

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

PETITIONER'S REPLY TO
PATENT OWNER'S PRELIMINARY RESPONSE

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I. Claim Construction: “whole genome sequencing”

In an attempt to distinguish Leary (Ex. 1002), Patent Owner (“PO”) misconstrues “whole genome sequencing” [“WGS”] as “a sequencing technique intended to sequence all or almost all of a genome.” POPR 27. PO appears to contend that Leary does not sequence every base in the genome and as such it does not disclose WGS, *see, e.g.*, Ex. 2007 at ¶¶30-33, despite Leary’s reporting that its sequencing resulted in “an 18-fold physical coverage of the human genome.” Ex. 1002 at 1. PO’s construction conflicts with a POSA’s understanding of WGS. The specification repeatedly acknowledges that “whole genome sequencing” processes may have “zero mean coverage regions,” which are portions of the genome that are not sequenced. Ex. 1001 at 24:59-62; 28:33-42.¹ For example, it recognizes that WGS “performs poorly in content regions having very high CG content” and “also fail[s] to provide adequate ... sequencing of repetitive elements in the genome,” *Id.* at 1:23-34.

Perhaps recognizing this, PO includes the qualifier “almost all of the genome” in its proposed construction. There is no support for this requirement, let alone guidance regarding how to determine what constitutes sequencing

¹ The passages PO does cite as support merely note that there are differences between “whole genome” and “whole exome” sequencing. *See* POPR 27-28. But PO does not contend that Leary’s mate-pair sequencing is intended to sequence only the exome, nor could it.

“almost all of the genome” or how to assess whether a given technique was “intended” to do so. For example, PO’s expert contends that an example in Leary “accounts for only 2.9 billion bp ... which is far less than the 3.2 billion bp actually present in the human genome.” Ex. 2007 at ¶30. But even under PO’s erroneous construction, the factual question of whether sequencing 2.9 billion bp was “intended to sequence all or almost all of a genome” is properly addressed at trial.

Importantly, the record confirms that Leary’s methods involved WGS under the contemporaneous plain meaning the claim term would have had to a POSA. Notably, Forsheew described Leary (its reference 18) as a “[p]reviously proposed method[] for personalized monitoring of tumor dynamics [that] relied on ... identification of rearrangements *using whole-genome sequencing* (18, 19).” Ex. 1030 at 10-11. *See also* Ex. 1015 at 4, 9 (describing “genome-wide rearrangement screens” and describing Leary as implementing “similar paired-end rearrangement screens”). “The Board is required to construe ‘only those terms ... that are in controversy, and only to the extent necessary to resolve the controversy.’” *Axalta Coating Sys., LLC v. PPG Indus. Ohio, Inc.*, No. IPR2022-00676, 2022 WL 4139422, at *3 (PTAB. Sept. 12, 2022). Thus, the Board should not deviate from the plain and ordinary meaning of “whole genome sequencing” by adopting PO’s construction.

II. Claim Construction: “capture probe”

PO proposes construing “capture probe” as “a nucleic acid sequence that hybridizes to target DNA to capture the DNA for physical collection; not a primer for amplification.” POPR at 21-22. This construction imports into the claimed “capture probe” (i) the concept of “physical collection,” and (ii) a negative limitation excluding “a primer for amplification.”

The intrinsic record is clear that the claimed “capture probe” is a nucleic acid that will “hybridize to one or more polymorphisms” in a nucleic acid sample. Ex. 1001, claim 1(c). Both “PCR primer capture probes and solution-based hybridization capture probes (e.g., biotinylated oligonucleotide baits)” indisputably are nucleic acid molecules that perform the function of hybridizing to one or more other nucleic acid molecules. Pet. 21; Quackenbush ¶¶100-106. Confirming that PCR primers are within the scope of the claimed “capture probes,” dependent claim 13 recites “wherein said plurality of *capture probes* further *comprise barcodes*,” which makes sense for primer-based capture probes but not for hybrid capture baits. *See* Quackenbush ¶¶104-105. A “barcode” incorporated into a PCR primer capture probe “would be incorporated into the PCR products,” where “the barcodes could then be used to deconvolute the data.” *Id.* ¶104 (citing Ex. 1007 (Mamanova)). By contrast, “[w]hen hybrid capture baits are used, the capture probes themselves are *not* typically incorporated into the target nucleic acid,” because “the capture probe (and any

elements it comprises, like a barcode) remain bound to the bead while the catch is carried forward.” *Id.* ¶105 (citing Ex. 1005 (Gnirke)). The POPR did not address this intrinsic evidence reflected in dependent claim 13.

Further, the specification never ascribes to the claimed “capture probes” the function of “captur[ing] the DNA for physical collection.” POPR 22. Nor does it “describe precisely how capture probes are used to capture DNA for physical collection.” *Id.* Indeed, variations of PO’s imported term “collect” appear only three times in the specification, none of which is relevant to the interpretation of “capture probe.” *See* Ex. 1001 at Abstract; 13:35-38; 38:40-43.

The portions of the specification PO cites explain that when a nucleic acid sample is contacted with a “capture probe” there will exist “a first subset of nucleic acid molecules comprising one or more capture probe hybridized nucleic acid molecules and a second subset of nucleic acid molecules comprising one or more capture probe free nucleic acid molecules.” Ex. 1001 at 32:26-33. As Dr. Quackenbush explains, this is precisely what happens when a nucleic acid sample is contacted with PCR primer-based capture probes. Quackenbush ¶¶130-131.

PO also argues that “the specification refers to capture probes and primers as separate and distinguishable from one another,” POPR 22-23, but none of the cited passages describe “primers” and “capture probes” as mutually exclusive or precludes a similarly structured nucleic acid from performing each function.

Mamano's (Ex. 1007) discussion of PCR primers and solution-phase hybridization probes as having the capability of performing overlapping functions is consistent with this understanding. *Cf.* POPR at 26.

Finally, PO contends that in related applications, "the patent examiner acknowledged that capture probes were different from PCR primers." POPR 23-25. But the cited applications involved the claim limitation "pulldown probe," and claims reciting "capture probe" were not before the Office. The specification does not use the term "pulldown probe" at all, nor does PO endeavor to establish their applicability or relevance to the claimed "capture probes." In any event, the related prosecution history supports Petitioner.

Taking the '337 application as an example, after the Examiner rejected the originally-examined claims, Ex. 2004 at 35-39, PO submitted a draft claim amendment which recited performing a "subsetting" step "with the aid of probes" Ex. 1078 at 3. At the subsequent interview, the examiner observed that the prior art's "amplification primers" "could be reasonably interpreted as 'probes' as currently recited in the claim," i.e., the claim proposed in Ex. 1078. PO acquiesced, because following the interview it introduced the claim amendment reciting "pulldown probes." Ex. 2004 at 19. The additional portion of the file history in Ex. 1078 "in fairness ought to be considered" now, FRE 106, and to the extent necessary, Petitioner requests that the Board take official notice of this portion of the file history under 37 C.F.R. § 42.62(c) and FRE 201(b).

In any event, Ground 3 adds to Leary the teachings of Chan, which specifically render obvious the use of solution-based hybridization capture probes. PO does not contend that this combination fails to teach “capture probes.” Instead, PO relies on a factually and legally erroneous enablement argument that Chan taken on its own “does not enable the claimed inventions.” *See* POPR at 52-53. *Cf. Raytheon Techs. Corp. v. Gen. Elec. Co.*, 993 F.3d 1374, 1380 (Fed. Cir. 2021) (obviousness looks at *all* “prior art or evidence of record”).

III. Alleged Secondary Considerations

PO’s allegations regarding secondary considerations are based on arguments first raised in the POPR. As prior panels of the Board have found, it is inappropriate “to hinge the outcome of a Decision to Institute” on such an incomplete record, where Petitioner “has not yet been given an opportunity for discovery, much less [to] present evidence at trial in response.” *Invata, LLC v. OPEX Corp.*, No. IPR2022-01604, 2023 WL 2597830, at *4 (P.T.A.B. Mar. 17, 2023). Here, there is no competent evidence of nexus between the alleged objective indicia and the claims; PO presents only a cursory attorney-created claim chart, Ex. 2012. And the alleged contribution of the ‘394 patent – high sensitivity in PO’s commercial product in 2022 (*see* POPR 55-56) – is not claimed or even discussed in the specification. Such speculative and attenuated allegations fail to undercut the reasonable likelihood that at least one claim of the ‘394 patent is unpatentable.

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Dated: April 14, 2023

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. section 42.6, that on April 14, 2023, a complete copy of the foregoing document **PETITIONER'S REPLY TO PATENT OWNER'S PRELIMINARY RESPONSE, EXHIBIT 1078** and **PETITIONER'S UPDATED EXHIBIT LIST** were served upon the following, by ELECTRONIC MAIL:

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