

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

Foresight Diagnostics Inc.,
Petitioner,

v.

Personalis, Inc.,
Patent Owner.

IPR2023-00545 (U.S. Patent No. 11,299,783)
IPR2023-00546 (U.S. Patent No. 10,450,611)

May 7, 2024



Overview of Grounds

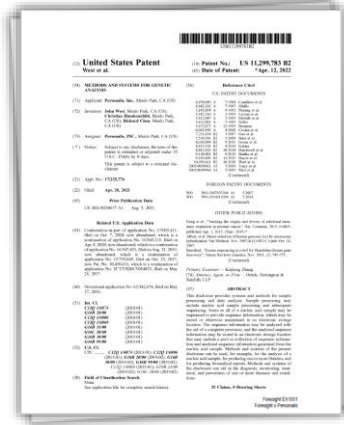
'611 Patent



IPR2023-00546

- Grounds 1/2 – Ley
- Grounds 3/4 – Newman

'783 Patent



IPR2023-00545

- Grounds 1/2 – Ley
- Ground 3 – Forshew + Dawson

Overview of the Challenged Claims – '611 Patent

'611 Patent

1. A method for personalized genetic testing, comprising:
 - (a) sequencing nucleic acid molecules from at least one biological sample of a subject to generate sequencing data, wherein said sequencing comprises sequencing 12 gigabases (GB) or more;
 - (b) computer processing said sequencing data to identify a plurality of nucleic acid sequences having a set of genetic variants, wherein said set of genetic variants are identified with respect to a reference;
 - (c) obtaining a probe set comprising a plurality of nucleic acid probe molecules having said plurality of nucleic acid sequences or complements thereof, wherein said plurality of nucleic acid probe molecules are configured to selectively enrich or amplify sequences comprising said set of genetic variants over other sequences in said at least one biological sample;
 - (d) using said probe set to selectively enrich or amplify sequences comprising said set of genetic variants over other sequences in an additional biological sample from said subject or at least one biological relative of said subject, to generate a sequencing library; and
 - (e) subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less to identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample from said subject or said at least one biological relative, wherein a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a).

- (a) WES or WGS of tumor
- (b) identify variants
- (c) obtain probe set targeting variants
- (d) use probe set to selectively enrich/amplify variants in additional sample
- (e) sequence enriched/amplified library
 - Library footprint <175 kb
 - Deeper sequencing than WES/WGS of (a)

Overview of the Challenged Claims – '783 Patent

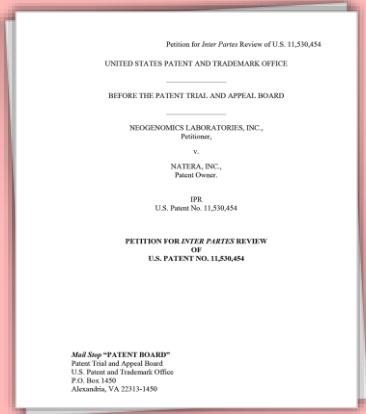
'783 Patent

1. A method for personalized genetic testing, comprising:

- (a) obtaining a personalized probe set for a subject, which personalized probe set comprises a plurality of nucleic acid probe molecules having a plurality of nucleic acid sequences or complements thereof, wherein said plurality of nucleic acid probe molecules are configured to selectively enrich or amplify sequences comprising a set of one or more genetic variants over other sequences in at least one biological sample of said subject, wherein said set of genetic variants are identified in sequence data for said at least one biological sample, further wherein said personalized probe set comprises nucleic acid probe molecules having oligo-nucleotide-directed genomic content comprising: (i) at least one variable portion from a result of said sequence data and (ii) at least one fixed portion independent of said result of said sequencing data
- (b) using said personalized probe set to selectively enrich or amplify sequences comprising said set of genetic variants over other sequences in at least an additional biological sample from said subject, to generate a sequencing library;
- (c) subjecting said sequencing library to sequencing to identify a presence or absence of at least a subset of said set of genetic variants in at least said additional biological sample from said subject, wherein a sequencing footprint of said sequencing of (c) is less than a sequencing footprint of said sequence data of (a); and
- (d) generating a report identifying (i) a presence or absence of a health condition or disease of the subject in said additional biological sample based on said identified at least a subset of (c) and (ii) genetic variants which inform a therapy choice or a change in therapy for the subject.

- (a) obtain probe set with (i) variable portion from result of a sequencing step and (ii) fixed portion independent of sequencing
- (b) use probe set to selectively enrich/amplify additional sample
- (c) sequence enriched/amplified library
- (d) generate report

PO Counsel: Challenged Claims Are “Not Remotely Inventive” By 2015



PO's Counsel



The '454 patent claims a routine and undeniably obvious method for monitoring cancer using cell-free DNA (“cfDNA”). The independent claims recite sequencing tumor DNA to identify tumor-specific mutations, followed by collecting a cfDNA sample from the blood stream of the cancer patient and then amplifying and sequencing the cfDNA to check if the tumor-specific mutations are present. Such a process for tracking cancer based on identifying the genetic fingerprint of a tumor and then simply looking for this signature in blood via standard techniques is, on its face, not remotely inventive.

Unpatentability Based on Ley – '611 Patent

Ley Overview

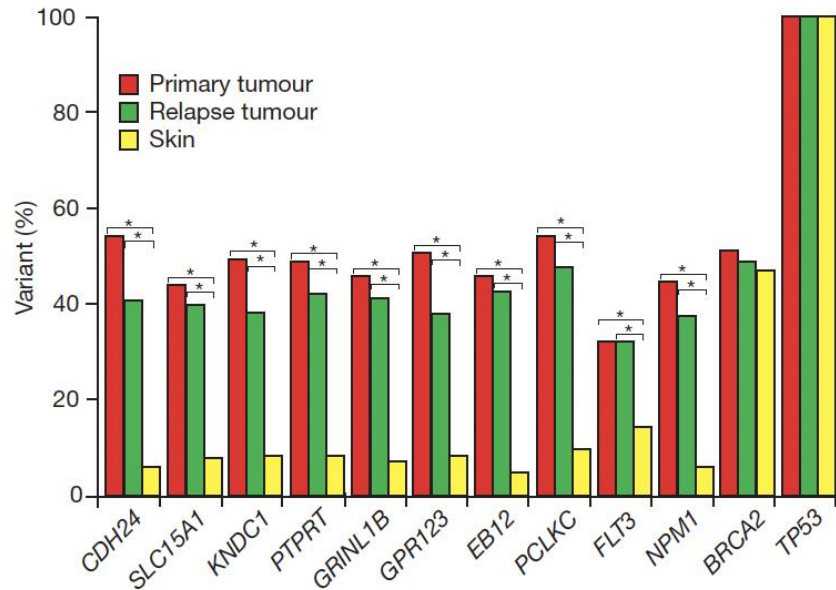


Figure 3 | Summary of Roche/454 FLX readcount data obtained for ten somatic mutations and two validated SNPs in the primary tumour, relapse tumour and skin specimens. The readcount data for the variant alleles in the primary tumour sample and relapse tumour sample are statistically different from that of the skin sample for all mutations ($P < 0.000001$ for all mutations, Fisher's exact test, denoted by a single asterisk in all cases). Note that the normal skin sample was contaminated with leukaemic cells containing the somatic mutations. The patient's white blood cell count was 105,000 (85% blasts) when the skin punch biopsy was obtained.

- WGS of tumor/normal tissue identifies variants
- Probe set created based on (i) variants identified in WGS; and (ii) known cancer gene
- Probe sets applied to enrich/amplify later-obtained relapse tumor sample
- Presence or absence of amplified variants identified by deep sequencing
- Report of results generated

Overview of the Challenged Claims – '611 Patent

'611 Patent

1. A method for personalized genetic testing, comprising:
 - (a) sequencing nucleic acid molecules from at least one biological sample of a subject to generate sequencing data, wherein said sequencing comprises sequencing 12 gigabases (GB) or more;
 - (b) computer processing said sequencing data to identify a plurality of nucleic acid sequences having a set of genetic variants, wherein said set of genetic variants are identified with respect to a reference;
 - (c) obtaining a probe set comprising a plurality of nucleic acid probe molecules having said plurality of nucleic acid sequences or complements thereof, wherein said plurality of nucleic acid probe molecules are configured to selectively enrich or amplify sequences comprising said set of genetic variants over other sequences in said at least one biological sample;
 - (d) using said probe set to selectively enrich or amplify sequences comprising said set of genetic variants over other sequences in an additional biological sample from said subject or at least one biological relative of said subject, to generate a sequencing library; and
 - (e) subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less to identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample from said subject or said at least one biological relative, wherein a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a).

- Not disputed
 - Step (a) WES or WGS of tumor
 - Step (b) identify variants
 - Step (c) obtain probe set
 - Step (d) enrich/amplify additional sample using probe set
- Disputes relate to step (e) and dependent claims

'611 Patent – Unpatentability Based on Ley

- **Claim 1**
 - Numerical Limitations
 - Sequencing “to identify a presence or absence of genetic variants”
- Claim 5
 - “Fixed” and “Variable” Portions
- Claims 10 and 28
 - Treatment

Ley Discloses The Disputed Aspects of Element 1(e)

(e) [i] subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less [ii] to identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample from said subject or said at least one biological relative, [iii] wherein a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a).

- Ley re-sequenced single exons of 12 genes, and all exons sum to less than 175 kb
- Ley's re-sequencing "identifies...said genetic variants" (already identified in step (a)) in a subsequent sample
- Ley's resequencing in (e) is orders of magnitude deeper than its WGS in step (a)

'611 Patent – Unpatentability Based on Ley

- Claim 1
 - **Numerical Limitations**
 - Sequencing “to identify a presence or absence of genetic variants”
- Claim 5
 - “Fixed” and “Variable” Portions
- Claims 10 and 28
 - Treatment

Ley's Re-Sequencing Targeted A Single Exon For Each Variant

(e) [i] subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less [ii] to identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample from said subject or said at least one biological relative,[iii] wherein a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a).



Dr. Furneaux
Expert Witness



Q. And Ley used these primers to create **amplicons of the exons** with the mutant alleles, correct?

A. That's what we're given to understand.

Table 3 | 454 Readcount data for somatic mutations and known SNPs

Gene	Consequence	Primary AML (100% blasts)			Skin			Relapse (78% blasts)		
		Variant	Ref	Variant (%)	Variant	Ref	Variant (%)	Variant	Ref	Variant (%)
CDH24	Y590X	5672	4890	53.70	564	10358	5.16	3108	4599	40.33
SLC15A1	W77X	3817	4962	43.48	875	10773	7.51	4714	7173	39.66
KNDC1	L799F	4640	4848	48.90	770	8972	7.90	3883	6342	37.98
PTPRT	P1235L	998	1058	48.54	126	1489	7.80	350	493	41.52
GRINL1B	R176H	2211	2674	45.26	318	4461	6.65	1447	2070	41.14
GPR123	T38I	4618	4569	50.27	850	9751	8.02	3660	6057	37.67
EBI2	A338V	12750	15453	45.21	458	10088	4.34	2646	3627	42.18
PCLKC	P1004L	992	855	53.71	341	3153	9.76	705	773	47.70
FLT3	ITD	4220	7810	35.08	3475	23159	13.05	3870	8495	31.30
NPM1	CATG ins	1550	1974	43.98	143	2390	5.65	2303	3910	37.07
BRCA2	N372H	778	752	50.85	763	876	46.55	285	303	48.47
TP53	P72R	8989	1	99.99	8161	0	100.00	7914	6	99.92

Ley's Re-Sequencing Targeted A Single Exon For Each Variant

(e) [i] subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less [ii] to identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample from said subject or said at least one biological relative,[iii] wherein a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a).



Dr. Quackenbush
Expert Witness



120. In Table 3, the ten genes were the panel of genes from which an exon containing a genetic variant was amplified from the original samples and from additional relapse sample from the same individual, and that these resulting amplicons were subsequently sequenced. One skilled in the art knew that the assay was designed to target only the exons of these genes containing the target genetic variants and that the use of such panels of probes was intended to amplify a small portion of the genome for subsequent sequencing rather than the genome in its entirety so that the sequencing coverage would be 175 kb or less.

Ley's Re-Sequencing Targeted A Single Exon For Each Variant

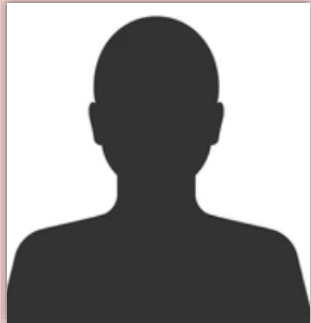


Dr. Quackenbush
Expert Witness



"[O]ne can easily set an **upper bound** on the sequence coverage Ley teaches **by using the entire length of the genes** that contained the genetic variant **rather than the much smaller sequence of the variant-containing exon**.

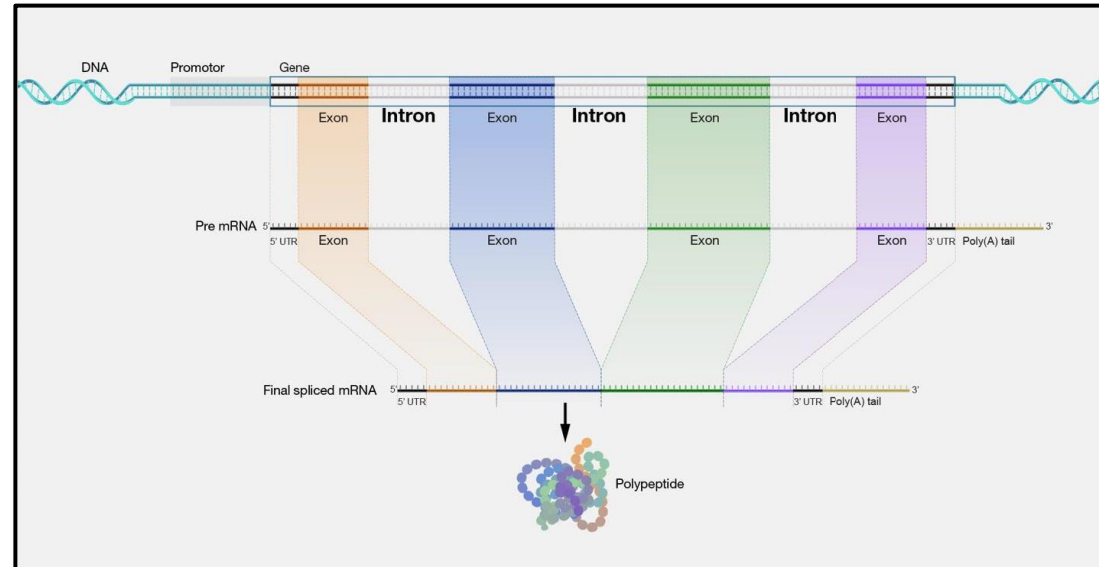
EX1061 at ¶121



Dr. Furneaux
Expert Witness



Declaration confirms
each gene contains
multiple exons:



EX2169 at ¶183

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Ley's Re-Sequencing Targeted A Single Exon For Each Variant



Dr. Quackenbush
Expert Witness



Harvard
University

“[E]ven if **all of the exons of every one of these genes** were to be sequenced, the sequence **would only cover 45.254 kb**, far less than the 175 kb....”

Gene	NCBI Accession	URL	Length (bp)
CDH24	NM_022478	https://www.ncbi.nlm.nih.gov/nuccore/NM_022478.4	3,529
SLC15A1	NM_005073	https://www.ncbi.nlm.nih.gov/nuccore/NM_005073.4	3,124
KNDC1	NM_001347864	https://www.ncbi.nlm.nih.gov/nuccore/NM_001347864.2	2,917
PTPRT	XM_047439848	https://www.ncbi.nlm.nih.gov/nuccore/XM_047439848.1	5,007
GRINL1B	AF326970.1	https://www.ncbi.nlm.nih.gov/nuccore/AF326970.1	327
GPR123	NM_001083909.3	https://www.ncbi.nlm.nih.gov/nuccore/NM_001083909.3	4,264
EBI2	NM_004951.5	https://www.ncbi.nlm.nih.gov/nuccore/NM_004951.5	1,685
PCLKC	NM_001171976.2	https://www.ncbi.nlm.nih.gov/nuccore/NM_001171976.2	4,500

Total coding sequence length of the ten genes in the Ley 2008 panel:

45,254

TP53	NM_000546.6	https://www.ncbi.nlm.nih.gov/nuccore/NM_000546.6	2,512
Total coding sequence length of the ten genes in the Ley 2008 panel:			45,254

Obvious To Sequence <175 kb In Targeted Re-Sequencing



Dr. Quackenbush
Expert Witness

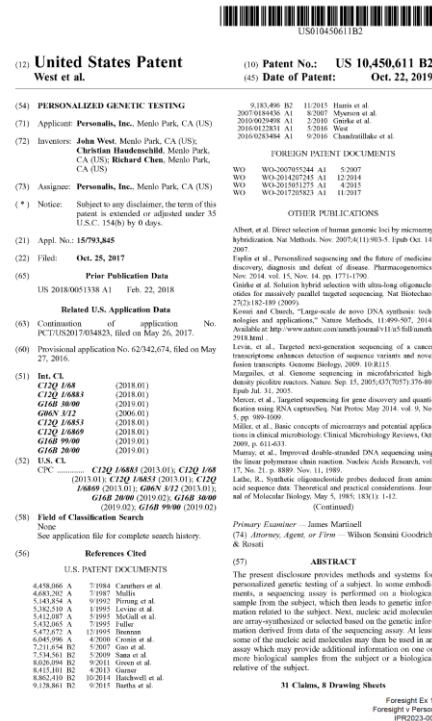


**Harvard
University**

168. A person of ordinary skill would have reasonably expected to be successful in reducing coverage to 175 kb or less by choosing an informative subset of genes to assay. Providing capture panels of smaller coverage was easier, in fact, than greater coverage, because smaller coverage was achieved by having fewer oligonucleotide probes—a simplifying factor in capture panel design and production. A smaller panel also simplified computational analysis because the resulting data would be limited to the few genes that were represented in a personalized panel (of the approximately 25,000 genes encoding in the genome).

Patent Fails To Disclose Or Establish Significance Of “175 kb or less”

’611 Patent



“The variants may be narrowed to at most about 500 variants. The variants may be narrowed to at most about 600 variants, 700 variants, 800 variants, 1000 variants, 1500 variants.... 500 variants may require the synthesis of at least about 500 sequences. The genomic region captured by each probe can be at least about 350 bases. Therefore, for at least about 500 sequences, the footprint of this assay may be about 175,000 bases.”

Ley's Re-Sequencing Is Deeper Than Its WGS (i.e., 588>>>33)

(e) [i] subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less [ii] to identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample from said subject or said at least one biological relative, [iii] wherein a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a).

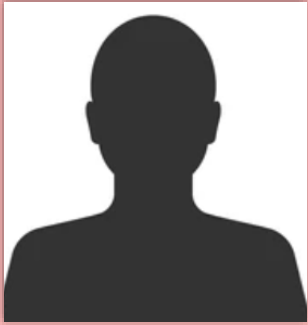
- No dispute that “said sequencing of (a)” – Ley’s WGS – had a depth of 13-33x.
- Depth of Ley’s “sequencing of (e)” for relapse tumor sample ranged from 588-12,635x across all genes.

Gene	Primary AML			Skin			Relapse		
	Variant	Ref	Total Depth	Variant	Ref	Total Depth	Variant	Ref	Total Depth
CDH24	5672	4980	10652	564	10358	10922	3108	4599	7707
SLC15A1	3817	4962	8779	875	10773	11648	4714	7173	11887
KNDC1	4640	4848	9488	770	8972	9742	3883	6342	10225
PTPRT	998	1058	2056	126	1489	1615	350	493	843
GRINL1B	2211	2674	4885	318	4461	4779	1447	2070	3517
GPR123	4618	4569	9187	850	9715	10565	3660	6057	9717
xxEBI2	12750	15443	28193	458	10088	10546	2646	3627	6273
PCLKC	992	855	1847	341	3153	3494	705	773	1478
FLT3	4220	7810	12030	3475	23159	26634	3870	8495	12365
NPM1	1550	1974	3524	143	2390	2533	2303	3910	6213
BRCA2	778	752	1530	763	876	1639	285	303	588
TP53	8989	1	8990	8161	0	8161	7914	6	7920

12365

588

Dr. Furneaux Relies On Misleading and Incorrect Application of Theoretical Depth Equation



Dr. Furneaux
Expert Witness



176. Ley’s Table 3 only provides N, the number of reads (i.e., Ley’s “readcount”). Knowing the number of reads (N) alone does not allow a person of ordinary skill in the art to calculate the sequencing depth (C). To calculate sequencing depth (C), the person of ordinary skill in the art must also know the relevant read length (L) and the relevant length of genes being studied (G). Dr. Quackenbush’s declaration does not provide the relevant read length (L) or length of genes being studied (G) that a person of ordinary skill in the art would have used to calculate Ley’s sequencing depth (C).

“[W]hat we're currently discussing and assuming and hoping is coverage, which is an empirical thing. It's not a theoretical thing.”

EX2169 at ¶176; EX1083 at 91:21-23



Dr. Quackenbush
Expert Witness



66. “Coverage,” “sequencing depth,” or “depth of sequencing” are terms that refer to the number of times genomic sequence has been sequenced. The

EX1061 at ¶166

Dr. Furneaux Admits Table 3 Reports The Sequencing Depth “That Actually Happened”



Dr. Furneaux
Expert Witness



Q. And so the raw read count numbers in the variant and reference numbers mean that they read **the variant 5,672 times** and **the reference 4,890 times**; is that a correct reading of the table?

A. Yeah, I think that’s a fair point, yeah.

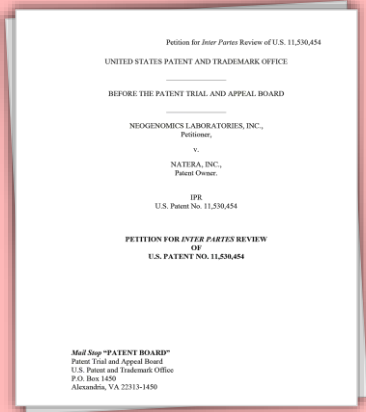
Q. And **so the sequencer read that position about 10,000 times?**

A. **Yep.**

Table 3 454 Readcount data for somatic mutations and known SNPs										
Primary AML (100% blasts)					Skin			Relapse (78% blasts)		
Gene	Consequence	Variant	Ref	Variant (%)	Variant	Ref	Variant (%)	Variant	Ref	Variant (%)
CDH24	Y590X	5672	4890	53.70	564	10358	5.16	3108	4599	40.33
SLC15A1	W77X	3817	4962	43.48	875	10773	7.51	4714	7173	39.66
KNDC1	L799F	4								
PTPRT	P1235L	9								
GRINL1B	R176H	2								
GPR123	T38I	4								
EBI2	A338V	1								
PCLKC	P1004L	9								
FLT3	ITD	4								
NPM1	CATG ins	1550	1974	43.98	143	2390	5.65	2303	3910	37.07
BRCA2	N372H	778	752	50.85	763	876	46.55	285	303	48.47
TP53	P72R	8989	1	99.99	8161	0	100.00	7914	6	99.92

The differences between variant frequencies in primary or relapse tumour samples and skin were highly significant for all somatic mutations ($P < 0.000001$, Fisher’s exact test, one tailed). The BRCA2 variant is a known heterozygous SNP in this genome, and the TP53 variant is a known homozygous SNP.

PO's Counsel Confirms Obviousness Of Increasing Depth



PO's Counsel



Looking to the '454 patent itself confirms obviousness. The patent does not disclose 50,000 as a special—let alone inventive—read depth. Instead, it buries 50,000 among an undifferentiated list of 14 different possible sequencing depths that span four orders of magnitude, from 100 to 500,000. EX1002 ¶ 175; EX1001 at 68:33-39. Depth of read is nothing more than a known result-effective variable to provide improved sensitivity, and it would have been routine to optimize this variable to provide the required sensitivity of detection. *In re Aller*, 220 F.2d 454, 456 (CCPA 1955) (“where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation”). Far from being inventive, the claimed sequencing depth of 50,000 is *prima facie* obvious.

'611 Patent – Unpatentability Based on Ley

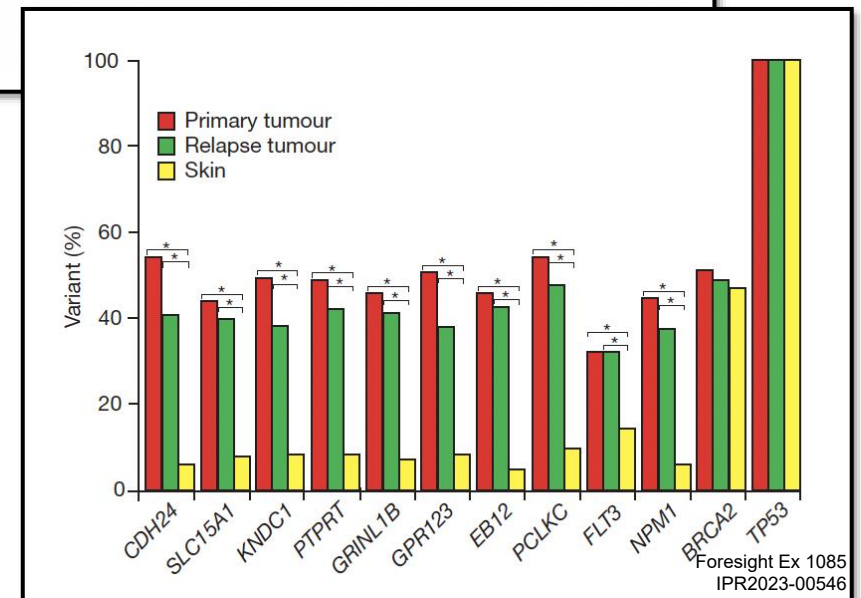
- Claim 1
 - Numerical Limitations
 - **Sequencing “to identify a presence or absence of genetic variants”**
- Claim 5
 - “Fixed” and “Variable” Portions
- Claims 10 and 28
 - Treatment

Ley's Resequencing Identifies the Presence of Said Set of Genetic Variants

(e) [i] subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less [ii] **to identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample from said subject or said at least one biological relative**, [iii] wherein a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a).

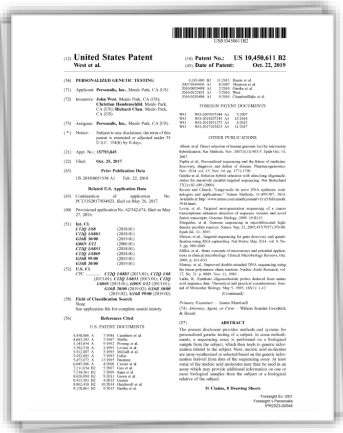
Institution Decision

sample for some validating or confirmatory purpose. In showing that variant alleles were present in both primary and relapse tumor samples, Ley's Figure 3 satisfies claim step 1(e) by "identify[ing] a presence or absence of at least a subset of said set of genetic variants in said additional biological sample." In particular, we understand Figure 3 to show that for each variant allele tested, the allele was present in roughly 30 to 50 percent of cells from either tumor sample.⁶



Claim Language Confirms That Identity of Said Variants Already Known

'611 Patent



A method for personalized genetic testing, comprising:

(a) sequencing nucleic acid molecules...;

(b) computer processing said sequencing data **to identify** a plurality of nucleic acid sequences having **a set of genetic variants, wherein said set of genetic variants** are identified with respect to a reference;

(c) obtaining a probe set ... configured to selectively enrich or amplify sequences comprising **said set of genetic variants** over other sequences in said at least one biological sample;

(d) using said probe set to selectively enrich or amplify sequences comprising **said set of genetic variants**...to generate a sequencing library; and

(e) subjecting said sequencing library to **sequencing** at a coverage of 175 kilobases (kb) or less **to identify a presence or absence of at least a subset of said set of genetic variants** in said additional biological sample from said subject or said at least one biological relative, wherein a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a).

Personalis's Proposed Construction Renders The Claim Nonsensical

Personalis's Construction

The plain meaning of “to identify” is “***to establish the identify of.***”

Personalis's Redrafted Claim 1

“sequencing...~~to identify~~ to establish the identity of a presence or absence of at least a subset of said set of genetic variants....”

“To Identify” Does Not Need Express Construction

(e) [i] **subjecting said sequencing library to sequencing** at a coverage of 175 kilobases (kb) or less [ii] ***to identify a presence or absence*** of at least a subset ***of said set of genetic variants*** in said additional biological sample from said subject or said at least one biological relative, [iii] wherein a sequencing depth of said sequencing of (e) is greater than a sequencing depth of said sequencing of (a).

Plain English

Does the sequencing data of (e) show whether a genetic variant that was identified in the WGS of step 1(b) is present?

Personalis

Does the sequencing data of (e) “determine the identity” of an unknown variant that is absent from the sample?

Nonsensical Claim Constructions Should Be Rejected

“If an argument offered in support of a particular claim construction is so convoluted and artificial that it would not be apparent to a skilled artisan reading the patent...the argument is simply unhelpful to the performance of our task.”

Dayco Prod., Inc. v. Total Containment, Inc., 258 F.3d 1317, 1324 (Fed. Cir. 2001)



Tallying Readcounts Necessarily Involves Determining The Identity (Ref or Variant)

Personalis POR

“The **mutation frequencies** are merely **quantified** during the validation protocol by **tallying readcounts.**”

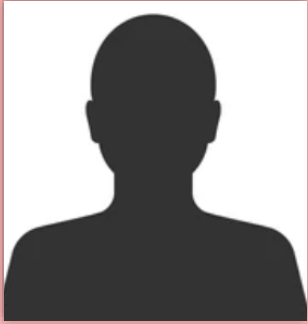
Ley (EX1012)

Table 3 | 454 Readcount data for somatic mutations and known SNPs

Gene	Consequence	Variant	Relapse (78% blasts)	
			Ref	Variant (%)
CDH24	Y590X	3108	4599	40.33
SLC15A1	W77X	4714	7173	39.66
KNDC1	L799F	3883	6342	37.98
PTPRT	P1235L	350	493	41.52
GRINL1B	R176H	1447	2070	41.14
GPR123	T38I	3660	6057	37.67
EBI2	A338V	2646	3627	42.18
PCLKC	P1004L	705	773	47.70
FLT3	ITD	3870	8495	31.30
NPM1	CATG ins	2303	3910	37.07
BRCA2	N372H	285	303	48.47
TP53	P72R	7914	6	99.92

EX1012, Table 3 (excerpted)

Dr. Furneaux Merely Parrots Counsel's Irrelevant, Cherry-Picked Dictionary Definition



Dr. Furneaux
Expert Witness



Q. So the dictionary entry itself was provided by counsel, correct?

A. **Correct, absolutely.**

Q. And did you consider any other dictionaries or dictionary entries when --

A. No.... And **I'm trusting the legal team to use this as a source.**

i•den•ti•fy (ī-děn'tə-fī') *v.* **-fied, -fy•ing, -fies** —*tr.* **1. To establish the identity of.** 2. To ascertain the origin, nature, or definitive characteristics of. 3. *Biology* To determine the taxonomic classification of (an organism). 4. To consider as identical or united; equate. 5. To associate or affiliate (oneself) closely with a person or group. —*intr.* To establish an identification with another or others. [Medieval Latin *identificāre*, to make to resemble : Late Latin *identitās*, identity; see IDENTITY + Latin *-ficāre, -fy.*] —**i•den'ti•fi'a•ble** *adj.* —**i•den'ti•fi'a•bly** *adv.* —**i•den'ti•fi'er** *n.*

'611 Patent – Unpatentability Based on Ley

- Claim 1
 - Numerical Limitations
 - Sequencing “to identify a presence or absence of genetic variants”
- **Claim 5**
 - **“Fixed” and “Variable” Portions**
- Claims 10 and 28
 - Treatment

Claim 5: “Variable” and “Fixed” Portion Are Defined By The Claim Language

“wherein each of said plurality of nucleic acid probe molecules includes oligonucleotide-directed genomic content comprising (i) at least one **variable portion** from a result of said sequencing of (a) and (ii) at least **one fixed portion** independent of said result of said sequencing of (a).”

- **Variable:** Ten “discovered” variants identified “from a result of said [WGS] data”
- **Fixed:** Two “known variants” (BRCA2, TP53)

Defining mutation frequencies in the tumour sample

Ley (EX1012)

To better define the percentage of tumour cells that contained each of the **discovered somatic mutations**, we amplified each mutation-containing locus from non-amplified genomic DNA derived from the *de novo* and relapse tumour samples, and from the skin biopsy obtained at presentation. The resulting amplicons were sequenced using the Roche/454 FLX platform, and the frequency of reads containing the reference and variant alleles were defined (Fig. 3 and Table 3). **Control amplicons containing a known heterozygous SNP in BRCA2 (encoding N372H) and a homozygous SNP in TP53 (encoding P72R) were analysed similarly.** The BRCA2 SNP

Personalis Does Not Even Try To Apply Its Proposed Construction To Its Assay

'783 Patent Claim Language	Personalis' NeXT Personal® assay
(a) obtaining a personalized probe set for a subject, which ... comprising: (i) at least one variable portion from a result of said sequence data and (ii) at least one fixed portion independent of said result of said sequencing data;	The NeXT Personal Test involves using personalized probes as well as known cancer-related clinical variants. Here we report a performance update of the NeXT Personal® platform. NeXT Personal utilizes hybridization-capture-based technology to quantify ctDNA in liquid biopsy samples. Its unified probe panel design and workflow simultaneously detects and monitors MRD, surveys known cancer-related clinical variants, and quantifies and tracks investigational variants of interest, by leveraging both tumor-informed and tumor-agnostic genomic information (Fig. 1). The tumor-informed MRD content is dedicated to personalized MRD detection and longitudinal monitoring, which utilizes cumulative tumor-derived signals to achieve ultra-high sensitivity down to 1 ~ 3 parts per million (PPM) limit of detection (LOD). The tumor-agnostic clinically relevant content surveys known and validated actionable genomic variants in 90 clinically relevant genes, and serves to inform therapy selection and detect existing or potentially emerging events such as new subclones or metastases. The investigational content provides capacity to track important cancer-related variants for research or investigational purposes. EX2003 at page 38. • For its own assay, Personalis asserts: – “personalized probes” satisfy the “variable portion” – probes for “known cancer-related variants” satisfy the “fixed portion”

Probes for Cancer Driver Genes Are Examples Of “Fixed” Content

Specification

In some embodiments, at least one variable portion corresponds to potential neoantigen causing genetic variants of the subject, and wherein the at least one fixed portion corresponds to one or more of (1) cancer driver genes, (2) genes involved in the pharmacogenomics of cancer drugs, (3) genes involved in Mendelian immunological diseases, (4) genes related to inherited forms of cancer, (5) genes associated with tumor escape from a targeted or immune cancer therapy, (6) HLA typing, and (7) genetic variants common in the population and used by B-allele methods to detect structural variation.

Personalis Product Literature

Similarly, variants not detected in the tumor may also be added during the panel design process. As custom content, users may define their own set of variants that may be representative of known clinical hotspots (ex. EGFR T790M), resistance hotspots, driver mutations (which may allow detection of a second primary tumor), or other therapy-specific and biologically important variants studied or monitored in clinical research. Capacity for user-supplied content can include up to thousands of variants. Alternatively, users may also leverage clinically relevant content developed and curated by Personalis in addition to, or instead of, user-supplied content (Figure 2.3).

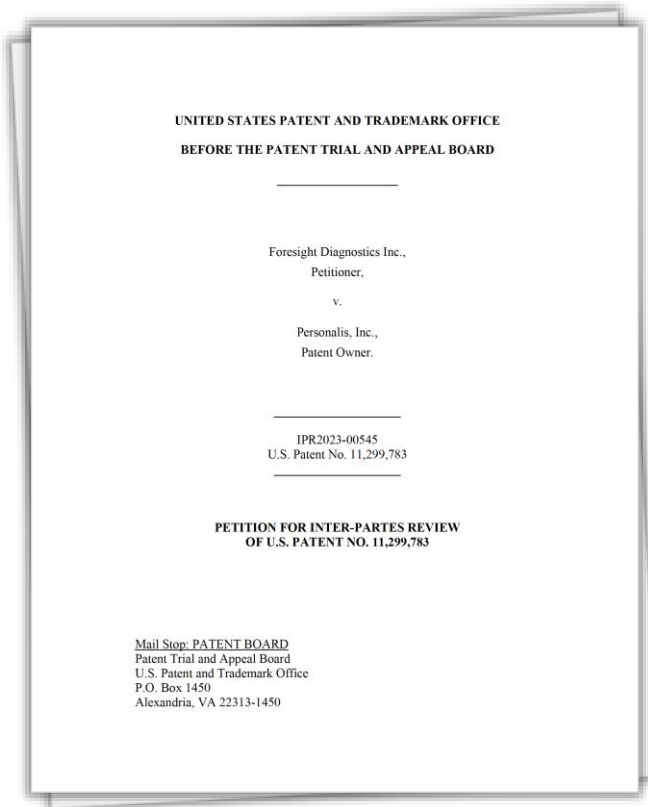
NeXT Personal™

The Next Generation in Molecular Residual Disease
Testing and Variant Monitoring for Solid Tumors



Personalis Ex. 2004.013
Foresight v. Personalis
IPR2023-00546

Personalis Does Not Dispute '783 Claim 17



9. Claim 17

Claim 17 recites, “The method of claim 1, wherein said at least one fixed portion comprises one or more known tumor variants.”

The fixed portion of *Ley* comprises probes for *BRCA2* and *TP53*. These two mutations were known tumor variants in the AML genome. *Ley* states that “[t]he *BRCA2* variant is a known heterozygous SNP in this [AML] genome, and the *TP53* variant is a known homozygous SNP” in the AML genome. Ex. 1012 at 70; Quackenbush ¶154. As Dr. Quackenbush notes, the literature also confirmed that *BRCA2* and *TP53* were known AML tumor variants. Exs. 1073-1074. Quackenbush ¶¶153-155.

Personalis Does Not Dispute '783 Claim 18

10. Claim 18

Claim 18 recites, “The method of claim 1, wherein said at least one fixed portion is selected from a group consisting of one or more of: ... (iv) genes related to inherited forms of cancer”

As discussed above, including with respect to claim 17, the *BRCA2* and *TP53* genes included in *Ley*’s fixed panel are genes related to inherited forms of cancer, including AML. Quackenbush ¶¶156-158.

10. Claim 18

Claim 18 recites, “The method of claim 1, wherein said at least one fixed portion is selected from a group consisting of one or more of: i) cancer driver genes, (ii) genes involved in the pharmacogenomics of cancer drugs, ...”

As explained above for step 1(a)’s “fixed portion” requirement, a POSA reading *Ley* would have also found it obvious to include probes targeted to genetic variants involved in the pharmacogenomics of cancer drugs, i.e., genetic variants that were known to have companion diagnostics, as well as to tumor-driver mutations that were known in the art. Quackenbush ¶¶220-222.

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

Foresight Diagnostics Inc.,
Petitioner,

v.

Personalis, Inc.,
Patent Owner.

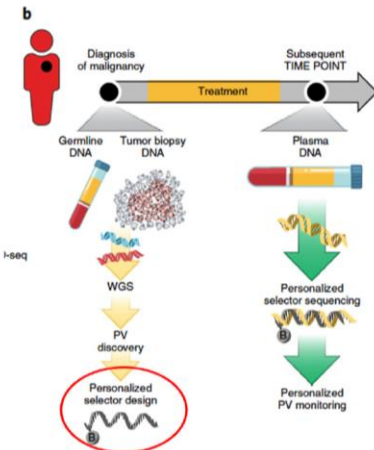
IPR2023-00545
U.S. Patent No. 11,299,783

PETITION FOR INTER-PARTES REVIEW
OF U.S. PATENT NO. 11,299,783

Mail Stop: PATENT BOARD
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Ley Contains Fixed and Variable Probes Under Personalis's Infringement Theory

(c) obtaining a probe set comprising a plurality of nucleic acid probe molecules having said plurality of nucleic acid	The Foresight Diagnostics Solid Tumor Recurrence test utilizes a probe set to selectively enrich or amplify sequences comprising genetic variants over other sequences in a biological sample. For example, The Foresight Diagnostics Solid
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'611 Patent Claim Language	Infringement Support						
sequences or complements thereof, wherein said plurality of nucleic acid probe molecules are configured to selectively enrich or amplify sequences comprising said set of genetic variants over other sequences in said at least one biological sample;	Tumor Recurrence test designs personalized probes directed to the particular phased variants detected in the tumor sample.  Source: Kurtz, Fig. 7b <table border="1"> <tr> <td>PhasED-Seq (Foresight Diagnostics)</td> <td>Hybrid capture-based NGS</td> <td>PVs, SNVs</td> <td>Baseline: tumor or plasma MRD monitoring: plasma</td> <td>Tumor-informed</td> <td>< 0.0001% TF</td> </tr> </table> Source: BloodPac annual meeting slides (attached hereto as Exhibit L); Chen, et al., Commercial ctDNA Assays for Minimal Residual Disease Detection of Solid Tumors, MolDiag&Ther (2021) at Table 1 (hereinafter "Chen," attached hereto as Exhibit M).	PhasED-Seq (Foresight Diagnostics)	Hybrid capture-based NGS	PVs, SNVs	Baseline: tumor or plasma MRD monitoring: plasma	Tumor-informed	< 0.0001% TF
PhasED-Seq (Foresight Diagnostics)	Hybrid capture-based NGS	PVs, SNVs	Baseline: tumor or plasma MRD monitoring: plasma	Tumor-informed	< 0.0001% TF		

5. The method of claim 1, wherein each of said plurality of nucleic acid probe molecules includes oligonucleotide-directed genomic content comprising (i) at least one **variable** portion from a result of said sequencing of (a) and (ii) at least one **fixed** portion independent of said result of said sequencing of (a).

The Foresight Diagnostics Solid Tumor Recurrence test includes both **variable** portions based upon the prior whole genome sequencing as well as **fixed** content that is related to genes with known oncogenic or clinically relevant variants.

Exemplary Embodiments Do Not Redefine Plain Claim Language

“wherein each of said plurality of nucleic acid probe molecules includes oligonucleotide-directed genomic content comprising (i) at least one **variable portion** from a result of said sequencing of (a) and (ii) at least one **fixed portion** independent of said result of said sequencing of (a).”

The specification provides an express definition of “variable portion” and “fixed portion” as follows:

In some applications, it may be desirable for the oligo-directed genomic content of the personalized assay to contain both *a variable portion (defined based on the genetic characteristics originally determined for the individual subject) and at least one fixed portion (which does not change from one subject to another).*

EX1001 38:42-47. The variable portion changes from subject to subject because it is “defined based on the genetic characteristics originally determined for the individual subject,” whereas the fixed portion “does not change from one subject to another.” *Id.*; see also *id.* 63:33-36 (“Thus, as discussed above, the genomic content

'611 Patent – Unpatentability Based on Ley

- Claim 1
 - Numerical Limitations
 - Sequencing “to identify a presence or absence of genetic variants”
- Claim 5
 - “Fixed” and “Variable” Portions
- **Claims 10 and 28**
 - **Treatment**

Ley's Variant Reports Inform Treatment



Dr. Quackenbush
Expert Witness



**Harvard
University**

140. In addition to the reasons given above for claim 2, Ley discloses claim 10. Ley's report discloses genetic variants which inform a therapeutic intervention. Specifically, "[a]lthough the patient experienced a complete remission with conventional therapies, she relapsed at 11 months and expired 24 months after her initial diagnosis was made. At relapse the bone marrow had 78% myeloblasts, and contained a new clonal cytogenetic abnormality, t(10;12)(p12;p13)." Ex. 1012 (Ley) at 67. Thus, Ley's report, which shows elevated levels of certain variants, informs a therapy choice or a change (e.g., switching away from conventional therapy, or resuming therapy upon relapse) for the subject. For example, in the Supplementary

Anticipation Does Not Require Actual Performance of a Method

Anticipation merely requires that Ley “discloses all of the claim limitations and enables the subject matter that falls within the scope of the claims at issue.”

In re Gleave, 560 F.3d 1331, 1334 (Fed. Cir. 2009)

“[A]nticipation does not require actual performance of suggestions in a disclosure,” so long as “those suggestions [are] enabling to one skilled in the art.”

Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.,
246 F.3d 1368, 1379 (Fed. Cir. 2001)



Ley's Disclosures Are Enabling



Dr. Furneaux
Expert Witness



Q. Correct. But **the patient was alive and receiving treatment for cancer when they took these samples**, correct?

A. **I totally agree.**

Ley's Approach Widely Adopted From 2008-2016

Dr. Quackenbush

86. Soon after, Leary (Ex. 1002) and McBride (Ex. 1015) demonstrated the use of the same concept, by using whole-genome sequencing to identify structural variants (as opposed to SNVs as in Ley), and to subsequently use those identified markers as targets for serial monitoring of tumor DNA in the blood plasma of patients with solid tumors. *See also* Ex. 1031 (Meyerson) at 687 (Table 1) (listing Ley and subsequent whole cancer genome studies).

94. Such reports were described in a number of prior art references, which depicted information about the relative abundance or a frequency of polymorphic alleles present in a patient's sample at multiple points in time over the course of treatment. For example, Ley's Figure 3 depicts sequence information regarding the relative abundance of particular somatic and germline mutations that were observed in samples taken at (i) primary onset, and (ii) relapse. Ex. 1012 (Ley) at 69 (Fig. 3) (reproduced below). These abundances are compared to the frequency of the same polymorphic alleles present in skin, which represents a control.

PO's Counsel

chemotherapeutic resistance [22,23].”). As detailed herein, MRD monitoring was routinely conducted as of 2013.

88. MRD monitoring generally follows two subsets of steps: 1) WGS or WES of the cancer/tumor and, optionally, the patient's healthy cells to obtain sequence data and 2) follow-up cfDNA sequencing. EX1003.002-.003; EX1004.001-.002. Essentially, this process finds differences between the healthy DNA and the cancerous DNA and compares the cfDNA with the cancerous DNA to look for remission or “tumor burden,” which can show treatment effectiveness and the size or advancement of the tumor. EX1003.002-.003, .010. Through this process, different treatments can be used until an effective combination is found, without the need to look for a recurrent tumor, which can involve very invasive surgeries. *Id.*

Unpatentability Based on Newman

Newman Discloses WES Of >12 GB



Dr. Quackenbush
Expert Witness



**Harvard
University**

189. Newman discloses that “[s]equencing was performed using 2 x 100 or 2 x 150 paired-end reads” Ex. 1043 at “Library preparation and sequencing” in

...

Based on the 150 bp read length, the sequencing comprises sequencing 12.3 GB (150 * 82,247,848) and 13.0 GB (150 * 86,781,192) respectively. Even based on the shorter 100 bp read length, the claim language instructs that one may combine the two samples (“sequencing nucleic acid molecules from *at least one biological sample* of a subject to generate sequencing data, wherein said sequencing comprises sequencing 12 gigabases (GB) or more”), which would result in sequencing comprising (8.2 GB (100 * 82,247,848)) + (8.7 GB (100 * 86,781,192)) = 16.9 GB.

Newman's 157-kb Selector Sequences <175kb

Dr. Quackenbush

Specification

“What ***Newman is targeting***
is ***157,000 bases.***”

probe can be at least about 350 bases. Therefore, for at least about 500 sequences, the footprint of this assay may be about 175,000 bases. Compared to an **exome**, where the footprint of the assay is typically at least **35 million bases**, this may result in 200× less sequencing. This dramatic

EX1001 at 35:1-5

- Reported exome size confirms that claim refers to amount of sequence targeted

Newman Discloses A Single Methodology (CAPP-Seq) Applicable Across Cancers



Consistent with our GBM spike analysis, iDES also achieved the lowest detection limit among all the methods tested in NSCLC patient samples, enabling quantitation of ctDNA down to 0.004% (4 in 10^5 cfDNA molecules) in a patient before clinical progression (Fig. 5c and Supplementary Table 5). To our knowledge, this is the lowest amount of ctDNA detected by deep sequencing in any NSCLC patient to date. Thus, by increasing analytical sensitivity without affecting molecule recovery, iDES can improve sensitivity for response monitoring, detection of minimal residual disease, and surveillance.

EX1043 at 553

We tested the reproducibility of our approach using two cohorts of genetically distinct healthy adult controls processed independently to assess batch effects (**Supplementary Table 2**). Each control cohort was used to build a different background database, which was subsequently applied to polish all NSCLC cfDNA samples analyzed in this work. Although the original training cohort had the highest background (**Supplementary Fig. 6b**), and thus yielded the greatest reduction in selector-wide error rates, differences were marginal overall (**Supplementary Fig. 7c**). This result is consistent with the highly stereotypical nature of most background patterns observed across cfDNA samples (**Supplementary Fig. 6**), and was also not dependent on the selector synthesis batch (cfDNA versus tumor genotyping NSCLC selectors; **Supplementary Table 2** and **Supplementary Fig. 6b**).

Of note, we used the same approach described above to build a background database for cfDNA from 12 normal controls profiled by a personalized GBM selector (see ctDNA detection limits for iDES, duplex sequencing, and other methods, below).

EX1043 at 559

Personalis Applies The Wrong Legal Standard For Anticipation



“Anticipation occurs when a prior art reference discloses each element of the claimed invention, not only where a particular embodiment within a reference discloses each element of the claimed invention. Instead, a reference may still anticipate if the reference teaches that the disclosed components or functionalities may be combined and one of skill in the art would be able to implement the combination.”

Unified Patents v. Intellectual Ventures, IPR2016-01643,
Paper 51 at 28-31 (PTAB March 26, 2018).

The Petition Relies On Newman's Directly Related Teachings

POR

Foresight fails to establish that claim 1 is anticipated because Newman does not disclose all elements “arranged as in the claim,” “without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370-71 (Fed. Cir. 2008).

POR at 47-48

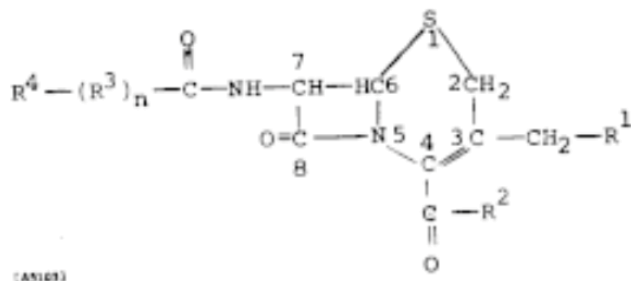
Net MoneyIN v. Verisign

 *Arkley*, 455 F.2d at 587 (“[T]he [prior art] reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.”).

545 F.3d at 1371

Arkley Involved “Picking and Choosing” From 230,000 Chemical Species

Appellants' claim has been rejected as *anticipated* by U. S. patent No. 3,218,318, issued to Edwin H. Flynn November 16, 1965, on an application filed in the United States August 31, 1962, and available against appellants' application by virtue of 35 U.S.C. § 102(e) as of its filing date. This reference discloses generically a class of cephalosporin-type compounds **587 having the following structural formula:



in which R^1 , taken alone, is $-\text{OH}$, $\text{C}_1\text{-C}_8$ acyloxy, or tertiary-amino, R^2 is $-\text{OH}$ when R^1 is $-\text{OH}$, R^2 is $-\text{OH}$ when R^1 is $\text{C}_1\text{-C}_8$ acyloxy, R^2 is $-\text{O}^-$ when R^1 is tertiary-amino, R^1 and R^2 , when taken together, are $-\text{O}-$, n is zero or 1, R^3 is $\text{C}_1\text{-C}_6$ alkylene, and R^4 is a heteromonomocyclic radical containing O, S, and/or N. Appellants “conservatively” estimate that over 230,000 compounds (including, concededly, theirs) are embraced within this generic disclosure, and the board in turn conceded that, “If this were the only anticipatory disclosure in the reference,” the disclosure would be “too diffuse” to support a 102 rejection.

Application of Arkley, 455 F.2d at 586-587 (C.C.P.A. 1972)

IPR2023-00545 ('783 Patent)

Unpatentability Based On Ley

Step 1(a): Ley Discloses a Personalized Probe Set

'783 Patent

obtaining a personalized probe set for a subject, which personalized probe set comprises a plurality of nucleic acid probe molecules having the plurality of nucleic acid sequences or complements thereof, wherein the plurality of nucleic acid probe molecules are configured to selectively enrich or amplify sequences comprising a set of genetic variants over other sequences in at least one biological sample of the subject, wherein the set of genetic variants are identified in sequence data for the at least one biological sample; (b) using the personalized probe set to selectively



Dr. Quakenbush
Expert Witness



112. As discussed above, Ley discloses “obtaining a personalized probe set for a subject,” namely the set of PCR primers that are used to generate PCR amplicons for subsequent sequencing. The probes are directed to the set of genes listed in Tables 2-3 and Figure 3. Ex. 1012 (Ley) at 69-70. Because the probe set

116. As discussed above, Ley identified 10 genetic mutations that are non-synonymous somatic mutations in the CDH24, SLC15A1, KNDC1, PTPRT, GRINL1B, GPR123, EB12, PCLKC, FLT3, and NPM1 genes in his initial whole-genome sequencing assay, which involved analyzing the mutations detected in both the primary tumor and skin samples and then applying a filtering process. Ex. 1012 (Ley) at 68-69. He also identified two “known” SNPs (genetic variants) in the BRCA2 and TP53 genes. Ex. 1012 (Ley) at 69 (Control amplicons containing a

Step 1(a): “Variable” and “Fixed” Portion

(a) wherein said personalized probe set comprises....:
(i) at least one variable portion from a result of said sequence data and (ii) at least one fixed portion independent of said result of said sequencing data....

- **Variable:** Ten “discovered” variants identified “from a result of said [WGS] data”
- **Fixed:** Two “known” variants (BRCA2, TP53)

Defining mutation frequencies in the tumour sample

Ley (EX1012)

To better define the percentage of tumour cells that contained each of the **discovered somatic mutations**, we amplified each mutation-containing locus from non-amplified genomic DNA derived from the *de novo* and relapse tumour samples, and from the skin biopsy obtained at presentation. The resulting amplicons were sequenced using the Roche/454 FLX platform, and the frequency of reads containing the reference and variant alleles were defined (Fig. 3 and Table 3). **Control amplicons containing a known heterozygous SNP in BRCA2 (encoding N372H) and a homozygous SNP in TP53 (encoding P72R) were analysed similarly.** The BRCA2 SNP

Step 1(b): Ley Applies Its Probe Set To The Relapse Tumor Sample

(b) using said personalized probe set to selectively enrich or amplify sequences comprising said set of genetic variants over other sequences **in at least an additional biological sample** from said subject, to generate a sequencing library;

Defining mutation frequencies in the tumour sample

Ley (EX1012)

To better define the percentage of tumour cells that contained each of the discovered somatic mutations, we amplified each mutation-containing locus from non-amplified genomic DNA derived from the *de novo* and relapse tumour samples, and from the skin biopsy obtained at presentation. The resulting amplicons were sequenced using the Roche/454 FLX platform, and the frequency of reads containing the reference and variant alleles were defined (Fig. 3 and

Personalis does not dispute Ley's disclosure of the corresponding "additional biological sample" limitation in '611 step 1(d)

Table 3 | 454 Readcount data for somatic mutations and known SNPs

Gene	Consequence	Primary AML (100% blasts)			Skin			Relapse (78% blasts)		
		Variant	Ref	Variant (%)	Variant	Ref	Variant (%)	Variant	Ref	Variant (%)
CDH24	Y590X	5672	4890	53.70	564	10358	5.16	3108	4599	40.33
SLC15A1	W77X	3817	4962	43.48	875	10773	7.51	4714	7173	39.66
KNDC1	L799F	4640	4848	48.90	770	8972	7.90	3883	6342	37.98
PTPRT	P1235L	998	1058	48.54	126	1489	7.80	350	493	41.52
GRINL1B	R176H	2211	2674	45.26	318	4461	6.65	1447	2070	41.14
GPR123	T38I	4618	4569	50.27	850	9751	8.02	3660	6057	37.67
EBI2	A338V	12750	15453	45.21	458	10088	4.34	2646	3627	42.18
PCLKC	P1004L	992	855	53.71	341	3153	9.76	705	773	47.70
FLT3	ITD	4220	7810	35.08	3475	23159	13.05	3870	8495	31.30
NPM1	CATG ins	1550	1974	43.98	143	2390	5.65	2303	3910	37.07
BRCA2	N372H	778	752	50.85	763	876	46.55	285	303	48.47
TP53	P72R	8989	1	99.99	8161	0	100.00	7914	6	99.92

The differences between variant frequencies in primary or relapse tumour samples and skin were highly significant for all somatic mutations ($P < 0.001$). The *BRCA2* variant is a known heterozygous SNP in this genome, and the *TP53* variant is a known homozygous SNP.

Step 1(c): Ley's Follow-up Amplicon Sequencing Has a Smaller Footprint Than WGS

(c) **subjecting said sequencing library to sequencing** to identify a presence or absence of at least a subset of said set of genetic variants in at least said additional biological sample from said subject, **wherein a sequencing footprint of said sequencing of (c) is less than a sequencing footprint of said sequence data of (a);**



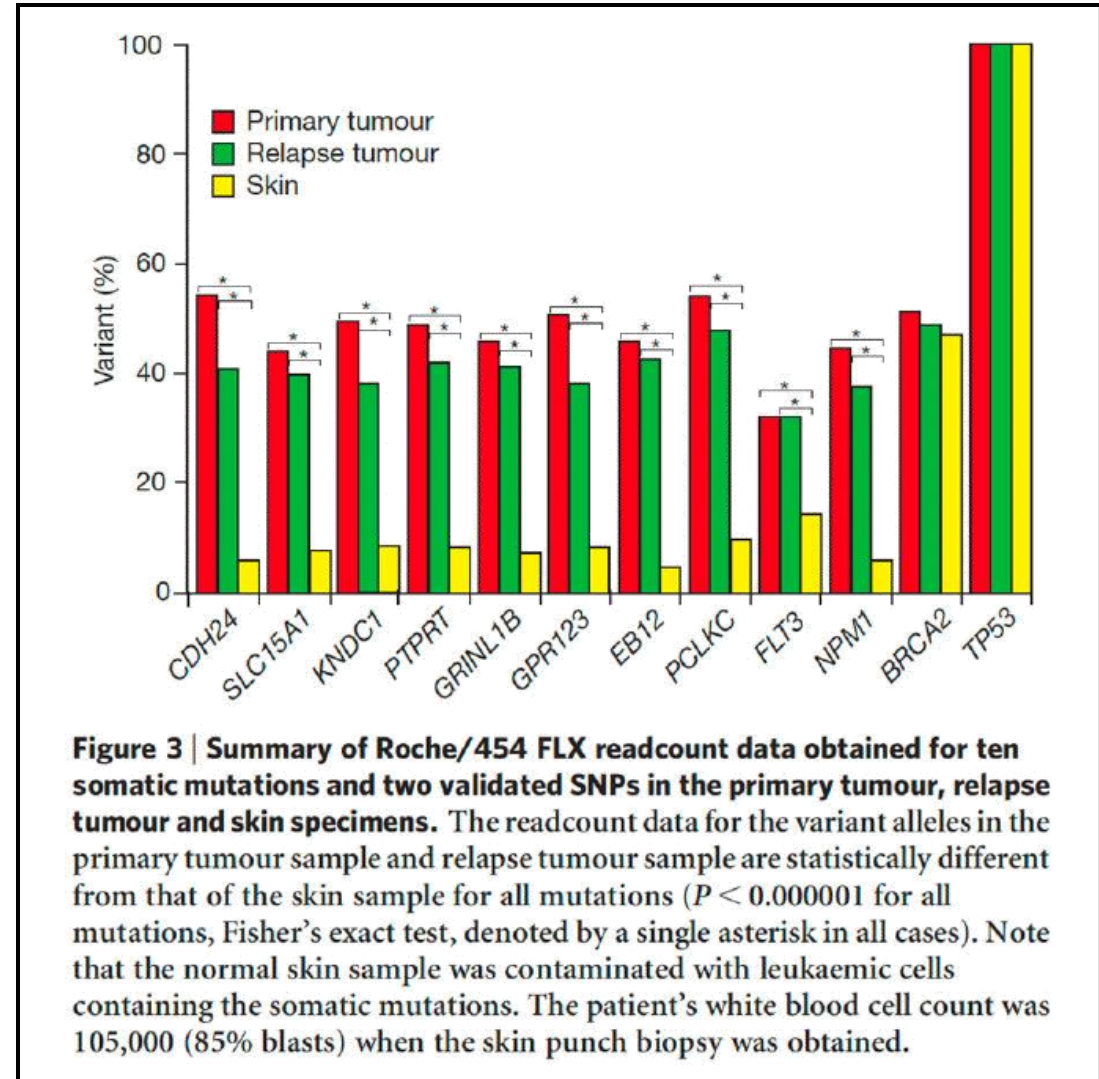
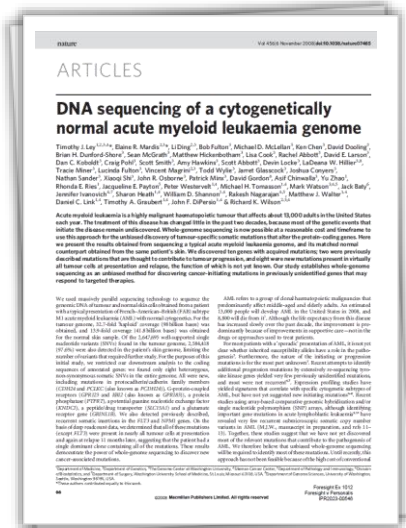
Dr. Quakenbush
Expert Witness



123. The sequencing footprint of the sequencing performed in step (“(c)”) is less than a sequencing footprint of the “sequence data of (a).” Specifically, the sequence data referenced in step (a) in Ley is derived from whole-genome sequencing. This whole-genome sequencing data necessarily has a larger sequencing footprint than the targeted sequencing performed following amplification in this step (i.e., step 1(c)). In Ley’s methods, the sequencing of step (c) is performed using PCR amplicons that track the individual genes of interest identified in step (a), and thus are only small subsets of the whole genome. Accordingly, the sequencing footprint of the sequencing data of (c), which is generated by sequencing such amplicons, is necessarily less than the sequencing footprint of step (a)’s whole-genome sequence data. This is consistent with how Patent Owner reads this limitation onto the accused products. Ex. 1072 (Patent Owner’s Infringement Contentions) at 4-5 (contending that limitation is met where variants “were tracked with probes of 120bp in length” while “the first sequencing step used to identify said variants (in the case of Foresight, whole genome sequencing)” has a larger footprint).

Step 1(d): Ley Generated the Claimed Report

(d) **generating a report** identifying (i) a presence or absence of a health condition or disease of the subject in said additional biological sample based on said identified at least a subset of (c) and (ii) genetic variants which inform a therapy choice or a change in therapy for the subject.



EX1012 at 69;
EX1020, ¶123

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

“Informing A Therapy Choice Or Change In Therapy” Is Patent Ineligible Printed Matter



Praxair

“Claim limitations directed to **printed matter are not entitled to patentable weight unless** the printed matter is **functionally related** to the substrate on which the printed matter is applied.”

Praxair Distribution, Inc. v. Mallinckrodt Hosp. Prod. IP Ltd., 890 F.3d 1024, 1031 (Fed. Cir. 2018)

Praxair’s Ineligible “Providing Information” Limitation

[P]roviding to the medical provider[:]

(i) **information** that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide and

(ii) **information** that, in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure (PCWP), leading to pulmonary edema, **the information of (ii) being sufficient to cause a medical provider** considering inhaled nitric oxide treatment for a plurality of neonatal patients who

(a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, **to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid** putting the one or more patients at risk of pulmonary edema.

“Informing A Therapy Choice Or Change In Therapy” Is Patent Ineligible Printed Matter

Step 1(d)

(d) *generating a report*

identifying (i) a presence or absence of a health condition or disease of the subject in said additional biological sample based on said identified at least a subset of (c) and (ii) genetic **variants which inform a therapy choice or a change in therapy for the subject.**

Praxair’s Ineligible “Providing Information” Limitation

[P]roviding to the medical provider[:]

(i) **information** that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide and

(ii) **information** that, in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure (PCWP), leading to pulmonary edema, **the information of (ii) being sufficient to cause a medical provider** considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, **to elect to avoid treating** one or more of the plurality of patients **with inhaled nitric oxide in order to avoid** putting the one or more patients at risk of pulmonary edema.

Unpatentability Based On Forshew + Dawson

ForsheW's Variable Portion Was Based On The WGS Data

Dr. Quackenbush

255. ForsheW expressly discloses the use of a variable portion from a result of the whole-genome sequencing data in the context of its breast cancer patient. As discussed above, in the breast cancer patient whose cancer was tracked using TAm-Seq following an initial whole-genome sequencing step, the set of 10 nucleic acid probe molecules used to generate the amplicons for sequencing constitute a variable portion from a result of said sequencing data. Ex. 1030 (ForsheW) at 9 (“[w]hole-genome sequencing of tumor material was used to identify tumor mutations in a patient,” and “[t]en mutations were selected.”).

EX1020 at ¶255

PO's Counsel

“ForsheW discloses amplifying ten SNV mutations from a tumor sample that were identified based on WGS data, which are listed in Table S7. EX1003.010 [ForsheW] (WGS “of tumor material was used to identify tumor mutations...Ten mutations were selected, and short amplicons (<120 bp) were designed to cover the mutation loci....”).”

EX1080 at 22-23

Forshew and Dawson Motivate Including Fixed Probes For TP53



Dr. Quackenbush
Expert Witness



**Harvard
University**

coding regions (exons and exon junctions) of *TP53*,” among multiple other genes.

Id. at 3. Thus, Forshew disclosed including probes for variants in *TP53* independent of any prior sequencing data in its other assays. Including such additional probes in addition to sequence-based probes in a single panel would require nothing more than the predictable use of techniques used in other examples of the very same reference.

257. Moreover, Dawson, on which Dr. Forshew is also an author, explains that *TP53* is also “known to be recurrently mutated in breast cancer.” Ex. 1070

258. Accordingly, a POSA would have found it obvious to include one or more “fixed” probes in Forshew’s breast cancer panel independent of any sequencing data in order to detect and amplify variants of *TP53* in the patient. In

Personalis's Multiplexing Argument Does Not Negate Motivation

Personalis Argument

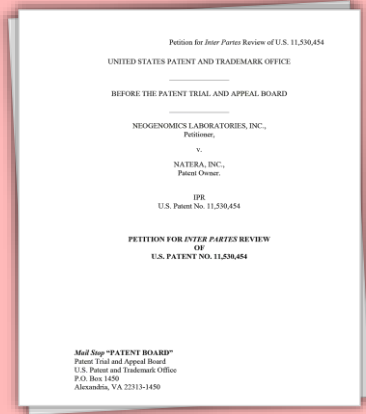
- Proposed combination would require 1,010 PCR primers
- Alleged difficulties with multiplex PCR negate motivation to combine

PO's Counsel

“At a minimum, ***Forsheew renders obvious the ability to use even greater multiplex amplification*** as part of the TAm-Seq protocol because a POSA would have known that significantly ***greater multiplex amplification was already well-established.***”

“In fact, it was known in the art to perform multiplex PCR for sequencing of a number of targets far in excess of 100....[Y]ears before the priority date it was ***known to amplify up to 9,216 targets in a single tube for sequencing.***”

Natural Motivation And Expectation of Success For Multiplex PCR



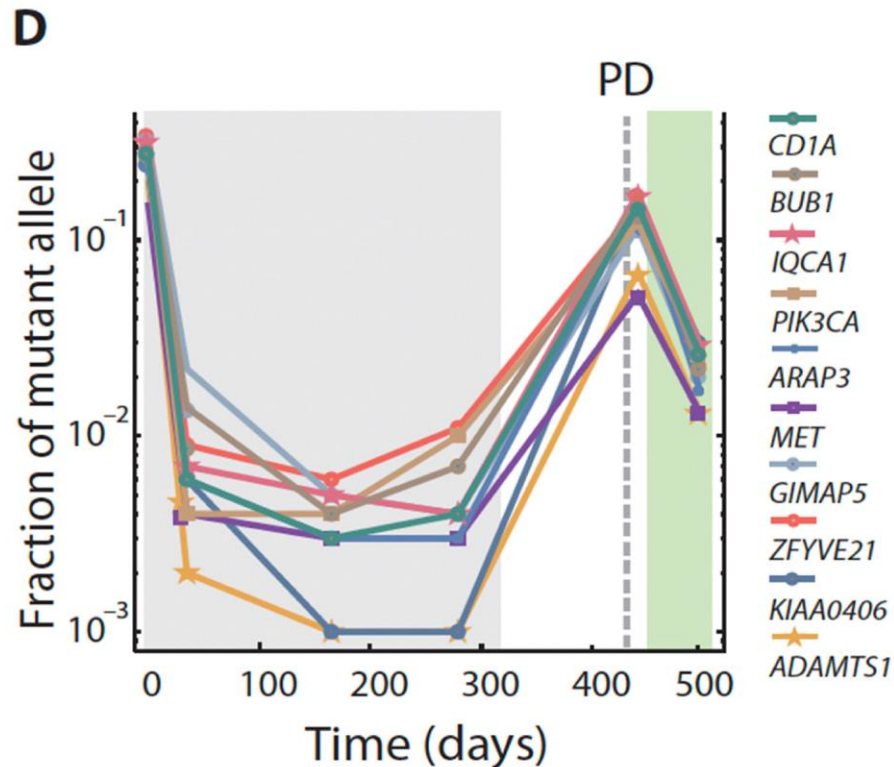
PO's Counsel



“[N]umerous other references teach **multiplex PCR** of far more than 20 targets. As such, a POSA would have had a **reasonable expectation of pursuing such an approach**. And the **motivation to do so is natural: including more targets** in the process **allows one to** track a broader spectrum of cancer-related mutations and hence **better track and detect the cancer over time**.”

ForsheW's Report Informs a Therapy Choice

ForsheW Fig. 4D



Dr. Quackenbush

265. Notably, ForsheW's Figure 4D "tracked dynamics of all mutations" analyzed with TAM-seq. *Id.* at 9. "The patient was treated with single-agent epirubicin (gray-shaded region). After 4 months off treatment, a CT scan showed progressive disease and the patient commenced further treatment with paclitaxel chemotherapy. The 10 mutations followed a common pattern of sharp decline in AF [allele fraction] upon onset of therapy and an increase in AF upon disease progression after termination of therapy." *Id.* Thus, ForsheW's report informs therapy choice or a change in therapy based on the allele fraction of the identified alleles, including because of the observed relationship between therapy and disease status.

Dependent Claims

Disputed Dependent Claims

- Capture probes (Claim 22)
- cfDNA (Claims 3, 8, 15, 16)

Claim 22: Obvious To Use Hybrid Capture Probes



Dr. Quackenbush
Expert Witness



224. Ley discloses the use of PCR primers as probes for the amplification and/or enrichment of target DNA over normal DNA in the sample to prepare its sequencing library. However, by the 2016 priority date of the '783 patent, a POSA would have also been familiar with the use of hybrid capture techniques for similar purposes. As explained in Section V.C.3, above, PCR and hybrid capture 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) (describing pros, cons, and overlapping applications of “[c]urrently employed targeted enrichment techniques”). Accordingly, a POSA would have found it obvious to use create hybrid capture probes targeting the same sequences as Ley because doing so would have involved only the predictable usage of techniques known in the art to be interchangeably useful for the same purpose. Indeed, well before the priority date, “an increasing number of protocols and vendors [had] begun offering out of the box solutions for hybrid capture, meaning, the research need not do development work but merely choose between a preset targeted enrichment regions (e.g. whole exome) or *specify their own custom enrichment region.*” Ex. 1006 (Mertes 2011) at 379. Thus, a POSA would have readily been able to obtain “out of the box” hybrid capture reagents for a “custom enrichment region” including a panel of probes directed to the genetic variations one would monitor in Ley’s methods and the variations thereof discussed in this section.

225. The '783 patent’s specification confirms that those skilled in the art considered these techniques to be interchangeable as of the priority date. In defining the terms “probe,” “nucleic acid probe,” “capture probe,” and “bait,” the '783 patent explains:

The terms “probe,” “nucleic acid probe,” “capture probe,” “bait,” as used herein, generally refer to a nucleic acid molecule comprising a single-stranded portion capable of hybridizing to a complementary nucleic acid sequence. A probe can be used for detection or enrichment of nucleic acid molecules. A probe can be target-specific such that a region of interest may be pulled-down, isolated, enriched, amplified, or labeled. A probe can be used for targeted sequencing. A probe may hybridize to a targeted sequence when attached to a solid substrate or when in-solution, e.g. as for hybrid capture. A probe may be included in a set, or plurality, of probes. A probe set can comprise probes that overlap within a specific genomic region such that they are tiled or staggered. A probe set can include probes to a genomic region or a panel comprising multiple genomic regions. Probes can be amplification based or capture hybridization-based. Non-limiting examples of probes include molecular inversion probes, amplification probes, biotinylated affinity probes, or any probe comprising a detectable label.

Ex. 1001 at 29:4-22.

Claims 3, 8, 15, 16: Obvious To Monitor cfDNA For Targeted Resequencing



Dr. Quackenbush
Expert Witness

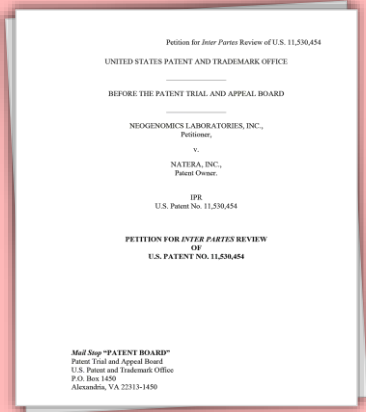


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195. As discussed above, Ley discloses performing targeted resequencing using the panel of variable and fixed probes on primary and relapsed tumor samples. Given that a benefit of the assay is the ability to observe the course of a patient's cancer and response to treatment, a POSA would have found it obvious to repeat the assay at additional time points, resulting in the collection of more than two biological sample (i.e., a plurality) following the initial sample for analysis and sequencing using the Ley's personalized probe sets. A POSA would have reasonably expected success in doing analyzing multiple samples, given that it would have involved merely applying the techniques already proven to be successful at multiple time points. Indeed, soon after Ley, Leary (Ex. 1002) and McBride (Ex. 1015) demonstrated the use of a similar assay design, by using whole-genome sequencing to identify genetic structural variants (as opposed to SNVs as in Ley), and to subsequently use those identified markers as targets for serial monitoring of tumor DNA in the blood plasma of patients with solid tumors at multiple (e.g., 6) time points. *See also* Ex. 1031 (Meyerson) at 687 (Table 1) (listing Ley and subsequent whole cancer genome studies).

198. I incorporate by reference my discussion of claim 2. Ley discloses collecting samples from tissue samples, specifically a tumour sample. *See, e.g.*, Ex. 1012 (Ley) at 69. However, those skilled in the art would have been familiar with the release of tumor DNA into the bloodstream, resulting in cell-free tumor DNA circulating in the blood. *See* Section V.E ("Related Applications of Next Generation Sequencing"). A POSA would have been motivated to use plasma samples -- where such cell-free DNA is present in solution -- in addition to or instead of tissue samples like tumor samples to ease sample collection. A POSA would have reasonably expected success in applying Ley's methods to biological samples derived from plasma in light of the successful reports of others, like Leary (Ex. 1002) and McBride (Ex. 1015) doing so in the serial monitoring of tumor DNA in the blood plasma of patients with solid tumors.

PO's Counsel: cfDNA Monitoring "Routine" By 2013



PO's Counsel



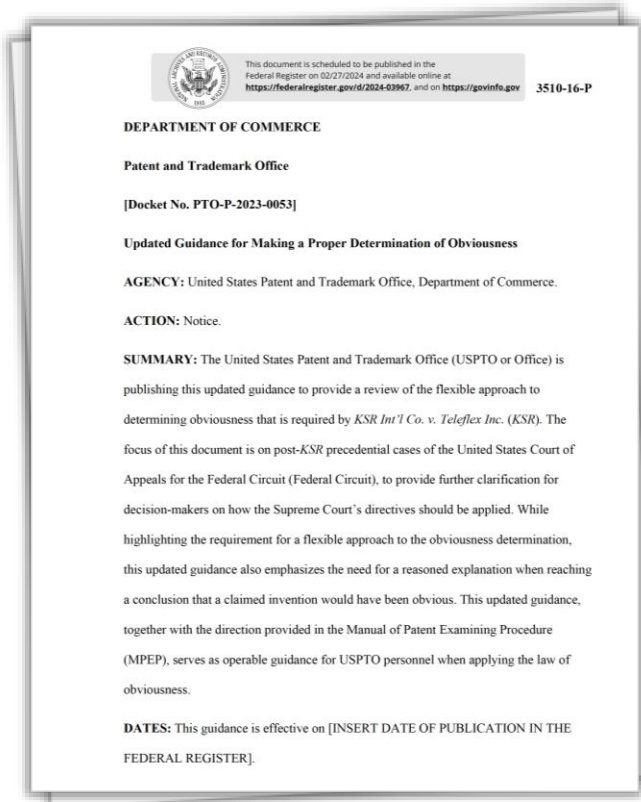
E. Minimal Residual Disease Monitoring

Minimal residual disease ("MRD") monitoring is the monitoring of residual cancer that remains after a patient has undergone treatment, *e.g.*, surgery and/or treatment with radiation or chemotherapy. EX1130.002; EX1002 ¶ 87. MRD monitoring generally involves WGS or WES of the cancerous DNA to identify cancer-related (*e.g.*, tumor-specific) SNVs, and follow-up monitoring (involving multiplex PCR and sequencing) of these SNVs in cfDNA. EX1002 ¶¶ 88-93. This was developed to provide patient-specific care and allows detection of recurrent tumors without the need for invasive surgeries, and can also be used to monitor treatment progress as the level of cfDNA correlates with the size of the tumor. *Id.* ¶¶ 87-88. MRD monitoring was routinely conducted by at least 2013 through a range of different approaches. *Id.* ¶¶ 87-93.

Citing, inter alia,
Forsheew and Leary

No Secondary Considerations

February 27, 2024 Director's Guidance



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

No Credible Nexus Evidence Because Dr. Furneaux Failed To Analyze Next Personal



Dr. Furneaux
Expert Witness



- Q. So what I'm asking you, Dr. Furneaux, is if **you yourself would need more information** than what's given here in this article in order **to determine whether you believe the NeXT Personalis assay is praiseworthy?**
- A. Yes, I think it's no secret that **one of the challenges** in doing this particular endeavor **has been lack of information that allows me to make a clear opinion.**

No Credible Nexus Evidence Because Dr. Furneaux Failed To Analyze Next Personal



Dr. Furneaux
Expert Witness



- Q. So for your declaration, you ***didn't review***, for example, ***whether the Personalis NeXT assay works for its intended purpose***?
- A. Again, let me emphasize, ***I have actually not*** considered those aspects and ***looked at the Personalis assay in detail.***

Personalis Relies On A Different Assay For <175kb Than For Alleged 1PPM Sensitivity

(e) subjecting said sequencing library to sequencing at a coverage of 175 kilobases (kb) or less to identify a presence or absence of at least a subset of said set of genetic variants in said additional biological sample from said subject or said at least one biological relative, wherein a

The NeXT Personal test involves sequencing the sequencing library to identify a subset of genetic variants in the additional biological sample.

Figure 3: NeXT Personal: Advanced, Higher Sensitivity, Personalized, Tumor-Informed Liquid Biopsy for MRD & Variant Tracking

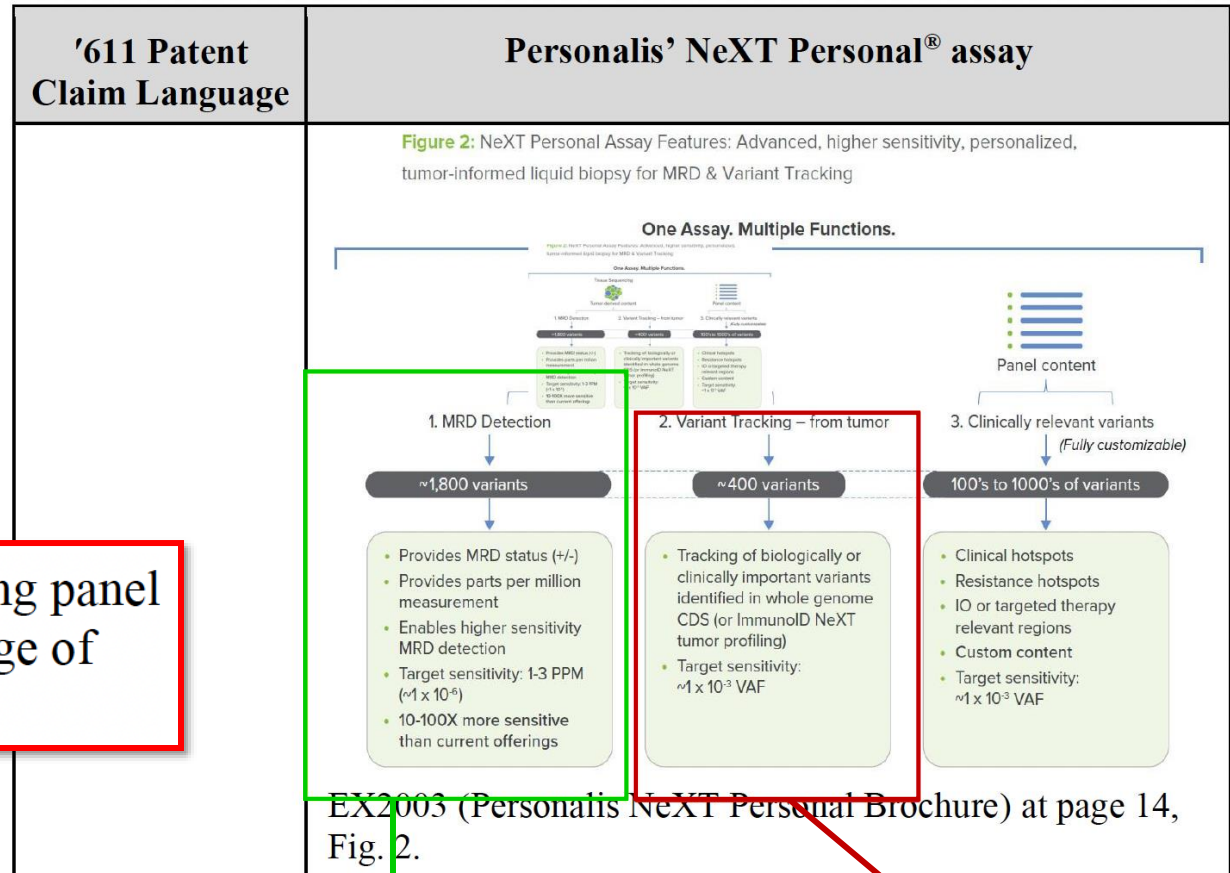
EX2004 (Personalis NeXT Personal Brochure) at page 17, Fig. 2.

The NeXT Personal test also involves a variant tracking panel that identifies a subset of ~400 sequences, at a coverage of less than 175 kilobases.

for inclusion in a personalized MRD panel (Figure 3). The majority of these patient-specific SNVs are located in non-coding regions of the genome. Finally, Personalis' extensive investment into the Illumina® NovaSeq® series enables ultra-deep sequencing (~100,000 raw depth), while keeping costs in line with other MRD tests that interrogate many fewer loci.

EX2003 (Personalis NeXT Personal Brochure) at page 15.

The NeXT Personal test also involves a variant tracking panel that identifies a subset of ~400 sequences, at a coverage of less than 175 kilobases.



Alleged 1 ppm sensitivity

Alleged <175kb
(no calculation or evidentiary support)

