

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORESIGHT DIAGNOSTICS INC.,

Petitioner,

v.

PERSONALIS, INC.,

Patent Owner.

IPR2023-00224

U.S. Patent No. 11,384,394

**PATENT OWNER'S SUR-REPLY TO PETITION FOR *INTER PARTES*
REVIEW OF U.S. PATENT NO. 11,384,394**

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

PATENT OWNER'S UPDATED 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	Raphael, B., et al., “Identifying driver mutations in sequenced cancer genomes: computational approaches to enable precision medicine,” <i>Genome Medicine</i> 2014, 6:5
2003	Swanton, C., “Plasma-Derived Tumor DNA Analysis at Whole-Genome Resolution,” <i>Clinical Chemistry</i> 59:1 6-8 (2013)
2004	Excerpt from U.S. Patent Appl. No. 14/810,337 prosecution history
2005	Excerpt from U.S. Patent Appl. No. 15/996,215 prosecution history
2006	Mardis, E., et al., “Cancer genome sequencing: a review,” <i>Human Molecular Genetics</i> , 2009, Vol. 18, Review Issue 2
2007	Declaration of Dr. Henry Morrice Furneaux
2008	Feldman, A., et al., “Discovery of recurrent t(6;7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genomic sequencing,” <i>Blood</i> , January, 20 2011 Volume 117, Number 3
2009	Murphy, S., et al., “Mate Pair Sequencing of Whole-Genome-Amplified DNA Following Laser Capture Microdissection of Prostate Cancer,” <i>DNA Research</i> 19, 395–406, (2012)
2010	<i>Curriculum Vitae</i> of Dr. Henry Morrice Furneaux
2011	“Whole Genome Sequencing,” NIH National Cancer Institution, Genetics Dictionary, available at https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/whole-genome-sequencing (last accessed Mar. 23, 2023)
2012	Embodying Product Claim Chart for U.S. Patent No. 11,384,394
2013	“Whole Genome Sequencing,” Centers for Disease Control and Prevention, available at https://www.cdc.gov/pulsenet/pathogens/wgs.html (last accessed Mar. 23, 2023)
2014	Schwarze, K; Buchanan, J; Taylor, Jc; Wordsworth, S (May 2018). “Are whole Exome and whole Genome Sequencing

Exhibit No.	Description
	Approaches Cost-Effective? A Systematic Review of the Literature.” Value in Health, 21:S100. doi:10.1016/j.jval.2018.04.677
2015	Transcript of the deposition of John Quackenbush, Ph.D., taken on January 31, 2018 in <i>Guardant Health, Inc. v. Foundation Medicine, Inc.</i> , Case IPR2017-01170, IPR2017-01447, IPR2017-01448

I. Leary Does Not Teach “Whole Genome Sequencing”

Petitioner quibbles with Patent Owner’s proposed construction for “whole genome sequencing,” contending that it is not precise enough in the language it uses to acknowledge that “whole genome sequencing” need not sequence the entirety of a genome. Reply at 1. Yet, for the purposes of institution, Petitioner’s quibbles are simply irrelevant because Leary does not come anywhere close to “whole genome sequencing” under any reasonable interpretation of the term.

Petitioner contends that Leary’s “sequencing resulted in ‘an 18-fold physical coverage of the human genome.’” *Id.* This, however, is the same statement from Leary that Petitioner originally cited in its Petition. Petitioner’s continued reliance on this “18-fold physical coverage statement” in its Reply is inexplicable given Patent Owner’s rebuttal in its preliminary response.

As Patent Owner explained, the relevant passage from Leary reads in full as follows:

The total amount of genome base pairs covered by the mate-paired analysis (*that is, distance between mate-paired tags × number of mate-paired tags*) was 53.6 Gb per sample, or an 18-fold physical coverage of the human genome.

Ex. 1002 at 1 (emphasis added). Both in its original Petition and in its Reply, Petitioner ignores the bolded parenthetical. This language, however, is critical because it establishes that Leary’s “18-fold physical coverage” *does not* refer to the

sequence information that is generated, but only to the circularized molecules that are generated *before* sequencing. *See* Ex. 2007 ¶¶ 34-35.

In other words, the circularized molecules that are prepared prior to sequencing “physically” cover the genome 18 times. But Leary does not disclose sequencing the entirety of these molecules so as to actually sequence the genome 18 times. Just the opposite, in Leary, only the 25 base pairs at the *ends* of the circularized molecules—*i.e.*, the mate pairs—are sequenced. *Id.* The “~1.4 kb” in between the mate-paired tags were not sequenced at all. *Id.* As such, DNA sequence data was only generated for about 3-4% of each molecule. The other 96-97% of each molecule was not sequenced. Given that the molecules that were used in the sequencing covered the genome 18 times, and given that only about 3% of each individual molecule was sequenced, one easily sees that *at most* about half (*i.e.*, 0.03×18) of a genome was sequenced in Leary. Patent Owner’s expert, Dr. Furneaux, provided a detailed analysis confirming this. *See id.* Petitioner never presents any rebuttal. Not even petitioner contends that sequencing only half a genome reflects “whole genome sequencing.”

What’s more, as Dr. Furneaux explained, the mate-paired tags in Leary are actually *overlapping*. *See id.* ¶ 31. The overlap factor is roughly 1.7, meaning that every nucleotide that is sequenced is actually sequenced 1.7 times on average. *See id.* ¶¶ 32-33. Thus, as Dr. Furneaux explains, in the example in Table 1 of Leary

involving 59,019,031 mate-paired tags and 2.9 billion bases sequenced, only about 1.71 Gb of the genome is potentially covered. *See id.* ¶ 33. As such, the mate-paired sequencing in Leary—which is the only thing Petitioner relies upon—is not whole genome sequencing, but rather a process that sequences at most half a genome. In its Reply, Petitioner is silent with respect to Dr. Furneaux’s cogent analysis proving that this is so. *See id.*

Petitioner nevertheless contends that Leary must be performing “whole-genome sequencing” because the later Forsheew paper supposedly described Leary as such. *See Reply* at 2. Petitioner, however, includes nothing to clarify what Forsheew was even referring to, whether it be the mate-paired sequencing or something else in Leary. In fact, as Patent Owner established in its Preliminary Response, contemporaneous literature that actually refers to mate-pair sequencing distinguishes it from whole-genome sequencing. *See, e.g., Ex. 2008.004* (“Whole-genome sequencing currently demands resources beyond the reach of most cancer investigators....Therefore, we used a mate-pair genomic DNA sequencing approach for lymphoma translocation discovery.”); *see also Ex. 2009.011*. Petitioner is again silent with respect to this evidence.

II. PCR PRIMERS ARE NOT CAPTURE PROBES

Relying heavily on the opinion testimony of its expert, Dr. Quackenbush, Petitioner asserts that a “capture probe” encompasses a “PCR primer.” Dr.

Quackenbush, however, previously distinguished “primers” from other types of oligonucleotides that are not primers, explaining that a primer is a specific type of oligonucleotide that is used in PCR and that primes a PCR reaction:

Q. What are other oligonucleotides that are not primers?

A. *Primers typically refer to oligonucleotides that are used in PCR, since they initiate the reaction, hence the term primers. They prime the reaction.* But if I looked at a DNA fragment, I would not know ahead of time, if I simply had a native strand of DNA, whether it was designed to be used as a primer or for any other type of assay.

It could be used for a simple hybridization assay. Right?

So oligonucleotides are the generic term, and primer is a context-specific term, where generally -- again, molecular biology -- biologists are really imprecise in how they use language, but *generally used as an initiation oligonucleotide for polymerase chain reaction.*

Ex. 2015 at 89:13-90:4. In view of this testimony, there is no basis to believe that when the claims of the '394 Patent refer to a “capture probe” they are intending to sweep in “primers.” As Patent Owner explained, the '394 Patent over and over distinguishes “primers” from “capture probes.” *See, e.g.,* Ex. 1001 at 32:26-34, 23:23-36, 32:56-60, 41:33-36. Several embodiments describe the use of capture probes as a separate step that occurs after the step of amplification using primers. *See, e.g., id.* at 64:29-43, 65:38-50, 66:53-67.

Petitioner has little response to this intrinsic evidence except to assert that the '394 Patent never describes “primers” and “capture probes” as “mutually exclusive,” as if there is some sort of legal rule that two different terms cannot be understood as being “mutually exclusive” absent an explicit directive to this effect in the specification. In fact, the law is to the contrary. *See, e.g., Bell Atl. Network Servs., Inc. v. Covad Commc'ns Grp., Inc.*, 262 F.3d 1258, 1271 (Fed. Cir. 2001) (“In this case, in addition to the Summary of the Invention, the Detailed Description of the Preferred Embodiments continues to use the terms ‘mode’ and ‘rate’ to refer to two separate and distinct concepts.”). Here, not only does the specification distinguish “primers” and “capture probes,” but Petitioner’s own expert has confirmed in previous cases that a “primer” is a specific type of oligonucleotide used for a specific purpose.

As to the file history that Patent Owner cited confirming that “primers” and “capture probes” are not the same thing, Petitioner criticizes it as irrelevant because it involved the claim term “pulldown probe.” But tellingly, Petitioner never once states that a “pulldown probe” is different from a “capture probe,” nor does it cite any evidence to suggest that the two terms are different. Petitioner’s expert, Dr. Quackenbush, previously used the term “pull” to describe what hybridization capture probes do. *See, e.g., Ex. 2015 at 88:8-10* (“So in that context what one does

is one allows a hybridization to occur and then ***pulls*** the captured targets out of solution.”).

Finally, Petitioner points to claim 13 of the '394 Patent, which refers to the capture probe including a “barcode.” Citing its expert, Petitioner contends that this means a “capture probe” must encompass a PCR primer because the “probes themselves are ***not*** typically incorporated into the target nucleic acid.” Reply at 3 (citing Quackenbush ¶ 105). Yet, Petitioner cites no reason to believe that claim 13 of the '394 Patent needs to refer to whatever scheme its expert believes is most “typical.” As the '394 Patent explains, a “barcode” is merely a type of “sample identifier.” Ex. 1001 at 55:14-18. There is no reason whatsoever why the “capture probes” used in the invention cannot include a “barcode” so as to aid in capturing nucleic acids associated with a particular sample. Indeed, as Dr. Quackenbush previously explained, “you know, this idea of fishing things out of solution is widely used, and, again, I wouldn't begin to comment on how many possible iterations and permutations of techniques and technologies people have dreamed up.” Ex. 2015 at 91:17-21. Nothing about dependent claim 13 overcomes the otherwise clear intrinsic evidence in the specification distinguishing “primers” from “capture probes.” Indeed, “claim differentiation does not serve to broaden claims beyond their meaning in light of the specification...” *Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1302 (Fed. Cir. 1999).

Respectfully submitted,

WEIL, GOTSHAL AND MANGES LLP

Dated: April 27, 2023

By: /Derek C. Walter/

Derek C. Walter
Lead Counsel
Reg. No. 74,656
Weil, Gotshal & Manges LLP
201 Redwood Shores Parkway
Redwood Shores, CA 94065-1134
Telephone: 650-802-3000

Counsel for Patent Owner Personalis, Inc.

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 et seq., the undersigned certifies that this document complies with the type-volume limitations. This document contains 1,412 words as calculated by the “Word Count” feature of Microsoft Word 2016, the word processing program used to create it.

Respectfully submitted,

WEIL, GOTSHAL AND MANGES LLP

Dated: April 27, 2023

By: /Derek C. Walter/
Derek C. Walter
Lead Counsel for Personalis, Inc.
Reg. No. 74,656

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. 11,384,394 and EXHIBIT 2015** are being served on April 27, 2023, via email pursuant to 37 C.F.R. § 42.107 to counsel for Foresight Diagnostics, Inc., at the addresses below:

Andrew E. Krause
Reg. No. 76,276
IRELL & MANELLA LLP
1800 Avenue of the Stars, Ste. 900
Los Angeles, CA 90067
T: 310-277-1010
F: 310-203-7199
akrause@irell.com

Jordan Nafekh (pro hac vice to be
requested)
IRELL & MANELLA LLP
1800 Avenue of the Stars, Suite 900
Los Angeles, California 90067
T: 310- 277-1010
F: 310- 203-7199
jnafekh@irell.com

Alan J. Heinrich (pro hac vice to be
requested)
IRELL & MANELLA LLP
1800 Avenue of the Stars, Suite 900
Los Angeles, California 90067
T: 310-277-1010
F: 310- 203-7199
aheinrich@irell.com

Amir Naini
Reg. No. 45,770
NAINI P.C.
2632 Wilshire Blvd., Suite 268
Santa Monica, CA 90403
T: 310- 592-3030
F: 310-453-9008
amir@nainipc.com

Dated: April 27, 2023

By: /Derek C. Walter/
Derek C. Walter
Reg. No. 74,656