NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

GUARDANT HEALTH, INC.,
Appellant

v.

KATHERINE K. VIDAL, UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE,
Intervenor

2021-1104

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2019-00652.

Decided: May 5, 2023

MICHAEL T. ROSATO, Wilson, Sonsini, Goodrich & Rosati, PC, Seattle, WA, argued for appellant. Also represented by SONJA ROCHELLE GERRARD; RICHARD TORCZON, Washington, DC.

SARAH E. CRAVEN, Office of the Solicitor, United States Patent and Trademark Office, Alexandria, VA, argued for

intervenor. Also represented by THOMAS W. KRAUSE, AMY J. NELSON, FARHEENA YASMEEN RASHEED, MICHAEL TYLER.

Before MOORE, *Chief Judge*, CLEVENGER and DYK, *Circuit Judges*.

MOORE, *Chief Judge*.

Guardant Health, Inc. (Guardant) appeals a Patent Trial and Appeal Board *inter partes* review final written decision holding claims 1–11, 13, and 17–20 of U.S. Patent No. 9,834,822 would have been obvious. We vacate and remand.

BACKGROUND

DNA molecules comprise strands of units called nucleotides, which when repeated are called polynucleotides. Cell free DNA (cfDNA), i.e., DNA present outside a cell, is readily accessible for testing through extraction from bodily fluids, such as blood. '822 patent at 30:21–24, 35:62–67. Guardant owns the '822 patent, which is directed to systems and methods "for the detection of rare mutations and copy number variations in" cfDNA. '822 patent at Abstract. One step in detecting mutations in cfDNA is converting sample polynucleotides into "tagged parent polynucleotides." *Id.* at 18:19–22. Parent polynucleotides are tagged by attaching "unique or non-unique identifiers, or molecular barcodes" to the parent strand. *Id.* at 38:4–6; *see id.* at 6:26–28, 15:20–27. The identifier or barcode is itself often a polynucleotide sequence. *Id.* at 15:37–38, 32:61–63. Claim 1 recites:

> 1. A method, comprising:
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> > a) providing a population of cell free DNA ("cfDNA") molecules obtained from a bodily sample from a subject;

b) *converting the population of cfDNA molecules into a population of non-uniquely tagged parent polynucleotides*, wherein each of the non-uniquely tagged parent polynucleotides comprises (i) a sequence from a cfDNA molecule of the population of cfDNA molecules, and (ii) an *identifier* sequence comprising one or more polynucleotide barcodes;

c) amplifying the population of non-uniquely tagged parent polynucleotides to produce a corresponding population of amplified progeny polynucleotides;

d) sequencing the population of amplified progeny polynucleotides to produce a set of sequence reads;

e) mapping sequence reads of the set of sequence reads to one or more reference sequences from a human genome;

f) grouping the sequence reads into families, each of the families comprising sequence reads comprising the same identifier sequence and having the same start and stop positions, whereby each of the families comprises sequence reads amplified from the same tagged parent polynucleotide;

g) at each genetic locus of a plurality of genetic loci in the one or more reference sequences, collapsing sequence reads in each family to yield a base call for each family at the genetic locus; and

h) determining a frequency of one or more bases called at the locus from among the families.

Id. at claim 1 (emphases added).

Foundation Medicine, Inc. (FMI) petitioned for *inter partes* review (IPR) of claims 1–13 and 17–20 of the '822 patent, arguing the claims would have been obvious over a combination including U.S. Patent No. 9,752,188 (Schmitt) and the Fan article.[1] The Board instituted IPR and held all petitioned claims, except claim 12, would have been obvious. *Found. Med., Inc. v. Guardant Health, Inc.*, No. IPR2019-00652, 2020 WL 4873209, at *28 (P.T.A.B. Aug. 18, 2020) (*FWD*). Guardant appealed, and FMI thereafter withdrew. The Director intervened to defend the Board's decision. We have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

I

Guardant argues the Board erroneously construed "converting the population of cfDNA molecules into a population of non-uniquely tagged parent polynucleotides" to mean "the number of different identifiers can be at least 2 and fewer than the number of polynucleotides in the sample." *See FWD*, 2020 WL 4873209, at *11. The proper construction of "non-uniquely tagged," according to Guardant, is the following "express definition" in the '822 patent's written description: "the number of different identifiers can be [] at least 2 and fewer than the number of polynucleotides *that map to the mappable base position*." '822 patent at 41:44–47 (emphasis added); *see* Appellant's Opening Br. at 26. The Director responds that the Board properly determined the plain and ordinary meaning of non-uniquely tagged means at least two but fewer than the number of parent polynucleotides in the sample. Intervenor's Br. at

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[1] Christina Fan et al., *Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood*, 105(42) PROC. NATL. ACAD. SCI. 16266–71 (2008).

26. The Director asserts the '822 patent's reference to "the number of polynucleotides that map to the mappable base position" is a single embodiment and that the "polynucleotides that map to the mappable base position" refer to a particular set of polynucleotides. *Id*. at 26–33 & n.7. We agree with the Director.

Claim construction is a legal question that may be based on underlying factual determinations. *HTC Corp. v. Cellular Commc'ns Equip., LLC*, 877 F.3d 1361, 1367 (Fed. Cir. 2017). We review the Board's claim construction based on the intrinsic record de novo and its factual findings for substantial evidence. *Id.* Claim terms are generally given their plain and ordinary meaning, i.e., the meaning the terms would have to a person of ordinary skill in the art when read in the context of the specification and prosecution history. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). We depart from the plain and ordinary meaning in only two instances: lexicography and disavowal. *GE Lighting Sols., LLC v. AgiLight, Inc.*, 750 F.3d 1304, 1309 (Fed. Cir. 2014). The bar for lexicography is exacting. *Thorner v. Sony Comput. Ent. Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012). Lexicography applies only where the patentee "clearly set[s] forth a definition of the disputed claim term" and "clearly express[es] an intent" to redefine the term. *Id.*

The '822 patent does not clearly set forth a definition of non-uniquely tagged parent polynucleotides that displaces the term's plain and ordinary meaning. The passage providing Guardant's purported definition reads in full: "A set of polynucleotides in the composition *that map to a mappable base position* in a genome can be non-uniquely tagged, that is, the number of different identifiers can be [] at least 2 and *fewer than the number of polynucleotides that map to the mappable base position*." '822 patent at 41:41–47 (emphases added). By its plain terms, this "definition" merely explains non-uniquely tagging the particular subset of the population of polynucleotides that map to a

mappable base position. Thus, even if the passage were definitional, Guardant ignores that the definition applies only to polynucleotides within the population that "map to a mappable base position," not the invention as a whole. '822 patent at 41:41–47; *see* Appellant's Opening Br. at 26. This is consistent with the '822 patent's other disclosures. Elsewhere, the '822 patent does not describe the population of polynucleotides as only those that map to a mappable base position. The written description makes clear that "[*i*]*n some embodiments* each polynucleotide in a set is mappable to a reference sequence."[2] '822 patent at 6:1–2 (emphasis added). It follows that other embodiments include polynucleotides that do not map to a mappable base position and thus are outside of the definition asserted by Guardant.

Guardant also argues the Board's construction encompasses prior art systems that the '822 patent distinguishes. Specifically, Guardant argues the patent distinguishes its invention from prior art systems of "uniquely tag[ging] every, or nearly every, different parent molecule in the sample," which "can be cumbersome and expensive." '822 patent at 41:1–2, 6. We do not agree. The portion of the written description Guardant cites does not distinguish the '822 patent's invention from prior art systems—It never mentions prior art systems and instead consistently refers to the "methods disclosed herein." *See id.* at 38:1–41:53. Even if the '822 patent was distinguishing prior art systems as "cumbersome and expensive," such criticism is not a clear "expression[] of manifest exclusion" of claim scope. *Epistar Corp. v. Int'l Trade Comm'n*, 566 F.3d 1321, 1335

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[2] The parties agreed below, and do not dispute here, that a mappable base position is "a position in the reference sequence to which polynucleotide molecules can be confidently mapped." *FWD*, 2020 WL 4873209, at *7 n.6; *see* Appellant's Opening Br. at 10.

(Fed. Cir. 2009) ("A patentee's discussion of the shortcomings of certain techniques is not a disavowal of the use of those techniques in a manner consistent with the claimed invention."); *see Thorner*, 669 F.3d at 1366 ("Mere criticism of a particular embodiment . . . [alone] is not sufficient to rise to the level of clear disavowal."). We therefore hold there is no error in the Board's construction of non-uniquely tagged parent polynucleotides.

II

Guardant next challenges the Board's finding that Schmitt teaches non-uniquely tagged parent polynucleotides under the Board's construction and its finding that a skilled artisan would have had a reasonable expectation of success in combining Schmitt's hybrid Duplex Consensus Sequencing (DCS) method with cfDNA. Guardant also argues the Board erroneously found a lack of nexus related to objective indicia of nonobviousness. We hold substantial evidence supports the Board's finding that Schmitt teaches non-uniquely tagged parent polynucleotides and its finding regarding the reasonable expectation of success. We do, however, vacate the Board's obviousness determination and remand for further fact finding because the Board's objective indicia of nonobviousness analysis is not supported by substantial evidence.

A. Schmitt

Guardant argues that, even under the Board's construction, the Board's finding that Schmitt teaches non-uniquely tagged parent polynucleotides is not supported by substantial evidence. We review the Board's legal determination of obviousness de novo and any underlying findings of fact for substantial evidence. *Outdry Techs. Corp. v. Geox S.p.A.*, 859 F.3d 1364, 1367 (Fed. Cir. 2017). Substantial evidence is "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *FTC v. Ind. Fed'n of Dentists*, 476 U.S. 447, 454 (1986) (citation omitted). What a prior art reference discloses is a

question of fact. *In re Kahn*, 441 F.3d 977, 985 (Fed. Cir. 2006).

The Board found Schmitt's use of n-mer[3] tags in its hybrid DCS method teaches non-uniquely tagged parent polynucleotides. *FWD*, 2020 WL 4873209, at *13. Guardant argues the Board incorrectly mapped Schmitt's "n-mer tags" onto claim 1's "identifiers." According to Guardant, the identifiers disclosed in Schmitt are not the n-mer tags standing alone, which are fewer than the millions of parent polynucleotides, but are the n-mer tags *plus* the sheared ends of endogenous DNA. The n-mer tags and sheared ends together result in trillions of different identifiers that exceed the number of parent polynucleotides and therefore, according to Guardant, fall outside the scope of the Board's definition. *See* Appellant's Opening Br. at 40–41. The Director responds that Guardant falsely conflates the identifiers used to describe the non-unique barcodes (i.e., n-mer tags) with the unique molecular identifiers (i.e., the n-mer tags plus sheared DNA ends) and that the Board's finding is supported by substantial evidence. *See* Intervenor's Br. at 37–38. We agree with the Director.

Guardant's argument confuses two different meanings of identifier. The Board construed non-uniquely tagged to mean that the "number of different identifiers (the *tag count*) is . . . fewer than the number of parent polynucleotides in the sample." *FWD*, 2020 WL 4873209, at *10 (emphasis added). This is consistent with claim 1. Claim 1 describes the non-uniquely tagged parent polynucleotides having two parts: (1) "a sequence from a cfDNA molecule"; and (2) an "*identifier* sequence comprising one or more polynucleotide barcodes." '822 patent at claim 1 (emphasis added). The Board's findings regarding Schmitt map onto

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[3] An n-mer sequence is a tag where n is the number of nucleotides. *FWD*, 2020 WL 4873209, at *11 n.11. A 4-mer tag, for example, is a sequence of four nucleotides. *Id.*

the claim language and the Board's construction. Schmitt discloses a "hybrid DCS method," where sheared ends of target polynucleotides are tagged with "a shorter n-mer tag (such as 1 or 2 or 3 or 4 or more . . . bases)." Schmitt at 9:10–12. In finding Schmitt's hybrid method teaches a population of non-uniquely tagged parent polynucleotides, the Board found Schmitt's 4-mer tag would produce 65,536 "unique identifiers," i.e., the "tag count." *FWD*, 2020 WL 4873209, at *12 (citing J.A. 1072 ¶ 127 & n.7 (Dr. Gabriel's declaration); J.A. 4459 ¶ 69 (Dr. Quackenbush's declaration)). When these unique identifiers are added to the sheared ends (i.e., the claimed "sequence from a cfDNA molecule of the population of cfDNA molecules"), they produce a "unique *molecular* identifier." Schmitt at 9:9–14 (emphasis added). Because the 65,536 4-mer tag identifiers are fewer than the millions of parent polynucleotides in a sample, the hybrid method produces a population where "more than one parent polynucleotide would necessarily share the same short [4]-mer tag," i.e., are non-uniquely tagged. *FWD*, 2020 WL 4873209, at *13–16 (citing J.A. 1071–72 ¶¶ 126–27 (Dr. Gabriel's declaration); J.A. 4459 ¶ 69 (Dr. Quackenbush's declaration)).

Schmitt's disclosure is like the method disclosed in the '822 patent, which explains that non-unique tags or barcodes are distinguishable and can be consistent with uniquely identifying a particular molecule. In other words, there may be non-unique barcodes that, when attached to a particular molecule, may result in a unique identifier for that molecule. Indeed, "barcodes are not necessarily unique to one another in the plurality. In this example, barcodes may be ligated to individual molecules such that the combination of the bar code and the sequence it may be ligated to creates a unique sequence that may be individually tracked." '822 patent at 39:13–18. The use of "non[-]unique barcodes in combination with sequence data of beginning (start) and end (stop) portions of sequence

reads may allow assignment of a unique identity to a particular molecule." *Id.* at 39:19–22.

Moreover, Schmitt itself distinguishes non-uniquely tagging from uniquely tagging. In addition to a 4-mer tag, Schmitt discloses a method with a 12-mer tag, wherein every target polynucleotide is labeled with "two distinct SMI sequences," Schmitt at 3:47–51, which results in more tags than the number of polynucleotides in the sample, i.e., *unique* tagging. Schmitt at 6:59–64; *see* J.A. 1071 ¶ 126 (Dr. Gabriel's declaration). In sum, while the combined sheared end and 4-mer tag might result in a unique molecular identifier, the population of parent polynucleotides is non-uniquely tagged based on the claimed identifier. Therefore, substantial evidence supports the Board's finding that Schmitt teaches non-uniquely tagged parent polynucleotides.

B. Reasonable Expectation of Success

Guardant argues Schmitt's method was "poorly suited for cfDNA" and a skilled artisan therefore would not have reasonably expected to successfully apply Schmitt's method to a population of cfDNA molecules. Appellant's Opening Br. at 42. It also argues the Board legally erred in excluding some of Guardant's evidence for being related to tagging efficacy or efficiency, which is not claimed. *Id.* at 42–44; *FWD*, 2020 WL 4873209, at *26. The Director responds that substantial evidence supports the Board's finding that there would be a reasonable expectation of success in applying Schmitt's method to cfDNA. Intervenor's Br. at 40–44. We agree with the Director.

Claim 1 of the '822 patent claims the use of methods applied to cfDNA. The Board addressed the use of Schmitt with cfDNA, as recited in the Fan article, and relied on evidence of Schmitt's compatibility with the cfDNA sequencing platform used in Fan. *FWD*, 2020 WL 4873209, at *26. Guardant does not directly challenge this finding. Instead, it mounts a collateral attack arguing the Board should not

have rejected other evidence related to tagging efficiency that would have led it to a different finding. As the Board concluded, tagging efficiency, however, is not claimed. *Cf. Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) ("The reasonable expectation of success requirement refers to the likelihood of success in combining references *to meet the limitations of the claimed invention*." (emphasis added)). We therefore hold substantial evidence supports the Board's finding that a skilled artisan would have a reasonable expectation of success in using Schmitt's hybrid method to analyze cfDNA.

C. Objective Indicia of Nonobviousness

Guardant argues the Board erroneously found a lack of evidence that its commercial embodiment, Guardant360, is not coextensive with the claimed invention and therefore was not entitled to a presumption of nexus. *FWD*, 2020 WL 4873209, at *26–27. The Board's conclusion rested on its finding that Guardant did not cite Dr. Quackenbush's declaration in its briefing and its refusal "to search through Dr. Quackenbush's [d]eclarations for this evidence." *Id.* (citing *DeSilva v. DiLeonardi*, 181 F.3d 865, 866–67 (7th Cir. 1999) ("A brief must make all arguments accessible to the judges, rather than ask them to play archeologist with the record."")). Whether a presumption of nexus applies is a question of fact. *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019).

The Board's finding that Guardant360 is not coextensive with claim 1 of the '822 patent, and therefore its nexus and overall obviousness determinations, is not supported by substantial evidence. The Board's finding was falsely premised on Guardant's failure to cite evidence, such as expert testimony, establishing nexus. Contrary to the Board's reasoning, Guardant's response brief expressly relied on Dr. Quackenbush's opinion that Guardant360 embodies claim 1 to support its argument of a presumption of nexus. J.A. 640–41 (citing J.A. 4489–97 ¶¶ 156–66). On

those same pages, Guardant mapped Guardant360 to claim 1 while again referencing Dr. Quackenbush's testimony. J.A. 641. The Board simply overlooked Guardant's clear reliance on this evidence. Because the Board's finding that there was inadequate evidence to show that Guardant360 is coextensive with claim 1 was based on a clearly mistaken view of the evidence, we vacate the Board's obviousness determination and remand for further fact finding.[4]

The Board also erred as a matter of law in its treatment of the articles that both Guardant and Dr. Quackenbush relied on for mapping Guardant360 to claim 1. The Board reasoned the articles were insufficient because the articles *themselves*, as opposed to testimony interpreting those articles, "do not provide any legal or factual analysis." *FWD*, 2020 WL 4873209, at *27. This was premised on the Board's erroneous view that there was no expert testimony mapping claim 1 onto Guardant360. *Id.* In other words, the Board required Guardant's articles to establish nexus without expert testimony linking the articles' discussion of Guardant360 to claim 1 of the '822 patent. *See id.* This was error. Expert testimony is necessary in many cases. *See Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1330 (Fed. Cir. 2009) ("If the relevant technology were complex, the court might require expert opinions."); *cf. id.* ("No expert opinion is required to appreciate the potential value

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[4] The Director argues Guardant improperly incorporated arguments from Dr. Quackenbush's declaration in violation of 37 C.F.R. § 42.6(a)(3) ("Arguments must not be incorporated by reference from one document into another document."). Intervenor's Br. at 45–46. This argument is inapt because Guardant's response brief maps claim 1's elements to Guardant360 by relying on the evidence and expert declaration, not by incorporating legal arguments. J.A. 640–41.

to persons of such skill in this art" where "ordinary skill in the relevant art required only a high school education and limited marketing and computer experience."). Here, a person of ordinary skill in the art had "a doctorate degree (Ph.D.) in genetics, molecular biology, bioinformatics, or a related field, and at least five years of research in an academic or industry setting, including at least two to three years of research experience in the field of cancer genomics." *FWD*, 2020 WL 4873209, at *6. Guardant's reliance on Dr. Quackenbush's testimony interpreting the cited articles and mapping Guardant360 to claim 1 is appropriate in this instance. The Board erred as a matter of law in disregarding Guardant's evidence to establish a presumption of nexus. On remand, the Board must consider the articles in light of the parties' arguments and all other appropriate evidence.

CONCLUSION

We have considered the parties' remaining arguments and find them unpersuasive. For the reasons given, we vacate the Board's obviousness determination and remand for further fact finding consistent with this opinion.

VACATED AND REMANDED

COSTS

Costs awarded to Guardant.