: “All” Was Unachievable at the Relevant Time



Mr. West
Named Inventor



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.

The '394 Patent

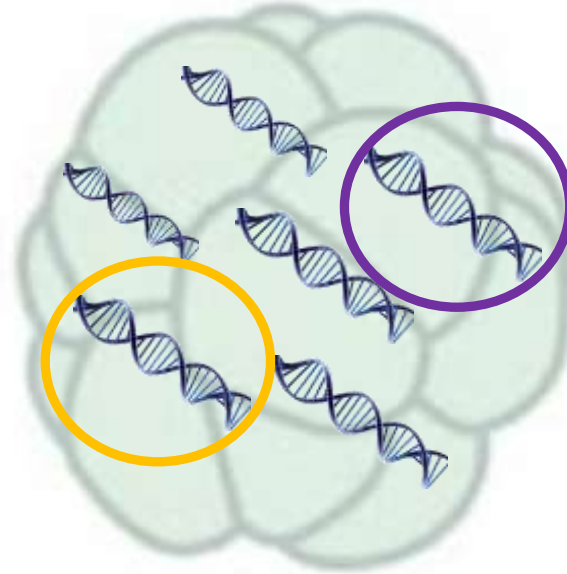
- **Ground 1**
 - Capture Probes
 - WGS
 - **Second Sample**
 - Resequencing
- Ground 2
- Ground 3

Leary Discloses A First And Second Nucleic Acid Sample

Single Tumor Sample Contains Multiple Nucleic Acid Samples

1(c): generating a second subset of nucleic acid molecules from a **second nucleic acid sample** of said individual... wherein said first sample or said second sample is obtained from said subject at a first time point

Tumor Sample



- Claims expressly permitted taking first and second sample at the same time
- Same **tumor** sample can provide **“first”** and **“second”** **nucleic acid** samples
- “Leary also discloses that the second sample may be a plasma sample.”

The '394 Patent

- **Ground 1**
 - Capture Probes
 - WGS
 - Second Sample
 - **Resequencing**
- Ground 2
- Ground 3

Prior Art Does Not Need To Be Defective To Motivate Improvement

Sur-Reply

supposedly meet limitation 1(d). Foresight fails to articulate how sequencing Leary's PCR product was incomplete or inaccurate such that a POSA would conduct additional re-verification sequencing. Without reason to believe that Leary's PCR product sequencing was incomplete or inaccurate, there was no such motivation. Foresight's argument that someone *could* re-sequence the PCR products, Reply 17, does not provide any reason why they *would* have done so. This is especially true

Sur-Reply at 18

Petition

An ultimate goal of using the unique identified PCR primer capture probes is "to serve as potential biomarkers," and to use "PCR assays to detect them in the presence of increasing amounts of normal DNA." *Id.* Thus, a POSA would have been motivated to sequence the unique rearrangement in each patient, at least to aid monitoring and the design of biomarkers, and for use in further clinical applications. Quackenbush ¶149.

sequencing step. *Id.* ¶150. A POSA would have been particularly motivated to use a confirmatory sequencing step in the context of Leary's methods, given that the purpose of the analysis is to predict the status of the patient's cancer. As the

Petition at 41-43

The '394 Patent

- Ground 1
 - Capture Probes
 - WGS
 - Second Sample
 - Resequencing
- **Ground 2**
- Ground 3

Personalis Admits Ley Discloses WGS

Ley (EX1012)

Acute myeloid leukaemia is a highly malignant haematopoietic tumour that affects about 13,000 adults in the United States each year. The treatment of this disease has changed little in the past two decades, because most of the genetic events that initiate the disease remain undiscovered. Whole-genome sequencing is now possible at a reasonable cost and timeframe to use this approach for the unbiased discovery of tumour-specific somatic mutations that alter the protein-coding genes. Here we present the results obtained from sequencing a typical acute myeloid leukaemia genome, and its matched normal counterpart obtained from the same patient's skin. We discovered ten genes with acquired mutations; two were previously described mutations that are thought to contribute to tumour progression, and eight were new mutations present in virtually all tumour cells at presentation and relapse, the function of which is not yet known. **Our study establishes whole-genome sequencing** as an unbiased method for discovering cancer-initiating mutations in previously unidentified genes that may respond to targeted therapies.

Our study establishes whole-genome sequencing

Sur-Reply

Ley took on the cost and data burden of **performing WGS to discover single-base alterations.** EX1002 6-7. Two years later, Leary designed its new PARE approach that omitted 1,400 bases from each fragment to target structural chromosomal rearrangements instead of single-base alterations. *Supra* Section

Petition Established Motivation To Combine Leary and Ley For SNPs



Dr. Quackenbush
Expert Witness



**Harvard
University**

214. Specifically, Ley performed targeted resequencing on mutations comprising SNPs and indels that were present in genes of a patient's tumor sample.

Ex. 1012 (Ley) at 69. Table 2 describes the mutations detected and analyzed in Ley, as well as their effect on the relevant genes:

Table 2 | Non-synonymous somatic mutations detected in the AML sample

Gene	Consequence	Type	Solexa tumour reads WT/variant	Solexa skin reads WT/variant	Conservation score of mutant base	Mutations in other AML cases*
CDH24	Y590X	Nonsense	9:9	16:0	0.998	0/187
SIC15A1	W77X	Nonsense	15:12	19:0	1.000	0/187
KNDG2	L799F	Missense	7:8	20:0	NA	0/187
PTPRF	P123SL	Missense	9:13	16:0	1.000	0/187
GRIN1B	R176H	Missense	15:10	14:0	NA	0/187
GPR123	T38I	Missense	11:11	13:0	NA	0/187
EBI2	A338V	Missense	7:12	18:2	1.000	0/187
PCSKC	P1004L	Missense	19:9	15:1	0.98	0/187
FLT3	ITD	Indel	18:12	8:0	NA	51/185
NPM1	CATG ins	Indel	36:6	33:0	NA	43/180

Ins, insertion; WT, wild type.
* Patient cohort defined in ref. 23.

successfully did so. Specifically, Ley detected via whole-genome sequencing, and then monitored using probe-based capture techniques similar to those employed by Leary, polymorphisms that were found in “the coding sequences of annotated genes.” Ex. 1012 (Ley) at 66; *see also id.* at 66, 70 (discussing desirability of “directed re-sequencing”); 69 (comparing allele frequencies for re-sequenced polymorphisms at time of primary tumor sampling and at relapse). The genes

The '394 Patent

- Ground 1
 - Capture Probes
 - WGS
 - Second Sample
 - Resequencing
- Ground 2
- **Ground 3**

Personalis Admits Chan Teaches WGS

Furneaux Declaration

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 exome¹², 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

Newman (EX2152)

32. Chan KC, et al. Cancer genome scanning in plasma: detection of tumor-associated copy number aberrations, single-nucleotide variants, and tumoral heterogeneity by massively parallel sequencing. Clin Chem. 2013; 59:211–224. [PubMed: 23065472]

Chan (EX1008)

Cancer Genome Scanning in Plasma: Detection of Tumor-Associated Copy Number Aberrations, Single-Nucleotide Variants, and Tumoral Heterogeneity by Massively Parallel Sequencing

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Chan Renders Obvious Hybrid Capture Baits

Chan (EX1008)

pared with many targeted approaches (8). With the continuing and, thus far, rapid reduction in sequencing costs, cost is not expected to be as much of an obstacle in the near future. One can also envision the possibility of using shotgun sequencing of a plasma sample upon presentation of a cancer patient, mining the shotgun sequencing data of plasma DNA for copy number aberrations and SNVs, and then specifically targeting such sequences for serial monitoring purposes. In this regard, solution-phase hybridization-based capture approaches have already been successfully used to enrich plasma DNA for noninvasive prenatal diagnosis (34, 35). Hence, we see that the targeted and shotgun approaches can be used in combination for cancer detection and monitoring.

Liao (EX1009) (Chan's Reference 34)

Current target-enrichment strategies include molecular inversion probes (12), microdroplet-based PCR (13), on-array capture (14), and in-solution capture (15). Molecular inversion probes, which consist of a common linker flanked by target-specific sequences, anneal to the target sequences and become circularized by ligase (12). Digestion removes the noncircularized background DNA, and the PCR amplifies the circularized target DNA via universal primers to a common linker. The unstable performance of such probes in differentiating heterozygous alleles complicates its application for quantitative analysis (12). Microdroplet-based PCR (e.g., the RainDance platform) uses up to 1.5 million separate PCRs to amplify targeted sequences in parallel, but it requires a relatively high DNA input (7.5 μg per sample) (13). The rationale of on-array capture is to hybridize a DNA library to immobilized probes. Nontargeted DNA fragments are removed by washing, and targeted fragments are harvested by elution (14). A vast excess of DNA in the library (20 μg per sample) over that of the probes is typically required to ensure complete hybridization (14). Considering the low concentrations of plasma DNA (3), microdroplet-based PCR and on-array capture might not be ideal for plasma DNA-based applications. Therefore, in this study we adopted the recently described in-solution capture strategy for targeted sequencing of plasma DNA, especially in view of the relatively small amounts of DNA required for this approach (15).

'033 Patent (IPR2023-00317)

Summary of Disputed Elements – '033 Patent

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

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

The '033 Patent

- **Ground 1**
- Ground 2
- Ground 3

Claims Do Not Require Direct Sequencing Or Preclude Intermediate Amplification Steps



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.*

Institution Decision at 27-28



Dr. Quackenbush
Expert Witness

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. Furneaux does not seem to require the narrow

EX1025 at ¶102

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

The '033 Patent

- Ground 1
- **Ground 2**
- Ground 3

ForsheW's DNA Quantities Are Sufficient

Personalis relies on amounts of DNA present in fractionated samples

Table 2. Mutations identified by TAM-Seq in a set of 62 plasma samples from ovarian cancer patients. Forty mutations were identified by TAM-Seq using stringent parameters for mutation calling. Plasma sam

Sample number	Plasma volume per amplification reaction (μl)	DNA amount per amplification reaction (ng)
1	70	0.9
2	160	4.2
3	160	5.7
4	120	9.9
5	120	1.4
6	120	2.1

ForsheW collected multiple 1 mL aliquots of plasma

Sample collection

“Peripheral blood samples were collected in EDTA tubes and centrifuged at 829g for 10 min within 1 hour of collection to limit degradation of cell-free DNA and leukocyte lysis. Aliquots (1 ml) of plasma were centrifuged in a bench-top microfuge at 14,000 rpm for 10 min. The supernatant was transferred to sterile 1.5-ml tubes and stored at -80°C before extraction.”

The '033 Patent

- Ground 1
- **Ground 2**
- Ground 3

Motivation To Repeat Wagle's Assay On (I) Tumor Samples; And (II) Plasma Samples

219. However, to a POSA reviewing Wagle, it would have been obvious repeat steps (b)-(c) on subsequently obtained samples, such as applying Wagle's baits to subsequently obtained tumor samples or plasma samples that included cell-free tumor DNA. Chan discloses that approach—contacting subsequently obtained plasma samples with hybrid capture probes (baits) that target cancer-derived polymorphisms in cell-free tumor DNA circulating in those plasma samples. A

patients were analyzed with shotgun MPS.”). In other words, the ability to monitor tumor status over time using a noninvasive assay (requiring only a blood draw) would have motivated a POSA to combine Wagle's exemplary proof of concept and Chan's plasma sample time course approach involving multiple samples taken over time.