

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

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

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Ex. 1003	Quake <i>et al.</i> , WO 2011/057061 (Quake)
Ex. 1004	Matthew W. Anderson & Iris Schrijver, “Next Generation DNA Sequencing and the Future of Genomic Medicine,” <i>Genes</i> (2010) (Anderson)
Ex. 1005	Andreas Gnirke <i>et al.</i> , “Solution hybrid selection with ultra-long oligonucleotides for massively parallel targeted sequencing,” <i>Nature Biotechnology</i> (2009) (Gnirke)
Ex. 1006	Florian Mertes <i>et al.</i> , “Targeted enrichment of genomic DNA regions for next-generation sequencing, Briefings in Functional Genomics,” <i>Briefings in Functional Genomics</i> (2011) (Mertes)
Ex. 1007	Lira Mamanova <i>et al.</i> , “Target-enrichment strategies for next-generation sequencing,” <i>Nature</i> (2010) (Mamanova)
Ex. 1008	K.C. Allen Chan <i>et al.</i> , “Cancer Genome Scanning in Plasma: Detection of Tumor-Associated Copy Number Aberrations, Single-Nucleotide Variants, and Tumoral Heterogeneity by Massively Parallel Sequencing,” <i>Clinical Chemistry</i> (2013) (Chan)
Ex. 1009	Gary J.W. Liao <i>et al.</i> , “Targeted Massively Parallel Sequencing of Maternal Plasma DNA Permits Efficient and Unbiased Detection of Fetal Alleles,” <i>Clinical Chemistry</i> (2011) (Liao)
Ex. 1010	<i>Personalis v. Foresight</i> , First Amended Complaint, D. Colo., Case No. 1:22-v-01913, Dkt. 9, filed August, 17, 2022 (“FAC”)
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Ex. 1012	Timothy J. Ley <i>et al.</i> , “DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome,” <i>Nature</i> (2008) (Ley)
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Ex. 1015	David J. McBride, et al., “Use of Cancer-Specific Genomic Rearrangements to Quantify Disease Burden in Plasma from Patients with Solid Tumors,” <i>Genes, Chromosomes & Cancer</i> (2010) (McBride)
Ex. 1016	David M. Kurtz, et al., “Enhanced detection of minimal residual disease by targeted sequencing of phased variants in circulating tumor DNA,” <i>Nature Biotechnology</i> (2021) (Kurtz) (Ex. J to FAC)
Ex. 1017	https://www.aacc.org/science-and-research/clinical-chemistry/clinical-chemistry-podcasts/2013/cancer-genome-scanning-in-plasma-detection-of-tumor-associated-copy-number-aberrations
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Ex. 1025	Seo Young Oh, et al., “Improved DNA Extraction Method for Molecular Diagnosis from Smaller numbers of Cells,” <i>Korean Journal of Clinical Laboratory Science</i> (2014) (Oh)
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Ex. 1029	Hugo Lam, et al., “Performance comparison of whole-genome sequencing platforms,” <i>Nature Biotechnology</i> (2012) (Lam)
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Ex. 1041	H. Li, “Mapping short DNA sequencing reads and calling variants using mapping quality scores,” <i>Genome Res.</i> (2008) (Li)

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Ex. 1072	Plaintiff Personalis’ Infringement Contentions for United States Patent 11,299,783
Ex. 1073	C. Haferlach, <i>et al.</i> , “Mutations of the TP53 gene in acute myeloid leukemia are strongly associated with a complex aberrant karyotype,” Leukemia (2008)
Ex. 1074	S. Misawa, <i>et al.</i> , “Significance of chromosomal alterations and mutations of the N-RAS and TP53 genes in relation to leukemogenesis of acute myeloid leukemia,” Leukemia Research (1998) (Misawa)
Ex. 1075	S. Davies, <i>et al.</i> , “Indications for Hematopoietic Cell Transplantation in Acute Leukemia,” Biology of Blood and Marrow Transplantation (2008) (Davies)
Ex. 1076	B. Alter, <i>et al.</i> , “Clinical and molecular features associated with biallelic mutations in <i>FANCD1/BRCA2</i> ,” Journal of Medical Genetics (2007) (Alter)

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Ex. 1077	D. Bentley, <i>et al.</i> , “Accurate whole human genome sequencing using reversible terminator chemistry,” Nature (2008) (<i>Bentley</i>)
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I. INTRODUCTION

Foresight Diagnostics Inc. (“Petitioner”) requests *inter partes* review and cancellation of claims 1-9, 13-19, and 21-29 (the “Challenged Claims”) of U.S. Patent No. 11,299,783 (“the ’783 patent”), entitled “Method and System of Genetic Analysis.”

For the reasons set forth below, and as further explained in the declaration of Petitioner’s expert genome scientist John Quackenbush, Ph.D., Ex. 1020 (“Quackenbush”), all Challenged Claims should be cancelled.

II. GROUNDS FOR STANDING

Petitioner certifies that the ’783 patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging its claims on the grounds identified in this petition.

III. MANDATORY NOTICES

A. Real Party-In-Interest

Petitioner Foresight Diagnostics Inc. is the real party-in-interest with respect to this petition for *inter partes* review.

B. Related Matters

On August 2, 2022, Patent Owner filed a lawsuit against Petitioner alleging infringement of the ’783 patent and other patents assigned to Patent Owner. The case is pending in the United States District Court for the District of

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Colorado, bearing case number 1:22-cv-01913. Ex. 1010 (First Amended Complaint).

The '783 patent issued from Application No. 17/235,776, which claims priority to provisional Application No. 62/342,674. According to Patent Center, the applications listed below are related to the '783 patent as parents or children:

17/235,776 48929.4011/US04: METHODS AND SYSTEMS FOR GENETIC ANALYSIS				
Public view		Maintenance Fee Storefront Global Dossier Download Print		
Application #	Attorney Docket #	Patent #	Status	Filing or 371 (c) date
17/235,776	48929.4011/US04	11,299,783 Link Issued - 04/12/2022	Patented Case - 03/23/2022	04/20/2021

Continuity

Parent data

Application #	Description	Parent application #	Filing or 371 (c) date	Status	Patent #	AIA
17/235,776	is a Continuation in-part of	17/065,411	10/7/2020	Abandoned	-	Yes
17/065,411	is a Continuation of	16/843,115	4/8/2020	Abandoned	-	-
16/843,115	is a Continuation of	16/547,451	8/21/2019	Abandoned	-	-
16/547,451	is a Continuation of	15/793,845	10/25/2017	Patented	10,450,611	Yes
15/793,845	is a Continuation of	PCT/US2017/034823	5/26/2017	-	-	-
PCT/US2017/034823	Claims priority from a provisional application	62/342,674	5/27/2016	Expired	-	-

Child data

Application #	Filing or 371 (c) date	Status	Patent #	AIA	Description	Parent application #
17/747,436	5/18/2022	-	-	Yes	is a Continuation of	17/235,776
17/688,072	3/7/2022	-	-	Yes	is a Continuation of	17/235,776

Petitioner has also filed co-pending Petitions for *inter partes* review challenging the validity of Patent Owner's U.S. Patent Nos. 11,384,394 (IPR2023-00224) 11,408,033 (IPR2023-00317), and 10,450,611 (IPR2023-00546).

C. Lead and Back-up Counsel and Service Information

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IV. THE '783 PATENT

According to its face, the '783 patent issued on April 12, 2022 from Application No. 17/235,776. Ex. 1001, codes (45), (21). The '783 patent claims priority to Provisional Application No. 62/342,674, filed on May 27, 2016. *Id.*, code (60). According to Patent Center, the '776 Application was asserted to fall under the AIA's first inventor to file provisions:

17/235,776 48929.4011/US04: METHODS AND SYSTEMS FOR GENETIC ANALYSIS				
Public view		Maintenance Fee Storefront Global Dossier Download Print		
Application #	Attorney Docket #	Patent #	Status	Filing or 371 (c) date
17/235,776	48929.4011/US04	11,299,783 Issued - 04/12/2022	Patented Case - 03/23/2022	04/20/2021
Application type	Utility	Earliest publication #	US 2021-0238677 A1 Link Intl. registration # (Hague) -	
Examiner	KAIJIANG ZHANG	Earliest publication date	08/05/2021 Intl. registration publication date -	
Group art unit	1639	Assignee for publication	-	
Class/subclass	506/002.000	Confirmation #	4042	
AIA (first inventor to file)	Yes			
Entity status	Small			
Correspondence address	Inventors		Applicants	
182685 - ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis) IP Prosecution 2050 Main Street, Suite 1100 IRVINE, CA UNITED STATES	John West Menlo Park, CALIFORNIA (US) Christian Haudenschild Menlo Park, CALIFORNIA (US) Richard Chen		Personalis, Inc. Menlo Park (US)	

The '783 patent purports to disclose “systems and methods for sample processing and data analysis.” Ex. 1001, Abstract. The '783 patent goes on to assert that “[m]ethods and systems of the present disclosure can be used, for example, for the analysis of a nucleic acid sample, for producing one or more libraries, and for producing biomedical reports,” and that such methods and systems “can aid in the diagnosis, monitoring, treatment, and prevention of one or more diseases and conditions.” *Id.*

V. LEVEL OF ORDINARY SKILL IN THE ART

As Dr. Quackenbush explains, a POSA in the field of the '783 patent:

[W]ould have had an advanced degree (such as an M.D. or the equivalent of a Ph.D. in a life or physical sciences, engineering, or mathematics discipline), and through further education or postdoctoral experience, an understanding of various sequencing

and next generation sequencing methods, sample preparation methods, targeted enrichment methods, bioinformatics methods for interpreting sequencing data, and methods for identifying genetic variants in a sample. A POSA also would have had an understanding of clinical applications of sequencing technology to conditions associated with nucleic acid variation, such as cancer, non-invasive prenatal testing, and transplant rejection. Additionally, a POSA would have had an understanding of cancer biology as it relates to mutations associated with tumor diagnosis, progression, and treatment, as well as awareness of the various types of mutations that can occur in and influence the course of a patient's cancer.

Quackenbush ¶35.

VI. BACKGROUND KNOWLEDGE OF A POSA

A. Genes and Mutations

Genes contain the set of instructions for the development and maintenance of the cells of all organisms. Genes are made of deoxyribonucleic acid (“DNA”) and are located on chromosomes. Certain alterations, sometimes called “mutations,” “variations,” “variants,” or “polymorphisms,” can occur in all genes and portions of the human genome, contributing both to normal patterns of human variation as well as individual risk for developing diseases. Polymorphisms can include many types of genomic alteration, including insertions, deletions, point mutations, translocations, rearrangements, and copy

number variations. The entire collection of an individual's genetic variants is referred to as their "genotype." *Id.* ¶¶39-54.

Genetic mutations can be inherited (i.e., passed on from their parents to their offspring) or acquired (i.e., developed for the first time in a new cell). Inherited mutations are called "germline" mutations. Acquired, or non-inherited, mutations are called "somatic" mutations. Somatic mutations unique to a particular tumor can be a useful tool for detecting, tracking, and monitoring a patient's cancer. *Id.* ¶51.

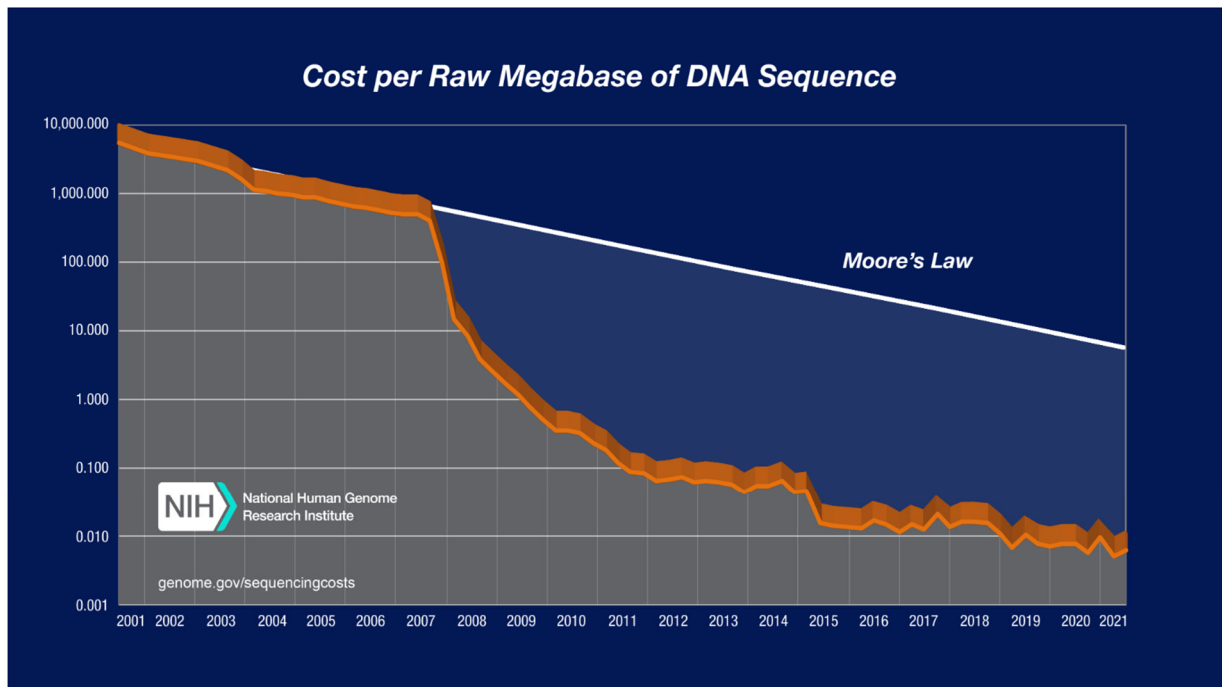
Mutations known in the art included single nucleotide polymorphisms ("SNPs"), copy number variants ("CNVs"), and insertions or deletions ("indels"). An SNP (sometimes called a single nucleotide variant ("SNV")) is a change in one DNA base pair that may result in the substitution of one amino acid for another in the protein that is encoded by the gene. A POSA would have also been familiar with translocations, which involve the relocation of a gene from one chromosomal location to another. By 2016, many publicly accessible databases existed in which a POSA would have been able to search for a large number of catalogued cancer-associated mutations. *Id.* ¶¶52-54.

B. Nucleic Acid Sequencing

A POSA would have been familiar with multiple techniques for nucleic acid "sequencing," i.e., determining the order of the bases in a nucleic acid molecule at the base-by-base level. For many years, sequencing was performed

using “Sanger” sequencing, which terminates the synthesis of a template strand of DNA at different lengths. These different length DNA strands can be “read” to derive the DNA sequence. *Id.* ¶¶55-59.

By around 2005, a new approach to sequencing called “next generation sequencing” (“NGS”), sometimes also called “massively parallel sequencing” or “sequencing by synthesis,” had been developed to allow multiplex sequencing of many different sequences simultaneously. By approximately 2008, techniques for NGS were well-known and commercially available. *See, e.g.*, Ex. 1013. NGS is a high-throughput method for determining the base-by-base sequences of nucleic acid molecules, such as DNA. NGS is exponentially faster, cheaper, and more efficient than Sanger sequencing, though both techniques provide accurate sequence information. Quackenbush ¶¶60-62. *See also* Ex. 1019 (<https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data>).



Sequencing cost per megabase - 2021

The development of NGS made more widely available “[t]he ability to sequence entire human genomes.” Ex. 1027. To obtain highly accurate sequencing information of the whole genome, a POSA would have understood that it was necessary to sequence, or “read,” accessible parts of the target genomic sequences multiple times to improve the accuracy of, and confidence in, sequencing results. Quackenbush ¶¶63-66.

C. Amplification and Enrichment

Both Sanger sequencing and NGS require sufficient quantities and/or relative abundances of target DNA. Thus, well before 2013, several techniques had been developed to generate or isolate copies of DNA molecules of interest to facilitate sequencing. A POSA would have been familiar with a number of such techniques, including PCR and solution-phase hybridization. *Id.* ¶¶67-70.

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Each technique has certain benefits over the others, but in many applications they were used relatively interchangeably by those skilled in the art. *Id.* ¶70. See Ex. 1006 (Table 1) (describing pros, cons, and overlapping applications of “[c]urrently employed targeted enrichment techniques” as of 2011).

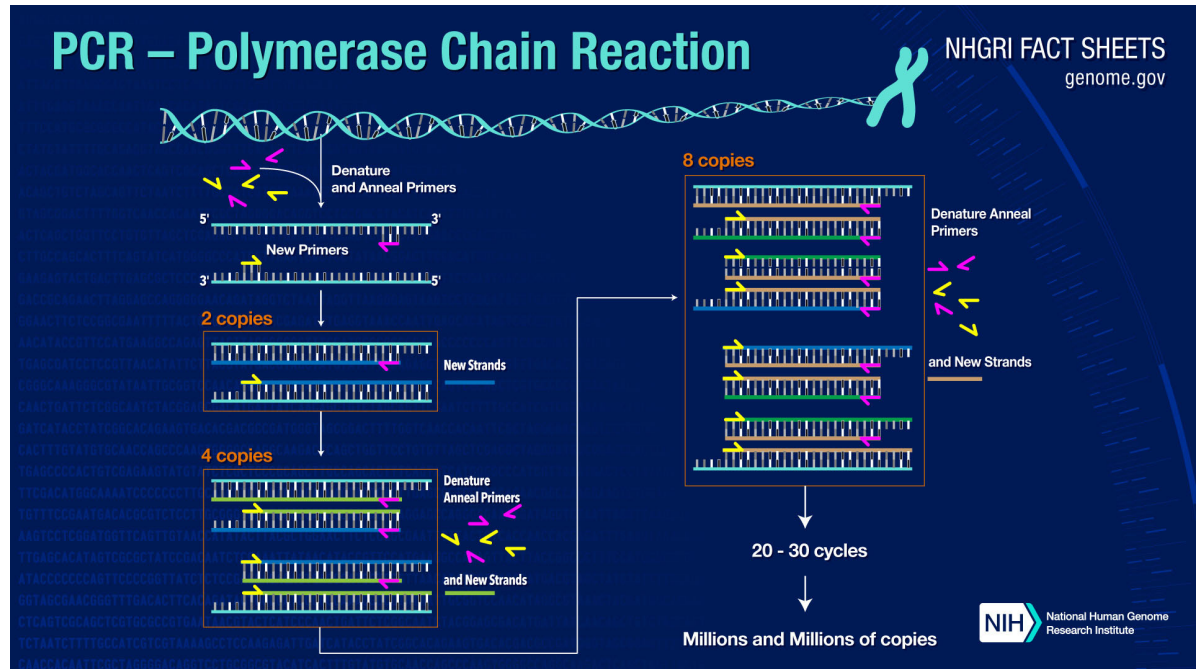
Table 1: Currently employed targeted enrichment techniques

Enrichment technique	Vendor	Features	Pros	Cons	Number of loci (target size)	Library prep for NGS
Hybrid capture						
Solid support	Agilent SureSelect, Roche NimbleGen SeqCap EZ	Medium to large target regions, custom and pre-configured target regions (i.e. whole exome), Multiplexing possible, ready to use kits	Ease of production, large target sets	Large amount of input DNA, high-tech equipment (3–10 µg)	10^4 – 10^6 (1–50 Mb)	Before enrichment
In solution	Agilent SureSelect, FlexGen FlexSelect, Mitoarray MSelect, Roche NimbleGen SeqCap EZ		Ease of use, small amount of input DNA (<1–3 µg)			
Circularization						
Molecular inversion probes	HaloGenomics	Custom kits and clinically relevant panel kits	No dedicated instruments, high specificity, input DNA (<1 µg)	exome kit not available yet	10^2 – 10^4 (0.1–5 Mb) 10 – 200 (0.1–1.5 Mb)	During enrichment (incorporated into hybridization probes)
Selector probes						
PCR						
Long range	Invitrogen SequaPrep, Qiagen SeqTarget system	Smaller target regions, coverage by tiling	Relatively easy to set up and automatable, even coverage	PCR conditions largely influence effectiveness, >10 µg DNA for Large sets	10^2 – 10^4 (0.1–5 Mb)	After enrichment
Multiplex	Multiplexon, Fluidigm	Smaller target regions, coverage by tiling, multiplex PCR of 150–200 amplicons (150–450 bp)	Easy to perform, reasonably economical in terms of, even coverage			
Micro droplet	RainDance	Smaller target regions, coverage by tiling, micro droplet PCR of up to 20 000 amplicons (150–1500 bp)	Even coverage, low input DNA	Relatively expensive, specialist equipment	10^2 – 10^4 (up to 10 Mb)	

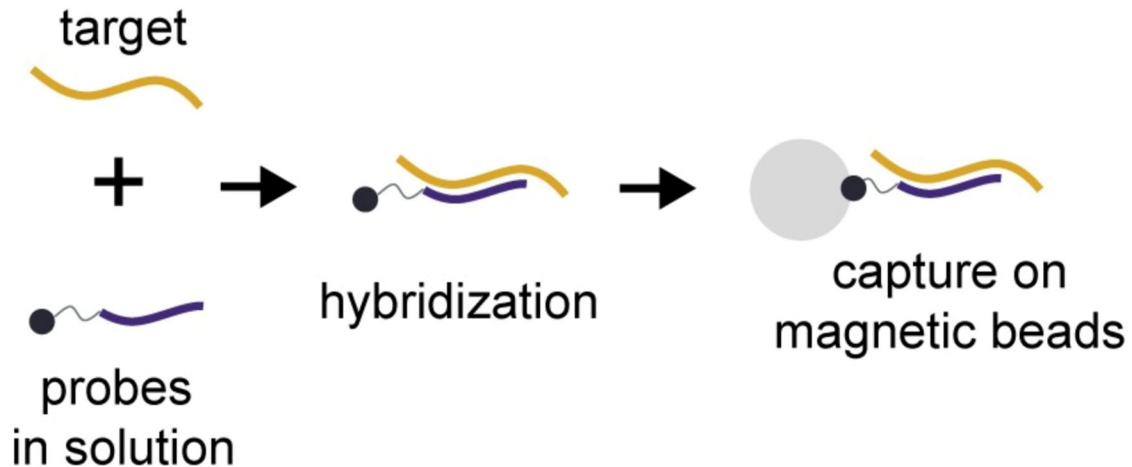
All major targeted enrichment techniques show relative pros and cons.

In PCR, DNA molecules are replicated in a manner that leverages the base pairing of complementary DNA strands. In PCR, strands of double-stranded DNA are first completely separated, leaving two complementary single-stranded DNA strands, which serve as templates for replication. PCR “primers” or “probes,” which are short oligonucleotides that are complementary to a small portion of the DNA templates, can then be created. These primers/probes then hybridize (i.e., bind through base pairing interactions) to, and thus “capture,” the target region of interest on the DNA template strand. After the PCR primer

hybridizes to that target sequence, an enzyme called a “polymerase” synthesizes a new nucleic acid molecule complementary to the single-stranded DNA template. This process can be repeated, resulting in the exponential amplification of the target sequence. *Id.* ¶¶71-76.



A POSA would also have been familiar with the use of solution-based hybridization techniques for target enrichment. In short, this technique works by mixing in solution the target DNA with an abundance of short nucleic acid “baits.” Like the primers in the PCR approach, these “baits” hybridize to the target DNA sequence of interest. The baits may also include an additional component, such as biotin, that binds to a magnetic bead following the hybridization step.



When such beads are mixed into the solution, the target sequence is captured through bead-probe binding, and the target DNA can be isolated by washing away the non-target, and hence unbound, DNA and then removing the beads and baits. These techniques were well-characterized and widely used well before the priority date, and a number of commercial vendors offered off the rack and on-demand solutions to implement this approach. *Id.* ¶¶77-79. *See also* Ex. 1005, Ex. 1006.

D. Personalized Biomedical Monitoring

Once “[w]hole-genome sequencing [became] possible at reasonable cost and timeframe,” *Ley* “use[d] this approach for the unbiased discovery of tumour-specific somatic mutations that alter the protein-coding genes.” *Id.* *Ley* established that a useful approach to cancer monitoring is to first fully characterize the patient’s tumor using whole-genome sequencing to identify polymorphisms of interest, and then serially monitor those polymorphisms to track the tumor over time. As Dr. Quackenbush explains, a POSA would have

appreciated that in *Ley's* approach, the results of the initial whole-genome sequencing step would help clinicians avoid “miss[ing] key mutations,” and allow them to create a specific set of probes to capture regions of interest harboring the identified mutations for further sequencing. Quackenbush ¶¶80-83. Shortly thereafter, *Leary* and *McBride* demonstrated the successful use of the same concept, using structural variants (as opposed to SNPs/SNVs in *Ley*) to serially monitor tumor DNA in the blood plasma of patients presenting with solid tumors. *Id.* ¶84. Those skilled in the art further developed ways to report the information obtained via such clinical protocols, and ways to leverage that information, for example by identifying appropriate clinical trials or targeted therapies. *Id.* ¶¶89-92.

Moreover, the use of whole-genome sequencing to develop targeted monitoring assays was not limited to cancer, because the fundamental properties of nucleic acids that enable this mode of analysis are universal. For example, by 2009, methods of analyzing nucleic acids to aid the diagnosis of transplant rejection had been developed. Ex. 1003. Those methods, similar to those applied in cancer surveillance, were based on the fact that a transplanted organ will have a different genetic fingerprint (a different genotype, coming from the organ donor) than the transplant recipient, and that once identified, that fingerprint may be used to detect transplant rejection by monitoring the levels of cell free DNA (cfDNA) observed in the transplant recipient's blood. The underlying science is

that the cfDNA will be a mix of DNA from the recipient and the donor and that the unique variants in the donor's DNA will allow that DNA to be detected. *See generally id.* ¶¶40-50, 69-70. *Quake* observed that such methods were analytically similar to those used to detect and monitor cancer. *Id.* ¶41. Following whole-genome sequencing, *Quake* explained that serial PCR or NGS assays could be employed to “detect, identify, and/or quantify” the donor specific markers in the transplant recipient following transplantation. *See id.* ¶¶47-48, 73-75; Quackenbush ¶¶85-88.

VII. KEY PRIOR ART

A. Ley

Ley is an article that was published in *Nature* by November 6, 2008. Ex. 1012; Quackenbush ¶98. *Ley* is therefore prior art to the '783 patent.

B. Forshew

Forshew is an article that was published on May 30, 2012 in *Science Translational Medicine*. Ex. 1030. Forshew is therefore prior art to the '783 patent. Quackenbush ¶99.

C. Dawson

Dawson is an article that was published in the *New England Journal of Medicine* on March 28, 2013. Ex. 1070. Dawson is therefore prior art to the '783 patent. Quackenbush ¶100.

VIII. GROUNDS FOR THE CHALLENGES

Petitioner challenges the claims of the '783 patent on the following grounds:

	Challenged Claims	Prior Art
1	1-2, 5-7, 9, 14-15, 17-19, 21, 23-25, 27	Anticipated (35 U.S.C. § 102(a)) by Ley (Ex. 1012)
2	1-9, 13-19, and 21-29	Obvious (35 U.S.C. § 103(a)) over Ley (Ex. 1012)
3	1-9, 13-19, and 21-29	Obvious (35 U.S.C. § 103(a)) over Forsheew (Ex. 1030) in view of Dawson Ex. (1070)

The references of the grounds were not previously considered by the Office during the prosecution of the '783 patent.

IX. CLAIM CONSTRUCTION

“[C]laim terms need only be construed ‘to the extent necessary to resolve the controversy.’” *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). Petitioner does not believe that any term requires express construction for purposes of this proceeding, and has applied the claims as a POSA would have understood them in view of Patent Owner’s application of the claims to Petitioner’s methods in the litigation, as explained for certain terms below.

While Petitioner and Dr. Quackenbush have identified claim 1, the claim containing the limitation requiring “generating a biomedical report,” in the prior art, this limitation is not entitled to patentable weight under the printed matter doctrine because it merely conveys information and is not functionally related to the substrate on which it is provided.

A. “probe”

The '783 patent explains that “probes” can be used, for example, in a hybridization array, by “synthesizing the plurality of nucleic acid probe molecules using at least one array” Ex. 1001 at 4:60-61; *see also id.* at 7:25-27 (probes include “synthesizing the plurality of nucleic acid probe molecules on a single solid substrate.”). The '783 patent also explains that “nucleic acid probe molecules comprise primers for amplifying the nucleic acid sequences.” *Id.* at 5:23-25. And again, the '783 patent states that “the plurality of nucleic acid probe molecules of the assay enrich or deplete a nucleic acid mixture of nucleic acid molecules for target regions, by hybridization or amplification.” *Id.* at 7:5-8. As Dr. Quackenbush explains, based on this intrinsic record, a POSA would have understood that the claimed “nucleic acid probe molecules” include PCR primers, hybrid capture baits, and other such nucleic acid probe molecules for selectively amplifying or enriching sequences. Quackenbush ¶¶95.

B. “report”

“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). The doctrine is not limited to content that is literally printed; the Federal Circuit holds that a “claim limitation is directed to printed matter ‘if it claims the content of information.’” *Id.* (citing *In re DiStefano*, 808 F.3d 845, 848 (Fed. Cir. 2015)).

Claim 1 recites “generating a report identifying” certain information, which may “inform a therapy choice or a change in therapy for the subject.” Thus, this claim element merely recites conveying information in a report, with no functional relationship to the substrate on which it is conveyed, so it is not entitled to patentable weight. *In re Ngai*, 367 F.3d 1336, 1339 (Fed. Cir. 2004) (“Ngai is entitled to patent his invention of a new RNA extraction method, and the claims covering that invention were properly allowed. He is not, however, entitled to patent a known product by simply attaching a set of instructions to that product.”).

It is appropriate for the Board to consider this issue on claim construction: “Because claim limitations directed to mental steps may attempt to capture informational content, they may be considered printed matter lacking patentable weight in an obviousness analysis.” *Praxair Distribution, Inc.*, 890 F.3d at 1033.

To the extent the limitation is entitled to patentable weight, Petitioner has applied the meaning of the term “report” would have had to a POSA in view of the '783 patent's specification. Figure 1 of the '783 patent, for example, is consistent with the plain meaning. It shows a therapeutic intervention, which can be a report, at the end of a process that includes personalized assays:

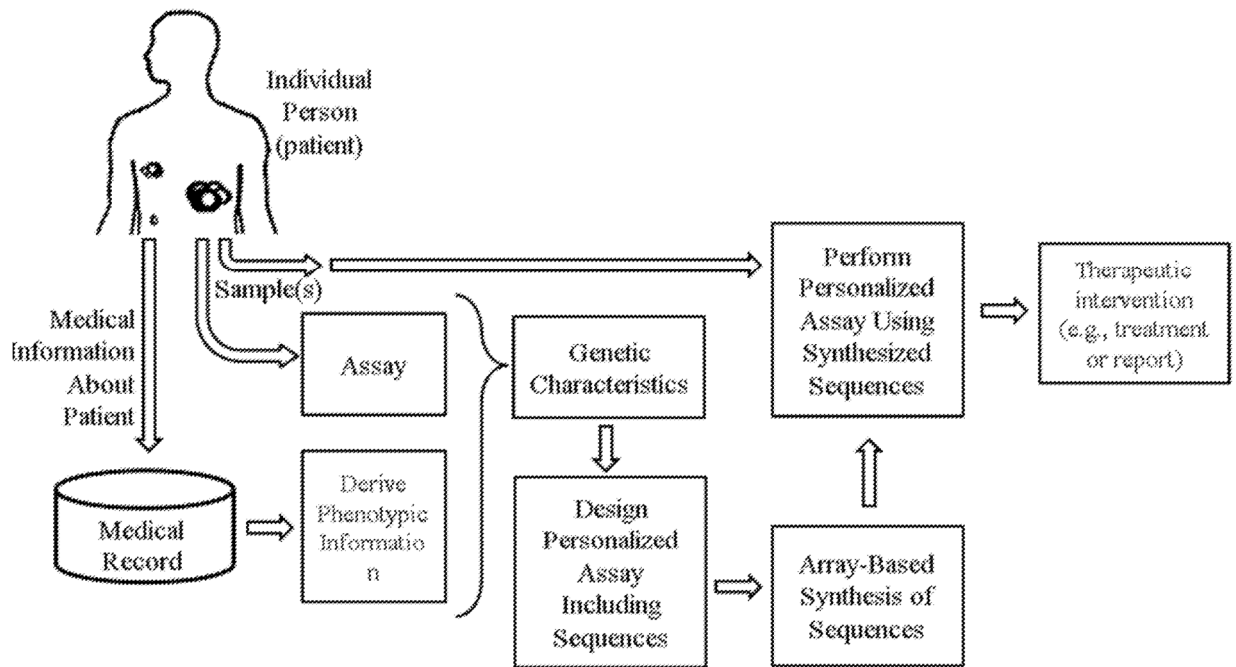


FIG. 1

The '783 patent also explains that “[s]ome embodiments comprise outputting a report that is indicative of a presence or absence of the at least the subset of the genetic variants in the subject or the at least one biological relative.” Ex. 1001 at 5:20-23. Thus, a POSA reading the specification of the '783 patent would have understood that the claimed “report” includes, for example,

providing information for treatment of a patient as well as providing an indication of genetic variation. *See* Quackenbush ¶¶96-97.

X. LISTING OF CHALLENGED CLAIMS

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 oligonucleotide-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.

2. The method of claim 1, wherein said at least one biological sample comprises a plurality of biological samples.

3. The method of claim 2, wherein said plurality of biological samples comprises a tissue sample and a plasma sample.

4. The method of claim 2, wherein the plurality of biological samples comprise: (i) cell-free deoxyribonucleic acid molecules (cfDNA), (ii) cell-free ribonucleic acid molecules (cfRNA), (iii) DNA or RNA from circulating tumor cells, or (iv) RNA or DNA from a tumor metastasis.

5. The method of claim 2, further comprising generating said sequence data of (a) from the plurality of biological samples.

6. The method of claim 1, wherein said sequence data of (a) comprises sequence information for at least an exome, a panel of genes, or a whole genome.

7. The method of claim 1, wherein identifying said presence or absence of a health condition or disease is based on a frequency of a genetic variant from said set of genetic variants.

8. The method of claim 1, wherein said additional biological sample of (c) is a blood sample.

9. The method of claim 1, wherein said health condition or disease is cancer.

13. The method of claim 1, further comprising repeating (b) and (c) one or more times and generating one or more additional reports.

14. The method of claim 1, wherein said at least one additional biological sample in (c) was obtained after said at least one biological sample in (a).

15. The method of claim 1, wherein said additional biological sample is a blood sample comprising: (i) cfDNA, (ii) cfRNA, (iii) DNA or RNA from circulating tumor cells, or (iv) RNA or DNA from a tumor metastasis.

16. The method of claim 1, wherein said additional biological sample and one or more subsequent biological samples are each blood samples comprising: (i) cfDNA, (ii) cfRNA, (iii) DNA or RNA from circulating tumor cells, or (iv) RNA or DNA from a tumor metastasis.

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

18. 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, (iii) genes involved in Mendelian immunological diseases, (iv) genes related to inherited forms of cancer, (v) genes associated with tumor escape from a targeted or immune cancer therapy, (vi) HLA typing, (vii) variants common in the population and used by B-allele methods to detect structural variation, and any combination thereof.

19. The method of claim 1, wherein said sequence data of (a) is derived from sequences of nucleic acids from said at least one biological sample, wherein said at least one biological sample comprises a tumor biopsy.

21. The method of claim 1, wherein said set of one or more genetic variants comprise one or more members selected from the group consisting of: (i) a single nucleotide polymorphism, (ii) an insertion or deletion, (iii) a copy number variation, and (iv) structural variation.

22. The method of claim 1, wherein said personalized probe set comprises hybrid capture probes.

23. The method of claim 1, wherein said set of genetic variants identified in sequence data are determined with respect to a reference.

24. The method of claim 1, further comprising, prior to (a), sequencing said least one biological sample to generate said sequencing data.

25. The method of claim 1, further comprising generating said personalized probe set for said subject based on said set of genetic variants identified in said sequence data for said at least one biological sample.

26. The method of claim 1, wherein (b) further comprises using said personalized probe set to selectively enrich or amplify sequences comprising said set of genetic variants over other sequences in a biological sample from another subject to generate said sequencing library.

27. The method of claim 1, wherein (c) further comprises identifying levels of gene expression, sequencing read counts, or read depth.

28. The method of claim 1, wherein said at least one additional biological sample comprises a plurality of additional samples obtained at different time points.

29. The method of claim 1, wherein the report of (d) further comprises reporting biomedical information of said subject that is predictive, prognostic, or diagnostic of one or more biomedical features selected from the group consisting of a disease state, efficacy of a drug therapy, prediction of optimal drug dosage, a recommendation of one or more therapies, and a recommendation of a course of treatment of a disease.

XI. THE BOARD SHOULD CANCEL THE CHALLENGED CLAIMS**A. Ground 1: Anticipation by Ley.**

As set forth below, and as explained by Dr. Quackenbush in paragraphs 101-178 of his declaration, claims 1-2, 5-7, 9, 14-15, 17-19, 21, 23-25, 27 are anticipated by *Ley*.

1. Claim 1

Claim 1 recites “A method for personalized genetic testing, comprising” enumerated steps (a) – (d). As discussed in detail below, *Ley* discloses each step.

Ley discloses a method of genetic testing that used “massively parallel sequencing technology to sequence the genomic DNA of tumour and normal skin cells obtained from a patient” with acute myeloid leukemia (AML). Ex. 1012 at 66. The genetic testing described in *Ley* was “personalized” given that the assay sequenced the patient’s tumor’s genome and compared “its matched normal counterpart obtained from the same patient’s skin.” *Id.* Through this personalized genetic testing, *Ley* “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....” *Id.* Quackenbush ¶¶102-104.

This method of personalized genetic testing includes each step of claim 1, as discussed below.

a) [1] obtaining a personalized probe set..., [2] wherein said plurality of nucleic acid probe molecules are configured to selectively enrich or amplify sequences..., [3] wherein said set of genetic variants are identified in sequence data for said at least one biological sample, [4] further wherein said personalized probe set comprises nucleic acid probe molecules having oligonucleotide-directed genomic content....

Ley discloses step 1(a) regarding “obtaining a personalized probe set for the subject” having a number of further-defined properties. Quackenbush ¶105. Ley’s “Methods Summary” explains the following workflow for its method of personalized genetic testing. Ex. 1012 at 71; Quackenbush ¶106.

The first part of this workflow involves whole-genome sequencing with the Illumina Genome Analyzer and Solexa sequencing platforms to identify variants of interest. Specifically, *Ley* describes “the use of whole-genome re-sequencing and variant discovery approaches using the Illumina/Solexa technology . . . to sequence a tumour genome of a single AML patient and the matched normal genome (derived from a skin biopsy) of the same patient.” Ex. 1012 at 67; Quackenbush ¶107.

Following whole-genome sequencing, and “[a]fter alignment to the human reference genome, sequence variants were discovered in the tumour genome and compared to the patient’s normal sequence, to the dbSNP database, and to variants recently reported for two other human genomes, revealing new single nucleotide and small insertion/deletion (indel) variants genome-wide.”

Ex. 1012 at 67. **Ley** explains that this approach detected somatic mutations “in genes not previously implicated in AML pathogenesis, demonstrating the need for unbiased whole-genome approaches to discover all mutations associated with cancer pathogenesis.” *Id.* **Ley** used a several methods to analyze and filter the sequencing results, and arrived at a set of non-synonymous mutations detected in the patient’s tumor sample comprising 8 SNVs and 2 insertion mutations for further analysis. *See id.* at 68-69, Table 2 (identifying mutations). Quackenbush ¶108.

Once the variants of interest, i.e., the “putative variants,” were identified, **Ley** then describes “validation using custom PCR and capillary sequencing” as well as sequencing of “validated somatic mutations” “by Roche/454 sequencing of PCR-generated amplicons made from primary genomic DNA....” Ex. 1012 at 71. Those skilled in the art would know that the creation of amplicons for sequencing necessarily involves the use of a probe set, specifically PCR primers directed to the validated somatic mutations. Quackenbush ¶109. In **Ley**, the probe set would thus necessarily include PCR primers that hybridize to the 10 non-synonymous (variable) mutations identified in the patient’s tumor (CDH24, SLC15A1, KNDC1, PTPRT, GRINL1B, GPR123, EB12, PCLKC, FLT3, NPM1) and the two fixed (control) mutations (BRCA2, TP53). *Id.*; *See* Ex. 1012 at 69.

Those skilled in the art would also understand that such PCR primers necessarily constitute nucleic acid molecules that are complementary to, and as a result hybridize to, the DNA sequences of the variant of interest. Moreover, by the nature of the PCR process, the resulting “amplicons” generated through PCR which are then sequenced on the Roche/454 platform in *Ley*’s workflow are amplified or enriched over the other sequences in the genome which are not targeted by the set of PCR primers. Quackenbush ¶110.

Subpart [1] of claimed step 1(a) is “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.” 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 consists of PCR primers, the probe set necessarily comprises a plurality of nucleic acid probe molecules having a plurality of nucleic acid sequences or complements thereof. Specifically, the PCR primers are by their nature relatively short nucleic acid sequences that are complementary to the variant DNA sequence they are intended to amplify. Quackenbush ¶¶111-112.

Subpart [2] of claimed step 1(a) is “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.” As discussed above, *Ley*’s nucleic acid probe molecules are PCR primers that are used to generate amplicons of the variants of interest for further sequencing. *Ley*’s use of such PCR primers to generate PCR amplicons necessarily involves amplifying those sequences over other sequences in the sample. Specifically, *Ley* uses its PCR primers to selectively amplify the 12 variants of interest over the other sequences present in the primary tumor, skin sample, and relapse tumor sample. *See, e.g.*, Ex. 1012 (*Ley*) at 69 (Fig. 3). Quackenbush ¶¶113-114.

Subpart [3] of claimed step 1(a) is “wherein said set of genetic variants are identified in sequence data for said at least one biological sample.” As discussed above, *Ley* used its initial whole-genome sequencing to identify 10 genetic mutations that are non-synonymous somatic mutations in the CDH24, SLC15A1, KNDC1, PTPRT, GRINL1B, GPR123, EB12, PCLKC, FLT3, and NPM1 genes. This involved analyzing the mutations detected in both the primary tumor and skin samples and then applying a filtering process. Ex. 1012 at 68-69. *Ley* also identified two “known” SNPs (genetic variants) in the BRCA2 and TP53 genes. *Id.* at 69. A POSA would understand that these two SNPs were “known” because they were previously identified in the literature from. *Id.* Quackenbush ¶116.

Accordingly, the variants ultimately included in *Ley's* probe set were identified in sequence data – namely whole genome sequence data – for at least one biological sample. *Ley* then explains that “[t]o better define the percentage of tumour cells that contained each of the discovered somatic mutations,” i.e., the somatic mutations identified using the whole-genome sequencing assay, “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.” Ex. 1012. at 69. A POSA would have immediately understood that the amplification of such sequences involves increasing the relative amount of the target DNA over the “non-amplified” genomic DNA present in the samples (each of the tumor samples and the skin sample). As discussed further below, “[t]he resulting amplicons were sequenced” *Id.*; Quackenbush ¶116. An “amplicon” refers to a nucleic acid sequence that is generated in abundance using PCR, and *Ley's* “Methods Summary” explains that these “discovered somatic mutations” “were further analysed by Roche/454 sequencing.” *Id.*; Ex. 1012 at 71.

Subpart [4] of claimed step 1(a) is “further wherein said personalized probe set comprises nucleic acid probe molecules having oligonucleotide-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.”

Ley's personalized probe set comprises nucleic acid probe molecules – specifically PCR primers – targeting mutation-containing regions in the 12 genes covered by *Ley's* panel of probes. Ex. 1012 at 69 (“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.”). Such PCR probes, by their nature, contain oligonucleotide-directed genomic content, specifically oligonucleotide sequences that base-pair or hybridize to their complementary sequences in each “mutation-containing locus.” *Id.*; Quackenbush ¶118.

With respect to the claimed requirement [4](i), the oligonucleotide-directed genomic content in *Ley's* PCR primers comprises the claimed “variable portion from a result of said sequence data.” Specifically, *Ley* discloses including primers for the non-synonymous somatic mutations detected in the AML sample. This part of *Ley's* panel is “variable...from a result of said sequence data” at least because “eight [of ten] somatic mutations that [Ley] detected are all single base changes, *and none has previously been detected in an AML genome.*” Ex. 1012 at 70; *see also id.* at 69-71 (“We cannot overemphasize the importance of parallel sequencing of the patient’s normal genome to determine which variants were inherited; the identification of the true

somatic mutations in this tumour genome would not have been feasible without this approach.”). Quackenbush ¶119.

With respect to the claimed requirement [4](ii), the oligonucleotide-directed genomic content of Ley’s PCR primers also comprises “at least one fixed portion independent of said result of said sequencing data.” For example, *Ley* discloses including primers for known mutations of the *BRCA2* and *TP53* genes. “The *BRCA2* variant is a known heterozygous SNP in this genome, and the *TP53* variant is a known homozygous SNP.” Ex. 1012 at 70 (Table 3, caption); *see also id.* at 69 (“Control amplicons containing a *known* heterozygous SNP in *BRCA2*...and a homozygous SNP in *TP53*...were analyzed similarly.”). The inclusion of these PCR primers was based on known genetic variants, which were known in the literature and to the authors prior to the whole-genome sequencing step, reflected by the selection of these variants because they contained “known” SNPs. Quackenbush ¶120; Exs. 1073-1074 (*TP53*); Ex. 1076 (*BRCA2*). Thus, these PCR primers constitute “fixed” probes independent of the variable probes that are selected and designed based on the identity of the patient-specific SNPs and other mutations identified via whole-genome sequencing of the patient’s tumor genome. Quackenbush ¶120.

b) “using said personalized probe set to selectively enrich or amplify sequences ...”

Ley discloses using the PCR probes described above, to “amplif[y] each mutation-containing locus from non-amplified DNA derived from the *de novo* and relapse tumour samples, and from the skin biopsy obtained at presentation.” Ex. 1012 at 69. By amplifying the mutation-containing loci from non-amplified DNA, *Ley* thus discloses the amplification of such sequences over the other (non-amplified) sequences in a biological sample. Because *Ley* amplifies the loci of interest in (i) primary tumor; (ii) skin biopsy at presentation; and (iii) relapse tumour, *Ley* discloses the use of the personalized probe set in at least an additional biological sample, i.e., the relapse tumour and the skin biopsy. The PCR amplicons are used to generate the claimed sequencing library: “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).” *Id.* at 69. Thus, *Ley* discloses all parts of step 1(b). Quackenbush ¶121.

c) “subjecting said sequencing library to sequencing...”

Sequencing the library created by amplifying the relapsed tumour sample with the set of PCR primers identified the presence or absence of the genetic variants included in *Ley*’s panel of genetic variants. Ex. 1012 at 6. The presence of the genetic variants in the multiple samples is depicted in *Ley*’s Figure 3,

which shows the relative frequency of each given variant in each sample based on the results of the sequencing assay. Quackenbush ¶122.

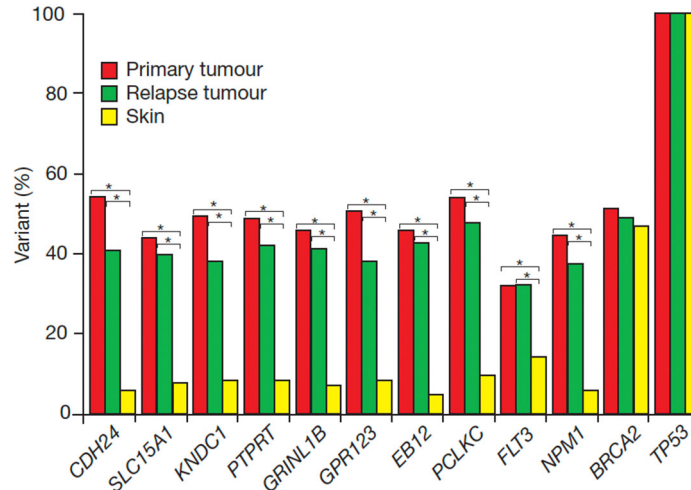


Figure 3 | Summary of Roche/454 FLX readcount data obtained for ten somatic mutations and two validated SNPs in the primary tumour, relapse tumour and skin specimens. The readcount data for the variant alleles in the primary tumour sample and relapse tumour sample are statistically different from that 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.

As Dr. Quackenbush explains, in *Ley's* method, “a sequencing footprint of said sequencing of (c) is less than a sequencing footprint of said sequence data of (a).” Quackenbush ¶123. In *Ley's* Table 3, the panel of ten genes analyzed with the targeted resequencing approach were genes from which an exon containing a genetic variant were identified in the initial whole-genome sequencing assay. In the resequencing assay, these ten variants were targeted, to the exclusion of the other genetic material analyzed in the initial whole-genome sequencing step. 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 rather than the genome in its entirety. *Id.* Dr. Quackenbush analyzed the sequences for these exons, and concluded that even if every exon of every identified gene were to be sequenced, the sequence would only cover 45,254 bases. Thus, the sequencing footprint is far less than the ~3 billion bases sequenced in Ley's whole-genome sequencing step. Quackenbush ¶124.

d) “generating a report....”

Ley further discloses generating a report that shows the presence or absence of a health condition or disease of the subject in the relapsed tumor sample. The Ley publication itself is a detailed analysis of sequencing data obtained from the AML patient whose genome was subject to whole genome sequencing. Ley discloses generating a report, for example, through tabular summary of results. Specifically, Ley's Table 1 is a table summarizing various results of sequencing including reported information at least based on comparison of results from said sequencing of (a) (e.g., “Runs” of “Tumour” and “Skin” samples) with results from at least said subjecting said sequencing library to said sequencing of (c) (e.g., “SNVs detected with respect to hg18 (no Y)” for “Tumor” and “Skin” samples). *Id.* at 68. Quackenbush ¶125.

Ley's Figure 3 also provides a report depicting, *inter alia*, sequence information regarding the relative abundance of particular somatic mutations that were observed in samples taken at (i) primary onset, and (ii) relapse. Ex.

1012 at 69. These abundances are compared to the frequency of the same polymorphic alleles present in the skin sample, which represents a control. Quackenbush ¶126.

Ley's report also discloses genetic variants which inform a therapy choice or a change in therapy for the subject. 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 (e.g., Figure 3), 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. Quackenbush ¶127.

Ley's Supplementary Information, Ex. 1042 provides a detailed case report and provides detailed information about a number of the various mutations that had been detected in the patient's cancer genome. The germline and somatic genetic variants detected in the patient are linked by *Ley* to the diagnosis of AML. *Ley* also presents the clinical and therapeutic implication of mutations in the SCL29A1 gene. “Biallelic mutations in SCL29A1 that result in a lack of detectable protein recently have been associated with cytarabine resistance in a human leukemia cell line, implicating SLC family members in chemotherapy resistance for AML.” *Id.* One skilled in the art would recognize

that cytarabine is a chemotherapy drug use in the treatment of AML and that the presence of the SCL29A1 would inform an oncologist that the use of this drug was contraindicated. Quackenbush ¶129.

Further, one skilled in the art would know that the characteristics of the disease and the patient's positive mutational in the FLT3 and NMP1 would contraindicate the use of allogenic stem cell transplant for this patient. *See* Ex. 1075 (“all adults with AML under age 60 years ... should be considered for allogeneic transplantation ... ***except for*** those with favorable risk cytogenetics and possibly those whose disease has normal cytogenetics and is FLT3/ITD negative and NPM1 positive.”). Quackenbush ¶130-131.

2. Claim 2

Claim 2 recites, “The method of claim 1, wherein said at least one biological sample comprises a plurality of biological samples.”

Ley performs its methods on at least the primary tumor sample, the relapse tumor sample, and the skin biopsy sample. *See, e.g.,* Ex. 1012, Fig. 3. Quackenbush ¶¶132-134.

3. Claim 5

Claim 5 recites, “The method of claim 2, further comprising generating said sequence data of (a) from the plurality of biological samples.”

As discussed above, Ley generates the sequence data of (a) through analysis of both the primary tumor sample and the skin biopsy sample (germline

DNA) using whole-genome sequencing. *See also* Ex. 1072 (Patent Owner contending that this claim is met in Petitioner's methods because "[t]he Foresight Diagnostics Solid Tumor Recurrence test utilizes both tumor biopsy as well as germline DNA in order to identify genetic variants for monitoring."). Quackenbush ¶¶135-137.

4. Claim 6

Claim 6 recites, "The method of claim 1, wherein said sequence data of (a) comprises sequence information for at least an exome, a panel of genes, or a whole genome."

As explained above with respect to claim 1, Ley's "sequence data of (a)" is sequence information from whole genome sequencing. Quackenbush ¶¶138-140.

5. Claim 7

Claim 7 recites, "The method of claim 1, wherein identifying said presence or absence of a health condition or disease is based on a frequency of a genetic variant from said set of genetic variants."

Ley's Table 3 shows the detection and quantification of variant genes in both primary tumor and relapsed tumor, as well as non-tumor (skin) tissue. Identifying the presence or absence of a health condition or disease (i.e., cancerous cells in a sample) is based on the frequency of one or more genetic variants from the set of variants. For example, the 10 non-synonymous mutations

are detected in tumor samples but not in the skin. The “control” BRCA2 and TP53 variants are detected at their expected levels in both tumor and normal tissues. Quackenbush ¶¶141-143.

6. Claim 9

Claim 9 recites, “The method of claim 1, wherein said health condition or disease is cancer.”

The health condition or disease addressed by *Ley* is acute myeloid leukemia, which is a form of cancer. Quackenbush ¶¶144-146.

7. Claim 14

Claim 14 recites, “The method of claim 1, wherein said at least one additional biological sample in (c) was obtained after said at least one biological sample in (a).”

The relapse tumor sample that is subjected to targeted resequencing in step 1(c) in *Ley* was necessarily obtained after the primary tumor sample that was subjected to whole-genome sequencing in step 1(a). Quackenbush ¶¶147-149.

8. Claim 15

Claim 15 recites, “The method of claim 1, wherein said additional biological sample is a blood sample comprising: (i) cfDNA, (ii) cfRNA, (iii) DNA or RNA from circulating tumor cells, or (iv) RNA or DNA from a tumor metastasis.”

The additional biological sample – *Ley*’s relapse tumor sample – necessarily contains both RNA and DNA from a tumor metastasis. Quackenbush ¶¶150-152.

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.

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.

11. Claim 19

Claim 19 recites, “The method of claim 1, wherein said sequence data of (a) is derived from sequences of nucleic acids from said at least one biological sample, wherein said at least one biological sample comprises a tumor biopsy.”

As discussed above, *Ley’s* initial whole-genome sequencing data is derived from sequences of nucleic acids taken from a primary tumor sample, i.e., a tumor biopsy. Quackenbush ¶¶159-161.

12. Claim 21

Claim 21 recites, “The method of claim 1, wherein said set of one or more genetic variants comprise one or more members selected from the group consisting of: (i) a single nucleotide polymorphism, (ii) an insertion or deletion....”

The genetic variants analyzed in *Ley’s* panel include at least SNPs and insertion or deletions. *See, e.g.*, Ex. 1012 at 69. A POSA would understand that a missense mutation, such as those listed in *Ley’s* Table 2, is a SNP that results in a non-synonymous mutation, meaning that it would change the protein encoded by the SNP-containing gene and potentially altering its function. Quackenbush ¶¶162-164.

13. Claim 23

Claim 23 recites, “The method of claim 1, wherein said set of genetic variants identified in sequence data are determined with respect to a reference.”

Ley discloses comparing the sequence data from the primary tumor sample to a sequenced skin sample, which constitutes a reference. *See* Ex. 1012 at 68-69. **Ley** also describes comparing the sequence data to other references, such as previously described human genomes. *Id.*; *see also id.* at 67 (“To begin evaluating the quantity and quality of the detected sequence variants in the tumour and skin genomes, we compared the overlap and uniqueness of this genome’s variants with respect to the James D. Watson and J. Craig Venter genomes, and to dbSNP.”). Quackenbush ¶¶165-167.

14. Claim 24

Claim 24 recites, “The method of claim 1, further comprising, prior to (a), sequencing said least one biological sample to generate said sequencing data.”

As explained above, **Ley** discloses performing whole-genome sequencing on the primary tumor sample prior to step 1(a) in order to generate said sequencing data. Quackenbush ¶¶168-170.

15. Claim 25

Claim 25 recites, “The method of claim 1, further comprising, generating said personalized probe set for said subject based on said set of genetic variants identified in said sequence data for said at least one biological sample.”

As discussed above, the personalized probe set disclosed in **Ley** is based on the sequencing data identified in the primary tumor using whole-genome sequencing. Specifically, **Ley** discloses including primers for the non-

synonymous somatic mutations detected in the AML sample. This part of *Ley's* panel is “variable . . . from a result of said sequence data” at least because “eight [of ten] somatic mutations that [Ley] detected are all single base changes, *and none has previously been detected in an AML genome.*” Ex. 1012 at 70. *See also id.* at 69 (“To better define the percentage of tumour cells that contained each of the discovered somatic mutations....”); *id.* at 71 (“[T]he identification of the true somatic mutations in this tumour genome would not have been possible without this approach.”). Quackenbush ¶¶171-173.

16. Claim 27

Claim 27 recites, “The method of claim 1, wherein (c) further comprises identifying levels of gene expression, sequencing read counts, or read depth.”

Ley's Tables 2 and disclose identifying sequencing read counts for each of the variants. Ex. 1012 at 69-70 (annotated below).

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*
<i>CDH24</i>	Y590X	Nonsense	9:9	16:0	0.998	0/187
<i>SLC15A1</i>	W77X	Nonsense	15:12	19:0	1.000	0/187
<i>KNDC1</i>	L799F	Missense	7:8	20:0	NA	0/187
<i>PTPRT</i>	P1235L	Missense	9:13	16:0	1.000	0/187
<i>GRINL1B</i>	R176H	Missense	15:10	14:0	NA	0/187
<i>GPR123</i>	T38I	Missense	11:11	13:0	NA	0/187
<i>EBI2</i>	A338V	Missense	7:12	18:2	1.000	0/187
<i>PCLKC</i>	P1004L	Missense	19:9	15:1	0.98	0/187
<i>FLT3</i>	ITD	Indel	18:12	8:0	NA	51/185
<i>NPM1</i>	CATG ins	Indel	36:6	33:0	NA	43/180

Ins, insertion; WT, wild type.

* Patient cohort defined in ref. 23.

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

Ley also discloses further identifying levels of gene expression in both the primary and relapse tumor samples. Specifically, *Ley* states “seven of the ten genes containing somatic mutations were detectably expressed in the tumour sample... We detected mRNA from the *CDH24*, *SIC15A1* and *EBI2* genes on the Affymetrix expression array, whereas expression of *GRINL1B* and *PCLKC* were detected by PCR with reverse transcription (RT-PCR; data not shown).” Ex. 1012 (*Ley*) at 70. Quackenbush ¶¶174-177.

B. Ground 2: Obviousness Over Ley

All Challenged Claims are obvious over *Ley* in view of the knowledge of a POSA. The obviousness analysis of the Challenged Claims incorporates by reference the anticipation analysis of *Ley* as to the claims addressed in Ground 1. A POSA would also have found the Challenged Claims obvious for the additional reasons set forth below.

1. Claim 1

In light of a POSA's knowledge as of the May 2016 priority date of the Challenged Claims, at least the following additional modifications to *Ley* would have been obvious.

First, a POSA would have found it obvious to apply *Ley's* approach to a variety of cancers other than the specific example of AML discussed in *Ley*. Indeed, such approaches were widely used before the priority date. Quackenbush ¶180; Exs. 1002, 1015, 1031.

In applying *Ley's* methods to AML and other cancers, the following additional modifications would have been obvious:

Step 1(a) – “fixed portion”: In addition to the PCR probes comprising the fixed portion already included in *Ley's* panel, 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 ¶¶181-182.

As Dr. Quackenbush explains, many effective cancer therapies are targeted to particular genetic mutations that are present in certain forms of cancer. Examples include the blockbuster drug Herceptin targeting HER2 positive breast cancer (i.e., forms of breast cancer carrying mutations in the HER2 gene), which was first introduced in 1998. *See* Ex. 1014 at 527 (“During

the ensuing 12 years, interest in these ‘drug-test’ combinations, also referred to as ‘companion diagnostics,’ has increased exponentially as more anticancer agents have been approved and more new drugs have entered clinical trials based on biomarker profiles.”). Quackenbush ¶183.

Relatedly, the identity of therapy/cancer pairs would have been readily ascertainable by one skilled in the art by accessing the treatment guidelines for a particular cancer promulgated by the National Comprehensive Cancer Network (called the NCCN Guidelines) which are widely used by oncologists to reference and define standard of care treatments. Similar information would have also been available from the FDA-approved prescribing information available for relevant drugs. To design a probe for relevant mutations identified in this manner, a POSA would have been able to determine the relevant sequence information from any one of the publicly available cancer databases, such as COSMIC, and then designed nucleic acid probes based on the techniques already known in the art and applied in the methods expressly disclosed by *Ley*. Accordingly, a POSA would have reasonably expected success in the predictable use of known information (regarding the sequences) and known techniques (the creation of nucleic acid probes to target such sequences) to add “fixed” probes to assays such as *Ley’s* in order to provide information relevant to the selection and response to mutation-specific therapy pairings. Quackenbush ¶184.

Additionally, as discussed above, a POSA would have been familiar with known mutations common in certain forms of cancer, which are recorded in databases based on population-level studies. Applying PCR-based or capture-based targeting approaches to such mutations using nucleic acid probe molecules was known and discussed by *Ley*: “[H]ypothesis-driven (for example, candidate gene-based) examination of tumour genomes by PCR-directed or capture-based methods is inherently limited, and will miss key mutations.” Ex. 1012 at 70. A POSA would have been motivated to combine candidate gene-based probes (fixed portion) in a panel with patient specific mutations discussed above (variable portion) in order to assess the cancer for known mutations in well-characterized and studied candidate genes in addition to patient-specific mutations. For example, as noted above, in many instances such genes may drive the course of the cancer and may be key targets for therapy. Further, such a combination of fixed and variable probes would overcome the limitations identified by *Ley* of a purely hypothesis-driven (fixed probe-only) approach. Quackenbush ¶185.

Based on the knowledge of cancer biology gained between *Ley’s* publication and the priority date, a POSA would have known that one reason a targeted approach may miss such mutations is because of tumor heterogeneity. Tumor heterogeneity refers to the fact that genetic variants present in a cancer are not always uniformly dispersed across a tumor spatially, and that certain key

variants may not be present in the tumor at all times during the cancer's progression. *See, e.g.*, Ex. 1071 (Burrell) at 338. As a result, it would have been obvious to include probes for selectively enriching such hotspot mutations (i.e., the claimed fixed probes) in the panel in order to detect in subsequent samples the mutations previously identified via the WGS assay, but also mutations that were known to be common in the patient's type of cancer. A POSA would have been motivated to monitor hotspot mutations for a particular cancer (i.e., the fixed probes) even in cases where they may not have been identified at the time of initial presentation or at the time of an initial whole-genome sequencing assay, as such mutations may present later in the course of the patient's cancer. Quackenbush ¶186.

A POSA would have been able to readily create probes for such mutations using already known techniques. Indeed, *Ley* already recognized that such probes were well-known in the art, and thus would have reasonably expected success in including such "fixed" probes in a cancer-monitoring panel. Further, such fixed probes would selectively amplify sequences comprising genetic variants in exactly the same way as *Ley's* variable probes selectively amplified sequences comprising patient-specific genetic variants. Quackenbush ¶187.

Step 1(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 POSA would have also found it obvious, based on the results of the genetic testing methods disclosed and rendered obvious by *Ley*, to generate a report identifying a presence or absence of a health condition based on the results of assaying a particular sample, and to identify genetic variants that inform a therapy choice or change in therapy for the subject. As an initial matter, although *Ley* expressly discloses testing biological samples at the onset of cancer and in a relapsed tumor, one skilled in the art would have found it obvious to perform *Ley’s* assays at multiple timepoints throughout the progression of the cancer in order to understand the course of the disease. Doing so would have involved only performing the tests on samples taken at different time points, and was successfully performed in multiple other studies that followed *Ley* and preceded the priority date. Quackenbush ¶188.

As explained in the anticipation ground above, *Ley’s* Supplementary Information, Ex. 1042 provides a detailed case report and provides detailed information about a number of the various mutations that had been detected in the patient’s cancer genome, including how reports on such information would have informed therapy choices (such as the contraindication of stem cell transplant for AML patients with FLT3 and NMP1 mutations). Quackenbush ¶¶189-191.

Moreover, a POSA would have known that an important aspect of reporting the results of cancer-monitoring assays is providing actionable information to healthcare providers. Thus, a POSA would have been motivated to generate “a result report that is focused on the abnormalities that can lead directly to the best available therapy, direct a patient to an ongoing clinical trial, or result in some other actionable response from the treating oncologist.” Ex. 1014 at 537. *Ley*’s Figure 3 is an example of such a result report which shows the presence or absence of a health condition at different time points over the course of the patient’s cancer, and it would have been obvious to report similar information at each time point for which a sample was collected and analyzed in *Ley*’s assays as well as in assays that were obvious variants of those disclosed in *Ley*. Moreover, it would have been obvious to identify genetic variants which inform a therapy choice or change in therapy in such a report, in particular in instances in which the panel of genetic variants included probes designed to detect and quantify genes associated with a companion therapeutic, as discussed above. Quackenbush ¶192.

For these reasons, in addition to anticipating claim 1, *Ley* in view of the knowledge of a POSA would have also rendered obvious additional variations of *Ley*’s methods. Quackenbush ¶193.

2. Claim 2

Claim 2 recites, “The method of claim 1, wherein said at least one biological sample comprises a plurality of biological samples.”

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 two or more biological samples 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, including in prior art reports. Exs. 1002, 1015, 1031. Quackenbush ¶¶194-196.

3. Claim 3

Claim 3 recites, “The method of claim 2, wherein said plurality of biological samples comprises a tissue sample and a plasma sample.”

Ley discloses collecting samples from tissue samples, specifically a tumour sample. Ex. 1012 at 69. Additionally, 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. Quackenbush ¶198. 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. Quackenbush ¶¶197-199.

4. Claim 4

Claim 4 recites, “The method of claim 2, wherein the plurality of biological samples comprise: (i) cell-free deoxyribonucleic acid molecules (cfDNA), (ii) cell-free ribonucleic acid molecules (cfRNA), (iii) DNA or RNA from circulating tumor cells, or (iv) RNA or DNA from a tumor metastasis.”

As noted above, it would have been obvious to specifically monitor cell free DNA in a plasma sample in *Ley's* methods. Moreover, in metastasized cancer, where the cancer has spread to multiple parts of the body, a POSA would have found it obvious to take biopsies from tumors located in different locations. As a result, it also would have been obvious in view of *Ley* to take biological samples that would thus necessarily include RNA or DNA from a tumor metastasis. Quackenbush ¶¶200-202.

5. Claim 8

Claim 8 recites, “The method of claim 1, wherein said additional biological sample of (c) is a blood sample.” *Ley* discloses collecting samples from tissue samples, specifically a tumor sample. Ex. 1012 at 69. 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. 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 recognize that a plasma sample is a type of blood sample, and would have reasonably expected success in applying *Ley’s* methods to plasma samples 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. Quackenbush ¶¶203-205.

6. Claim 13

Claim 13 recites, “The method of claim 1, further comprising repeating (b) and (c) one or more times and generating one or more additional reports.”

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 two or more biological samples following the initial sample for analysis and sequencing using *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. *See* Exs. 1002, 1015, 1031. Quackenbush ¶¶206-208.

7. Claim 14

Claim 14 recites, "The method of claim 1, wherein said at least one additional biological sample in (c) was obtained after said at least one biological sample in (a)."

As explained above, *Ley* anticipates claim 14. Moreover, when performing the methods rendered obvious by *Ley* to serially monitor a patient's cancer at 3 or more time points, the additional biological samples will necessarily be obtained after the initial biological sample, to monitor the cancer's progression. Quackenbush ¶¶209-211.

8. Claim 15

Claim 15 recites, "The method of claim 1, wherein said additional biological sample is a blood sample comprising: (i) cfDNA, (ii) cfRNA, (iii) DNA or RNA from circulating tumor cells, or (iv) RNA or DNA from a tumor metastasis."

As noted above for claims 2 and 3, it would have been obvious to specifically monitor cell free DNA in a plasma sample in *Ley's* methods. Moreover, the presence of components like cfDNA, cfRNA, and circulating tumor nucleic acids is an inherent result of cancer biology, and such substances will necessarily be present in the blood and blood plasma of cancer patients. Additionally, in metastasized cancer, where the cancer has spread to multiple parts of the body, a POSA would have found it obvious to take biopsies from tumors located in different locations. Accordingly, it also would have been obvious in view of *Ley* to take biological samples that would thus necessarily include RNA or DNA from a tumor metastasis. Quackenbush ¶212-215

9. Claim 16

Claim 16 recites, “The method of claim 1, wherein said additional biological sample and one or more subsequent biological samples are each blood samples comprising: (i) cfDNA, (ii) cfRNA, (iii) DNA or RNA from circulating tumor cells, or (iv) RNA or DNA from a tumor metastasis.”

As discussed above for claims 2, 3, and 15, it would have been obvious to specifically monitor cell free DNA in a plasma sample in *Ley's* methods, and the presence of components like cfDNA, cfRNA, and circulating tumor nucleic acids is an inherent result of cancer biology, so such substances will necessarily be present in the blood and blood plasma of cancer patients.

Additionally, in metastasized cancer, where the cancer has spread to multiple parts of the body, a POSA would have found it obvious to take biopsies from tumors located in different locations. Accordingly, it also would have been obvious in view of *Ley* to take biological samples that would thus necessarily include RNA or DNA from a tumor metastasis. Quackenbush ¶¶216-219.

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.

11. Claim 22

Claim 22 recites, “The method of claim 1, wherein said personalized probe set comprises hybrid capture probes.”

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. As Dr. Quackenbush explains, 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 they were well-known to be useful on a relatively interchangeable basis in many experimental protocols, and could also be used together as complements to one another. *See* Ex. 1006 at 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, 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. *Id.* at 379. Quackenbush ¶224. Moreover, the ’783 patent’s specification confirms that those skilled in the art considered these techniques to be interchangeable in many applications as of the priority date. Ex. 1001 at 29:4-22. Quackenbush ¶¶223-226.

12. Claim 26

Claim 26 recites, “The method of claim 1, wherein (b) further comprises using said personalized probe set to selectively enrich or amplify sequences comprising said set of genetic variants over other sequences in a biological sample from another subject to generate said sequencing library.”

As Dr. Quackenbush explains, applications of similar sequencing technologies were known to those skilled in the art to be applicable to the monitoring of cell-free DNA in various contexts, including organ transplant rejection and prenatal diagnostics. In those scenarios, when there are foreign cells present in the body those cells release into the blood stream cell free DNA with its own signature. In the context of a cancer patient that was also pregnant or the recipient of an organ transplant, a POSA would have found it obvious to selectively enrich or amplify sequences comprising the genetic variants of the patient's cancer over other sequences that may be present in the sample from another subject – such as circulating fetal DNA or organ donor-derived DNA – in order to generate the sequencing library. A POSA would have been motivated to select sequences unique to the tumor, as opposed to the foreign DNA from a fetus or donor organ, in order to precisely monitor the cancer over other medical issues of concern. Quackenbush ¶¶227-229.

13. Claim 28

Claim 28 recites, “The method of claim 1, wherein said at least one additional biological sample comprises a plurality of additional samples obtained at different time points.”

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 *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*, other studies disclosed the use of genetic variants identified in whole-genome sequencing assays as targets for serial monitoring of tumor DNA in the blood plasma of patients with solid tumors at multiple (e.g., 6) time points. Quackenbush ¶¶230-232.

14. Claim 29

Claim 29 recites, "The method of claim 1, wherein the report of (d) further comprises reporting biomedical information of said subject that is predictive, prognostic, or diagnostic of one or more biomedical features selected from the group consisting of a disease state, efficacy of a drug therapy, prediction of optimal drug dosage, a recommendation of one or more therapies, and a recommendation of a course of treatment of a disease."

As Dr. Quackenbush explains, a POSA would have found it obvious to, based on the results of the genetic testing in methods disclosed and rendered obvious by *Ley*, generate a report identifying a presence or absence of a health condition based on the results of assaying a particular sample, and to identify

genetic variants that inform a therapy choice or change in therapy for the subject.

In light of *Ley's* teachings, one skilled in the art would have found it obvious to perform *Ley's* assays at multiple timepoints throughout the progression of the cancer in order to understand the course of the disease. Doing so would have involved only performing the tests at samples taken at different time points, and was successfully performed in multiple other studies that followed *Ley* and preceded the priority date. Quackenbush ¶234.

Since an important aspect of reporting the results of cancer-monitoring assays is providing actionable information to healthcare providers, a POSA would have been motivated to generate “a result report that is focused on the abnormalities that can lead directly to the best available therapy, direct a patient to an ongoing clinical trial, or result in some other actionable response from the treating oncologist.” Ex. 1014 at 537. *Ley's* Figure 3 is an example of such a result report which shows the presence or absence of a health condition at different time points over the course of the patient's cancer, and it would have been obvious to report similar information at each time point for which a sample was collected and analyzed in assays that were obvious variants of those disclosed in *Ley*. Moreover, it would have been obvious to identify genetic variants which inform a therapy choice or change in therapy in such a report, in particular in instances in which the panel of genetic variants included probes designed to detect and quantify genes associated with a companion therapeutic,

as discussed above. Such a report would therefore necessarily provide information relating to at least the claimed “a recommendation of one or more therapies, and a recommendation of a course of treatment of a disease.” Quackenbush ¶¶233-236.

C. Ground 3: Obviousness Over Forshew in view of Dawson

As Dr. Quackenbush explains in paragraphs 237-344 of his declaration, all Challenged Claims are obvious over *Forshew* in view of *Dawson*.

1. Claim 1

Forshew in view of *Dawson* renders obvious each step of claim 1 by teaching to analyze multiple nucleic acid samples isolated from an individual by using its personalized genetic testing methods “to monitor tumor dynamics, and tracked 10 concomitant mutations in plasma of a metastatic breast cancer patient over 16 months.” Ex. 1030 at Abstract. This method “could facilitate analysis of circulating DNA as a noninvasive ‘liquid biopsy’ for personalized cancer genomics.” *Id.* Quackenbush ¶¶237-238.

a) Claim 1, step (a)

Forshew discloses step 1(a), “obtaining a personalized probe set for the subject” having a number of further-defined properties. The following overview of *Forshew* is applicable to each subpart of step 1(a). Quackenbush ¶239.

Forshew describes a method of serial monitoring of a patient’s cancer using a technique it refers to as “TAm-Seq.” *Forshew* explains that “TAm-Seq

can be flexibly adapted to sequence different genomic regions by designing primers to amplify regions of interest. We used this capability to study dynamics of multiple mutations in parallel.” Ex. 1030 at 8. In one exemplary usage of its techniques, *Forshew* explained that “[w]hole-genome sequencing of tumor material was used to identify tumor mutations in a patient with metastatic breast cancer undergoing two phases of chemotherapy,” and that “[s]erial plasma samples were collected over the course of 497 days, both before and after treatment” to “track[] dynamics of all mutations in parallel” using its TAM-Seq method. *Id.* at 9; Quackenbush ¶240.

Forshew discloses producing a plurality of PCR primers (also referred to as PCR probes), wherein the plurality of PCR probes hybridize to a plurality of genetic variants in a sample to amplify or enrich them over other sequences in the sample. For example, *Forshew* “designed primers to generate amplicons that tile[d] regions of interest in short segments of 150 to 200 bases....” Ex. 1030 at 2-3. Quackenbush ¶241. *Forshew* designed its probes using known techniques, including the use of computer software and reference to the COSMIC database. *Id.* ¶¶241-242.

Forshew also discloses the design and use of a set of probes in the form of PCR primers that hybridize to and amplify a plurality of variants (polymorphisms) in sequences encoding genes associated with cancer. For example, *Forshew* designed the PCR primers to hybridize to selected coding

sequences in genes that include mutations with known associations with cancers.

Ex. 1030 at 3. ***Forshaw*** states that “[w]e designed a set of 48 primer pairs to amplify 5995 bases of genomic sequence covering coding regions (exons and exon junctions) of *TP53* and *PTEN*, and selected regions of *EGFR*, *BRAF*, *KRAS*, and *PIK3CA* (table S1) by overlapping short amplicons (Fig. 1A).” The genes selected by ***Forshaw***, namely *TP53*, *PTEN*, *EGFR*, *BRAF*, *KRAS* and *PIK3CA*, were genes with known biomedically interpretable variants. Indeed, Forshaw notes that “[t]he sequenced regions cover mutations that account for 38% of all point mutations in the COSMIC database (v55) (32).” Ex. 1030 at 3. Quackenbush ¶243.¹

In addition, ***Forshaw*** also discloses generating such PCR probes based on whole-genome sequencing data. Ex. 1030 at 9 (“Whole-genome sequencing of tumor material was used to identify tumor mutations in a patient with metastatic breast cancer....”). Quackenbush ¶245. Accordingly, ***Forshaw*** discloses producing a set of PCR probes (primers) that hybridize to a plurality of genetic variants based on criteria including the use of known genetic variants as well as

¹ As Dr. Quackenbush explains, mutations logged in databases such as COSMIC were obtained, identified, and catalogued by observation in the wide variety of reports in the scientific literature concerning cancer mutations. Quackenbush ¶244.

via an initial sequencing step to determine personalized variants present in the tumor. *Id.* ¶246.

Subpart [1] of step 1(a) is “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.” *Forshew’s* methods include obtaining a plurality of personalized PCR probes, which are nucleic acid molecules that have complementary sequences to those identified in the patient. In one example, *Forshew* performed “[w]hole-genome sequencing of tumor material” “to identify tumor mutations in a patient with metastatic breast cancer.” Ex. 1030 at 9. From this sequence data, “[t]en mutations were selected, and short amplicons (<120 bp) were designed to cover the mutation loci.” *Id.* These amplicons were tracked using *Forshew’s* “TAm-Seq” process, which requires the creation of PCR probes to the genetic loci to generate the amplicons for sequencing. Thus, *Forshew* discloses or renders obvious this requirement of step 1(a). Quackenbush ¶¶247-248.

Subpart [2] of claimed step 1(a) is “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.” The PCR probes used in *Forshew’s* TAm-Seq process are configured to amplify the sequences containing the genetic variants of interest over other sequences present in the sample. As *Forshew*

explains, “[u]sing standard amplification primers tailored to the mutation loci, we [] used TAm-Seq to monitor the dynamics of 10 mutations in plasma DNA of a single patient with metastatic breast cancer, using minute amounts of input DNA.” Ex. 1030 at 10. The use of such “amplification primers” to generate amplicons necessarily involves amplifying the mutated sequences over other sequences present in the sample. Quackenbush ¶¶249-250.

Subpart [3] of claimed step 1(a) is “wherein said set of genetic variants are identified in sequence data for said at least one biological sample.” The genetic variants for which *Forshew* designed its TAm-Seq primers were identified in sequence data for at least one biological sample. Specifically, “[w]hole-genome sequencing of tumor material was used to identify tumor mutations in a patient,” “[t]en mutations were selected,” “[s]erial plasma samples were collected ... both before and after treatment,” and the TAm-Seq process was “performed ... in duplicate,” which “tracked dynamics of all mutations in parallel.” Ex. 1030 at 9. Accordingly, the ten mutations *Forshew* tracked are variants that were identified in the whole-genome sequencing data for at least one biological sample. Quackenbush ¶¶251-252.

Subpart [4] of claimed step 1(a) is “further wherein said personalized probe set comprises nucleic acid probe molecules having oligonucleotide-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.” A POSA would understand that *Forshe*w’s PCR primers (probes) are nucleic acid molecules having oligonucleotide-directed genomic content, i.e., sequences that are designed to bind or hybridize to nucleic acids in a sample having a complementary sequence. Quackenbush ¶¶253-254.

*Forshe*w expressly discloses the use of a variable portion from a result of the whole-genome sequencing data. Specifically, in the breast cancer patient whose cancer was tracked using TAm-Seq, 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 at 9 (“[w]hole-genome sequencing of tumor material was used to identify tumor mutations in a patient,” and “[t]en mutations were selected.”). Quackenbush ¶255.

Though *Forshe*w does not expressly disclose including PCR primers (probes) for sequences or markers that constitute a fixed portion in the breast cancer patient, it would have been obvious to include such probes in *Forshe*w’s panel for such a patient. Indeed, *Forshe*w discloses including such probes, for example, in the context of ovarian cancers where “mutations in the tumor suppressor gene *TP53* have been observed in 97% of cases.” Ex. 1030 at 1. *Forshe*w thus developed “[a] cost-effective method that could detect and measure allele frequency (AF) of *TP53* mutations in plasma” which may be “highly applicable as a biomarker.” *Id.* *Forshe*w discloses including in its set of probes or primers “primer pairs to amplify 5995 basis of genomic sequence

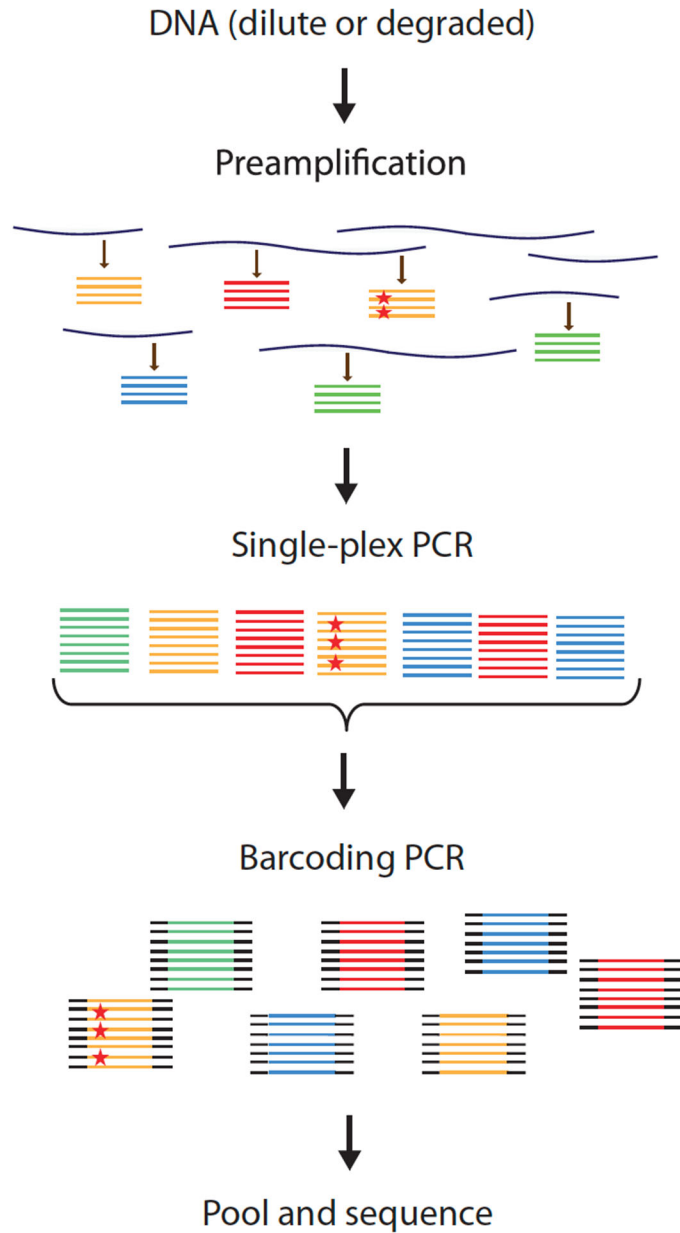
covering coding regions (exons and exon junctions) of *TP53*,” among multiple other genes. *Id.* at 3. Thus, ***Forshew*** discloses including probes for variants in *TP53* independent of any prior sequencing data in its other assays. Including such additional probes in addition to sequence-based probes in a single panel would require nothing more than the predictable use of techniques used in other examples of the very same reference. Quackenbush ¶256.

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 at 1207. ***Dawson*** further describes applying the TAM-Seq technique to detect variants of *TP53* in breast cancer patients. *Id.* Quackenbush ¶257. 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 light of ***Forshew’s*** disclosure, the design of such probes was known, and would have involved only routine skill in the art and the application of the exact techniques disclosed in the article, and which were applied to *TP53* variants in breast cancer in ***Dawson***. Accordingly, a POSA would have had a reasonable expectation of success in monitoring *TP53* using probes designed independent of ***Forshew’s*** whole-genome sequencing data given that it would simply involve the use of the techniques already disclosed in a related context. Quackenbush ¶258.

b) “using said personalized probe set to selectively enrich or amplify sequences ...;”

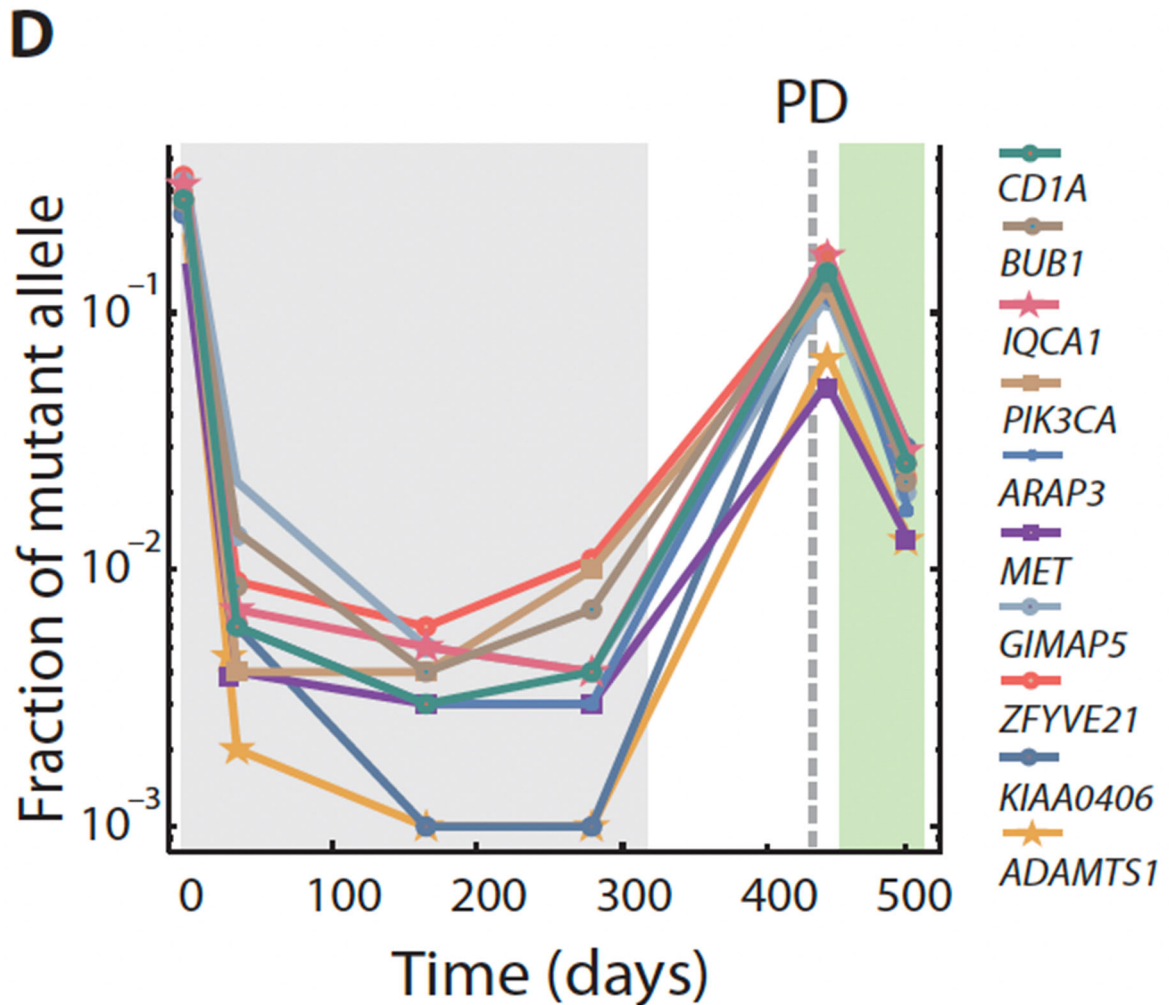
*Forshe***w’s** TAm-Seq process involves using the personalized probe set to selectively enrich or amplify the selected genetic variants over other sequences in at least an additional biological sample from the subject. Specifically, Forshe**w** discloses using its methods to “track[] dynamics of all mutations” in “[s]erial plasma samples [] collected over the course of 497 days, both before and after treatment.” Ex. 1030 at 9. In *Forshe***w’s** workflow, the primers are used to amplify the sequences of interest, before they are barcoded and pooled into a sequencing library (before a sequencing step). *See id.* at 2. Quackenbush ¶259.

B



**c) “subjecting said sequencing library to sequencing
...”**

As noted above, the sequencing library created in the preceding step 1(b) is then subjected to sequencing to identify the presence or absence of the genetic variants in multiple plasma samples over time. This is shown in Figure 4D, which is reproduced below. Quackenbush ¶260.

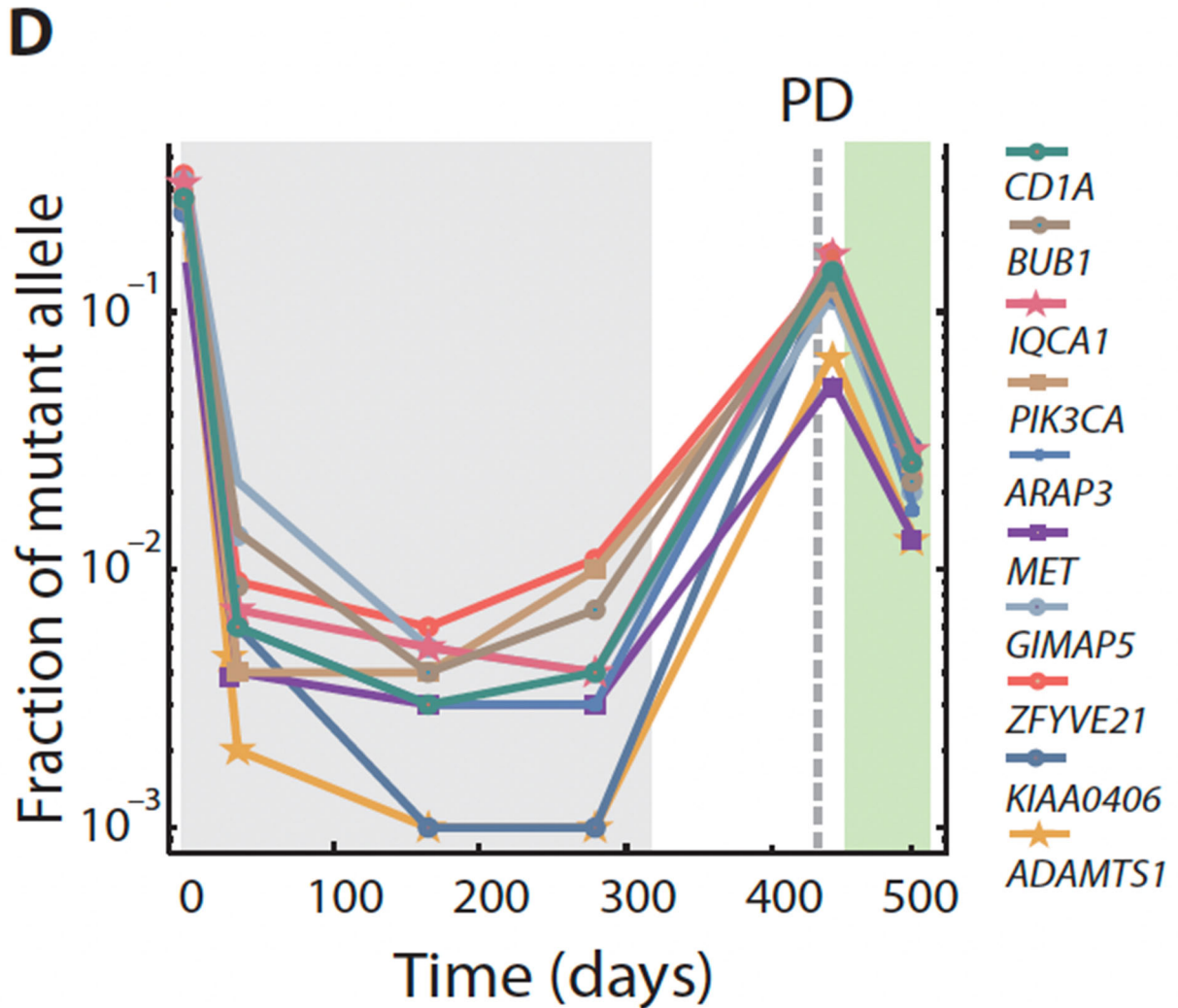


A POSA would have understood that the sequencing footprint of the targeted sequencing of 10 variant alleles (or even 11 with the addition of *TP53* probes according to the combination of *Forshe* and *Dawson*) will necessarily be less than the sequencing footprint of the whole-genome sequencing upon which the sequence data of step 1(a) is based. Quackenbush ¶261.

In *Forshew'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 at 4-5. Quackenbush ¶262.

d) “generating a report....”

Forshew further discloses generating a report that shows the presence or absence of a health condition or disease of the subject based on multiple plasma samples over time which inform a therapy choice or change in therapy for the subject. Specifically, Figure 4D shows a report depicting the fraction of the various mutant alleles over time, including in response to therapy (grey box). Quackenbush ¶¶263-264.



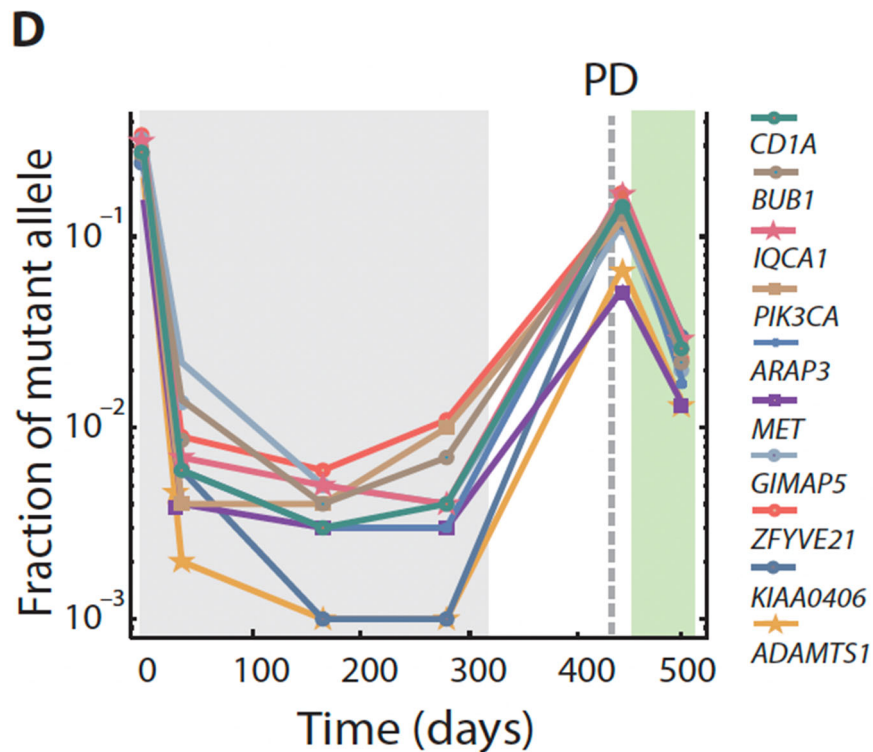
Notably, *Forshe*’s Figure 4D “tracked dynamics of all mutations” analyzed with TAm-seq, including over the course of chemotherapy treatment *Id.* at 9. “The 10 mutations followed a common pattern of sharp decline in AF [allele fraction] upon onset of therapy and an increase in AF upon disease progression after termination of therapy.” *Id.* Thus, *Forshe*’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. Quackenbush ¶¶265-266.

Accordingly, *Forshaw* in view of *Dawson* renders obvious claim 1.

2. Claim 2

As discussed above, *Forshaw* discloses analyzing plasma samples taken at multiple time points over the course of nearly 500 days. *See* Ex. 1030 (at 7. Quackenbush ¶¶267-269.



3. Claim 3

As explained above, *Forshaw* discloses that the plurality of samples comprise a tissue sample and a plasma sample. *See* Ex. 1030 at 9. Quackenbush ¶¶270-272.

4. Claim 4

Forsheew discloses collecting plasma samples in “a patient with metastatic breast cancer.” Ex. 1030 at 9. Such plasma samples necessarily include circulating cell-free DNA, RNA, and RNA or DNA from a tumor metastasis that was shed into the bloodstream. Quackenbush ¶¶273-275.

5. Claim 5

As explained above, *Forsheew* describes performing whole-genome sequencing on a tissue biopsy from a breast cancer patient. A POSA would have understood that to identify patient-specific mutations from whole-genome sequencing data, a standard practice is to take as an additional biological sample a control or normal tissue sample on which to perform whole-genome sequencing to provide a comparator for identifying tumor mutations. A POSA would recognize that this is almost certainly how *Forsheew’s* experiment was performed, and by comparing whole-genome sequencing data for the tumor sample with normal tissue, sequence data identifying mutations of interest can be generated. Quackenbush ¶277. As Dr. Quackenbush explains, *Ley* illustrates this standard practice. *Id.* ¶278-¶279.

6. Claim 6

As explained above, the sequence data of (a) in *Forsheew* is from a whole genome. Quackenbush ¶280-282.

7. Claim 7

*Forshe*w explains that identifying the presence or absence of the patient's cancer is based on monitoring the allele fraction of the genetic variants over time: "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 (Fig. 4D)." Ex. 1030 at 9. Quackenbush ¶¶283-285.

8. Claim 8

As discussed above, *Forshe*w discloses taking multiple additional biological samples over time. The samples taken in *Forshe*w are plasma samples, which are blood samples. Quackenbush ¶¶286-288.

9. Claim 9

The health condition or disease addressed by *Forshe*w is breast cancer. Quackenbush ¶¶289-291.

10. Claim 13

As explained above, *Forshe*w discloses repeating steps (b) and (c) multiple times on multiple plasma samples in order to track allele fraction over time. In Figure 4D, *Forshe*w provides a report of all the data monitored over the course of its study. A POSA would have found it obvious to generate such a report at each time point, adding the subsequently obtained information at each additional time point following data collection. Quackenbush ¶¶292-294.

11. Claim 14

Forsheiw's Figure 4D shows that multiple additional biological samples are obtained at multiple time points following the initial sample over the course of nearly 500 days. Quackenbush ¶¶295-297.

12. Claim 15

Forsheiw discloses collecting multiple plasma samples in “a patient with metastatic breast cancer.” Ex. 1030 at 9. Such plasma samples necessarily include circulating cell-free DNA, RNA, and RNA or DNA from a tumor metastasis that was shed into the bloodstream. Quackenbush ¶¶298-300.

13. Claim 16

Forsheiw discloses collecting multiple plasma samples in “a patient with metastatic breast cancer.” Ex. 1030 at 9. Such plasma samples necessarily include circulating cell-free DNA, RNA, and RNA or DNA from a tumor metastasis that was shed into the bloodstream. Quackenbush ¶¶301-303.

14. Claim 17

The fixed portion of *Forsheiw* in view of *Dawson* comprises probes for *TP53*. As discussed above, *TP53* is known to be a mutate variant tumor suppressor gene present in breast cancers. Quackenbush ¶¶304-306.

15. Claim 18

As discussed above, *TP53* genes included in the fixed panel rendered obvious by Forsheiw in view of Dawson constitute cancer driver genes (through

presence or absence of tumor suppression) and are genes related to inherited forms of cancer. Quackenbush ¶¶307-309.

16. Claim 19

As discussed above, *Forshe*'s initial whole-genome sequencing data is derived from sequences of nucleic acids taken from a tumor sample, i.e., a tumor biopsy. Quackenbush ¶¶310-312.

17. Claim 21

Given the types of mutations monitored in *Forshe* (which include SNPs) a POSA would have found it obvious to include probes for variants constituting SNPs, insertions or deletions, or structure variations, given that those represent the most common types of cancer mutations. Indeed, multiple other prior art references monitor such types of variations using similar assays. Quackenbush ¶¶313-315.

18. Claim 22

Forshe 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, including that such techniques 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 (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 *Forshew* in view of *Dawson* 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, 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 *Forshew*’s methods and the variations thereof discussed in this section. Quackenbush ¶317. This is consistent with the ’783 patent’s description of the knowledge of the art. *Id.* ¶318; Ex. 1001 at 29:4-22. Quackenbush ¶¶316-319.

19. Claim 23

As explained above, *Forshew* describes performing whole-genome sequencing on a tissue biopsy from a breast cancer patient. Although not expressly disclosed in *Forshew*, a POSA would have found it obvious to take as an additional biological sample a control or normal tissue sample on which to perform whole-genome sequencing in order to provide a comparator (or reference) for identifying tumor mutations. By comparing whole-genome sequencing data for the tumor sample with normal tissue, sequence data identifying mutations of interest can be generated. As Dr. Quackenbush explains, *Ley* confirms that this was standard practice. Quackenbush ¶¶320-323.

20. Claim 24

As explained above, *Forshe* discloses performing whole-genome sequencing on the primary tumor sample prior to step 1(a) to generate said sequencing data. Quackenbush ¶¶324-326.

21. Claim 25

As discussed above, the personalized probe set disclosed in *Forshe* is based on the sequencing data identified in the primary tumor using whole-genome sequencing. Specifically, *Forshe* discloses including primers for the mutations identified based on the whole-genome sequencing of the breast cancer patient's tumor. Quackenbush ¶¶327-329.

22. Claim 26

As explained with respect to Claim 26 in Ground 2 above, applications of similar sequencing technologies were known to those skilled in the art to be applicable to the monitoring of cell-free DNA in various contexts, including organ transplant rejection and prenatal diagnostics. A POSA would have been motivated to select sequences unique to the tumor, as opposed to the foreign DNA from a fetus or donor organ, in order to precisely monitor the cancer over other medical issues of concern in situations in which such a patient was afflicted with cancer. Quackenbush ¶¶330-332.

23. Claim 27

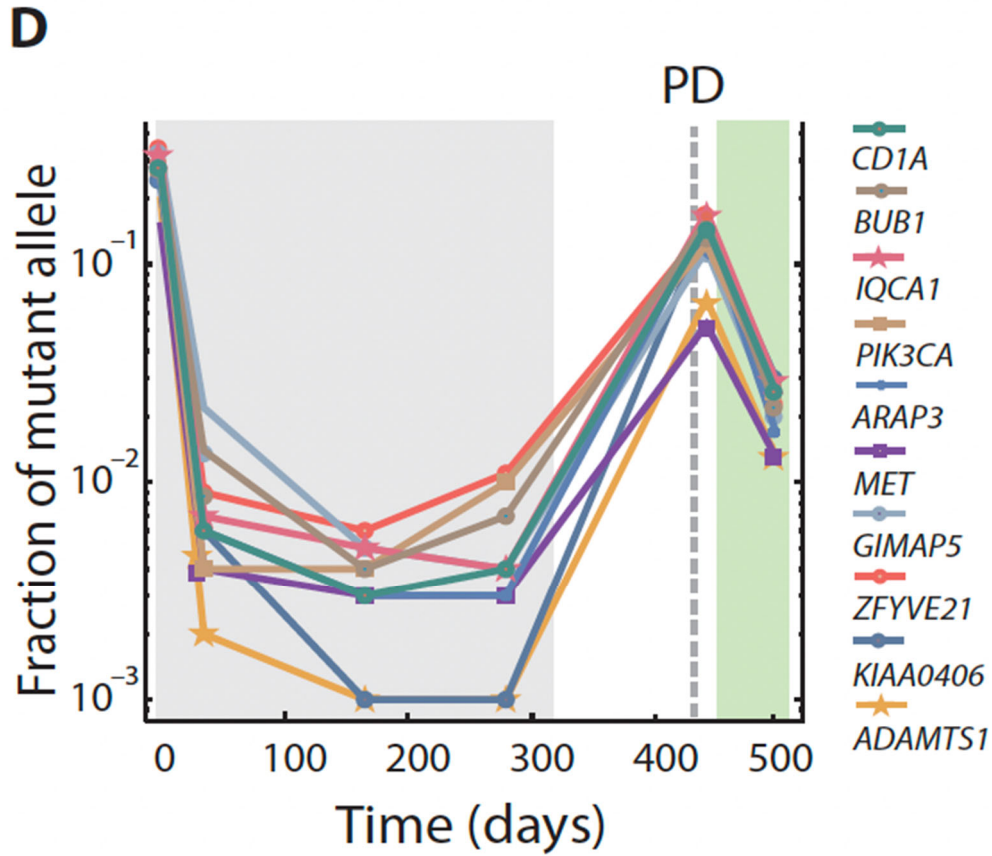
ForsheW renders obvious identifying sequencing read counts and read depth. For example, *ForsheW* explains that to detect mutations at lower frequencies, a higher number of sequencing read counts, and thus a greater read depth, should be utilized. Ex. 1030 at 3. Quackenbush ¶¶333-335.

24. Claim 28

As explained above, the additional biological samples in *ForsheW* comprise multiple plasma samples taken at multiple additional time points over the course of nearly 500 days following the initial sample collection and analysis. See Ex. 1030 at 7. Quackenbush ¶¶336-338.

25. Claim 29

The report of (d) disclosed in ForsheW's Figure 4(d) provides information regarding the fraction of mutant alleles over time, including during the time period when the patient is receiving therapy (gray box).



Thus, the report provided in Forsheew is at least prognostic and/or diagnostic regarding the efficacy of a drug therapy. Specifically, Forsheew shows where the therapy is working (reduction in allele fraction) and also provides information regarding the time point at which the cancer appears to begin resisting the therapy, where the allele fraction begins to increase near day 300. Quackenbush ¶¶339-342.

XII. CONCLUSION

Petitioner respectfully submits that the Board should institute IPR and cancel the Challenged Claims.

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

Dated: February 10, 2023

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

I hereby certify, pursuant to 37 C.F.R. § 42.24, that the petition contains 13,784 words, excluding the words in the table of contents, exhibit list, claim listing, mandatory notices under § 42.8, this certificate of word count, and the certificate of service. The word count is based on the word count of the Microsoft Word program used to prepare the petition.

Dated: February 10, 2023

Respectfully submitted,

/ Andrew E. Krause /
Andrew E. Krause

CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. sections 42.6 and 42.105, that a complete copy of the Petition for *Inter Partes* Review of U.S. Patent No. 11,299,783 and Exhibits 1001-1010, 1012-1020, 1023-1031, 1040-1059 and 1070-1078 are being served via Express Mail on February 10, 2023, the same day as the filing of the above-identified documents in the United States Patent and Trademark Office/Patent Trial and Appeal Board, upon the patent prosecution counsel of record for the Patent Owner:

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