UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS INC.,

Petitioner,

v.

PERSONALIS, INC.,

Patent Owner.

IPR2023-00546
U.S. Patent No. 10,450,611

SUR-REPLY TO PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,450,611

PATENT OWNER'S EXHIBIT LIST

Exhibit No.	Description
2001	The Scientist Staff, "2022 Top 10 Innovations," Dec. 12, 2022, available at https://www.the-scientist.com/features/2022-top-10-innovations-70792
2002	Swanton, C., "Plasma-Derived Tumor DNA Analysis at Whole-Genome Resolution," Clinical Chemistry 59:1 6-8 (2013)
2003	K.C. Allen Chan et al., "Cancer Genome Scanning in Plasma: Detection of Tumor-Associated Copy Number Aberrations, Single-Nucleotide Variants, and Tumoral Heterogeneity by Massively Parallel Sequencing," Clinical Chemistry (2013)
2004	Exemplary Embodying Product Claim Chart for U.S. Patent No. 10,450,611
2005	Tim Forshew, et al., "Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA," Science Translational Medicine (2012)
2006	Matthew W. Anderson & Iris Schrijver, "Next Generation DNA Sequencing and the Future of Genomic Medicine," *Genes* (2010)
2007	Dennis Lo, "Cancer Genome Scanning in Plasma, Clinical Chemistry Journal," Jan. 3, 2013 https://www.aacc.org/science-and-research/clinicalchemistry/clinical-chemistry-podcasts/2013/cancer-genomescanning-in-plasma-detection-of-tumor-associated-copynumber-aberrations

I. "PERSONALIZED GENETIC TESTING"

Petitioner Foresight Diagnostic Inc.'s ("Petitioner") does not dispute in its reply that the preamble "personalized genetic testing" is limiting, and instead contends that "the Petition establishes that the prior art's methods are 'personalized' under any reasonable understanding of the term." Pet. Reply at 1. For the reasons explained below and in Patent Owner's preliminary patent owner response, neither prior art reference discloses a method for personalized genetic testing.

A. Ley

Ley does not disclose a method for ***personalized*** genetic ***testing***. Rather, Ley discloses two distinct sets of experiments conducted for the purpose of ***discovering*** mutations that are responsible for initiation and pathogenesis of AML and other types of cancer across ***entire patient populations***. *See* POPR 9-10 (collecting cites); *id.* 20-21 (same); *see also* Ex. 1012 at 66 ("Our study establishes whole-genome sequencing as an unbiased ***method for discovering cancer-initiating mutations in previously unidentified genes that may respond to targeted therapies***). First, Ley describes a series of experiments that resulted in the discovery of 8 new genes with mutations that the authors hypothesized are responsible for AML in the general patient population. Second, Ley describes a distinctly separate experiment used to validate these results. There is no indication in Ley that these distinct teachings should be or may be combined together as a method for personalized testing rather

than just a collection of separate experiments for ***identifying*** and validating new mutations responsible for a specific type of cancer. *See NetMoneyIN, Inc., v. Verisign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008) ("Thus, it is not enough that the prior art reference discloses part of the claimed invention, which an ordinary artisan might supplement to make the whole, ***or that it includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention***").

The fact that one step of Ley's whole-genome sequencing protocol involved comparing a patient's tumor genome to "its matched normal counterpart obtained from the same patient's skin" does not make the protocol of Ley a method for personalized genetic testing. Ex. 1012 at 66. That is because this step is conducted to filter out the inherited mutations and identify only the somatic mutations; nothing in Ley's tumor-normal whole-genome sequencing protocol is personalized or customized to the particular patient being sequenced. *See* POPR at 20-21.

Furthermore, this does not reflect an intent to ***test*** this individual's personalized genetic profile, but rather to ***discover*** mutations that might correlate to a ***typical*** patient's AML, and to also demonstrate the whole-genome sequencing protocol as broadly applicable to AML and other cancers. Ex. 1012 at 67. In contrast, the claimed invention describes "personalized genetic testing," as using initial information gathered on an individual subject to design probes for ***subsequent testing*** that is "better focused on the ***personal characteristics of the subject***" and

"can yield information ***on the subject*** which is either more insightful, or less expensive, or both." Ex. 1001 at 28:16-27. Importantly, the whole-genome sequencing protocol ***is*** the focus in Ley and is not performed for the purpose of informing the design of the distinctly separate, targeted (amplicon) sequencing protocol Ley uses to validate the whole-genome sequencing results. Ley views the latter as ancillary to the whole-genome sequencing protocol. *See, e.g.,* Ex. 1012 at 70 ("Hence, these results justify the use of next-generation ***whole-genome sequencing approaches*** to reveal somatic mutations in cancer genomes.").

A POSA therefore would not have understood Ley as advocating for personalized testing when its express purpose was to use non-personalized, whole-genome sequencing to identify new candidate genes responsible for AML in the general patient population.

B. Newman

Newman does not disclose a method for personalized genetic testing. Rather, Newman discloses a series of protocols designed to develop and validate an iDES-enhanced method of CAPP-Seq; neither the original CAPP-Seq method nor the iDES-enhanced method in Newman rely on patient-specific capture panels. Ex. 1043 at 547 ("We recently described CAPP-Seq as an approach for highly sensitive quantitation of ctDNA ***in most patients with a given cancer type without the need for patient-specific optimizations***."); *id.* at 554. A POSA, reading Newman, would

only be motivated to use the non-personalized, iDES-enhanced CAPP-Seq protocol as a method to profile specific cancers across a patient population through deep sequencing. Nowhere does Newman describe the use of its so-called "personalized" selector for personalized genetic ***testing***, but rather only for ***validation*** of the iDES-enhanced CAPP-Seq protocol using a single, hypermutated tumor sample in a dilution series. *See, e.g.*, *id.* at 551 ("***To establish the detection limit of iDES-enhanced CAPP-Seq***, we designed a 'personalized' selector covering 1,502 nonsynonymous mutations identified by exome sequencing of a glioblastoma multiforme (GBM) tumor."). There would be no reason, and Petitioner has not provided one, why a POSA reading Newman would repeat the validation experiment, let alone use it for personalized genetic testing. Indeed, the validation experiment already "establish[ed] the detection limit" of the iDES-enhanced CAPP-Seq method proposed by Newman, so there would be no reason to repeat it. *Id*.

Petitioner contends that "the fact that a method that interrogates the genetic signature of an individual may also provide information useful on a more general level (such as to understand population-level cancer genetics)" does not "mean that such methods are not 'personalized.'" Pet. Reply at 4-5. But the specification requires that the personalized genetic testing use the initial information gathered to design probes for ***subsequent testing*** that are "better focused on the ***personal characteristics of the subject***" and "can yield information ***on the subject*** which is

either more insightful, or less expensive, or both." *See, e.g.*, Ex. 1001 at 28:16-27. In contrast, Newman's ***sole*** purpose is "to understand population-level cancer genetics." Pet. Reply at 4-5.

Further, Petitioner posits the existence of other supposed motivations for Newman's validation experiment. However, these alleged ulterior motives are neither mentioned nor alluded to within the four corners of the document; the only motivation articulated by Newman for the validation experiment was to establish the detection limit of the iDES-enhanced CAPP-Seq method. Finally, Petitioner's bald-faced assertion that the use of probes tailored to a particular patient "even a single time…is sufficient to invalidate the claims" flies in the face of Federal Circuit precedent. *NetMoney IN*, 545 F.3d at 1269 ("This statement… does not tell the whole story. ***Because the hallmark of anticipation is prior invention***, the prior art reference—in order to anticipate under 35 U.S.C. § 102—***must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements "arranged as in the claim***."). Therefore, Newman does not disclose a method for personalized genetic testing.

Respectfully submitted,

WEIL, GOTSHAL AND MANGES LLP

Dated: June 16, 2023

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 et seq., the undersigned certifies that this document complies with the word count limitation of 37 C.F.R. § 42.24(c)(4) because the sur-reply contains 1095 words, excluding the cover page, signature block, and the parts of the sur-reply exempted by 37 C.F.R. § 42.24(c).

Respectfully submitted,

WEIL, GOTSHAL AND MANGES LLP

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PATENT OWNER'S SUR-REPLY TO PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 10,450,611** is being served on June 16, 2023, via email pursuant to 37 C.F.R. § 42.6(e) to counsel for Foresight Diagnostics, Inc., at the addresses below:

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