NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

LABORATORY CORPORATION OF AMERICA HOLDINGS,
Appellant

v.

RAVGEN, INC.,
Appellee

2023-1342, 2023-1345

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2021-00902, IPR2021-01054.

Decided: January 6, 2025

GREGORY A. CASTANIAS, Jones Day, Washington, DC, argued for appellant. Also represented by AMELIA A. DEGORY, BRENDAN D. DUFFY, TRACY A. STITT, JENNIFER L. SWIZE; GASPER LAROSA, New York, NY; JOHN C. ALEMANNI, Kilpatrick Townsend & Stockton LLP, Raleigh, NC; TINA WILLIAMS MCKEON, Atlanta, GA.

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Before LOURIE, BRYSON, and STARK, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Laboratory Corporation of America Holdings ("Labcorp") appeals from two final written decisions of the U.S. Patent Trial and Appeal Board ("the Board") collectively holding that claims 55–63, 66–69, 80–96, and 127–133 of U.S. Patent 7,332,277 ("the '277 patent") had not been shown to have been obvious. *Lab'y Corp. of Am. Holdings v. Ravgen, Inc.*, No. IPR2021-00902, 2022 WL 16579960 (P.T.A.B. Nov. 1, 2022) (holding that claims 81–96 and 133 had not been shown to be unpatentable) ("*00902 Decision*"); *Lab'y Corp. of Am. Holdings v. Ravgen, Inc.*, No. IPR2021-01054, 2022 WL 16641665 (P.T.A.B. Nov. 1, 2022) (holding that claims 55–63, 66–69, 80, and 127–132 had not been shown to be unpatentable) ("*01054 Decision*").[1] The Board determined that Labcorp had failed to demonstrate that a person of ordinary skill in the art would have been motivated to combine the asserted prior art references. For the following reasons, we *affirm*.

BACKGROUND

Ravgen, Inc. ("Ravgen") owns the '277 patent, which is directed to non-invasive methods for sampling DNA and detecting genetic disorders in a fetus. '277 patent, Abstract. The '277 patent relates to, *inter alia*, analyzing cell-free fetal DNA ("cffDNA") found in a blood sample drawn from a pregnant mother with a cell lysis inhibitor

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[1] The final written decisions share nearly identical analyses of the issues relevant to the parties' dispute on appeal. Unless otherwise indicated, we cite the *01054 Decision* as representative.

added to the sample. *Id.* at col. 89, ll. 1–15; *see also id.* at col. 26, ll. 15–24, 40–44. The '277 patent provides a list of agents that can act as cell lysis inhibitors, including formaldehyde, formaldehyde derivatives, and formalin (collectively, "formaldehyde compounds"). *Id.* at col. 31, l. 57–col. 32, l. 3. Claims 55 and 132 are illustrative for the issues on appeal.

Claim 55 reads as follows:

> 55. A method comprising determining the sequence of a locus of interest on free fetal DNA isolated from a sample obtained from a pregnant female, wherein said sample comprises free fetal DNA and an agent that inhibits lysis of cells, if cells are present, wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor.

Id. at col. 472, l. 66–col. 473, l. 5. Claim 132 depends from claim 60, which depends from claim 59, which depends from claim 55. Claim 59 adds "wherein said agent is a cell lysis inhibitor." *Id.* at col. 473, ll. 13–14. Claim 60 adds "wherein said cell lysis inhibitor is selected from the group consisting of: glutaraldehyde, derivatives of glutaraldehyde, formaldehyde, derivatives of formaldehyde, and formalin." *Id.* at col. 473, ll. 15–18. And finally, claim 132 reads as follows:

> 132. The method of claim 60, wherein said cell lysis inhibitor is selected from glutaraldehyde, formaldehyde, and formalin.

Id. at col. 478, ll. 12–14.

In two *inter partes* review petitions, Labcorp challenged claims 55–63, 66–69, 80–96, and 127–133 of the '277 patent, arguing that the claims would have been unpatentable as obvious under 35 U.S.C. § 103. Specifically, Labcorp argued that a person of ordinary skill in the art would have been motivated to combine the

maternal blood processing method disclosed in a 2001 *Clinical Chemistry* article ("Chiu")[2] with the formaldehyde compounds disclosed in U.S. Patent 5,648,220 ("Bianchi") or in International Patent Application Publication WO 03/018757 ("Rao"), thereby rendering the claims obvious.[3]

Chiu reports a study on the effects of blood-processing protocols on fetal and total DNA quantification in maternal plasma. J.A. 17638–44. Bianchi discloses a method of labeling a cell where the plasma membrane of the cell is permeabilized so that substantially all the DNA of the cell remains in the cell. Bianchi at Abstract. Bianchi's method involves the use of paraformaldehyde. Bianchi at col. 3, ll. 36–53. And Rao discloses a method of stabilizing rare cancer cells in a blood sample using paraformaldehyde. Rao at p. 3, ll. 12–15, p. 24, ll. 2–17.

The Board determined that the challenged claims had not been shown to be unpatentable. *01054 Decision*, at *22–23. The Board found that a person of ordinary skill in the art would not have been motivated to combine Chiu and Bianchi because one "would have expected Bianchi's paraformaldehyde to create gaps in the cell membranes, providing a means for maternal DNA to escape into the sample." *01054 Decision*, at *14. The Board also found that a person of ordinary skill in the art would not have been motivated to combine Chiu with Bianchi or Rao because "formaldehyde was known to damage nucleic acids." *Id.* At bottom, the Board determined that "[Ravgen]'s reasoning and evidence on [motivation to

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[2] Chiu et al., *Effects of Blood-Processing Protocols on Fetal and Total DNA Quantification in Maternal Plasma*, 47:9 CLINICAL CHEMISTRY 1607–13 (2001), J.A. 17638–44.

[3] IPR2021-01054 included an additional reference in its proposed Chiu-Bianchi and Chiu-Rao combinations; however, the additional reference is not relevant to the issues on appeal.

combine] . . . outweigh[ed] [Labcorp]'s." *Id.* Labcorp timely appealed, and we have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

Labcorp raises both legal and factual challenges on appeal. It argues that the Board's motivation to combine analysis was legally flawed for three reasons. According to Labcorp, the Board (1) required a heightened and untenable standard for proving a motivation to combine, (2) did not adhere to precedents that require reading each reference as a whole, and (3) in effect engaged in *post hoc* claim construction to read additional limitations into the claims. Labcorp also argues that the Board's factual findings were not supported by substantial evidence. We address those arguments in turn.

I

Obviousness is a question of law based on underlying findings of fact. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007). We review the Board's legal conclusion on obviousness *de novo* and its findings of fact for substantial evidence. *HTC Corp. v. Cellular Commc'ns Equip., LLC*, 877 F.3d 1361, 1369 (Fed. Cir. 2017). What a reference teaches and the presence or absence of a motivation to combine references are questions of fact. *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1196–97 (Fed. Cir. 2014).

A

Labcorp's first argument—that the Board imposed an improperly heightened standard for obviousness—mischaracterizes the analysis of the Board in an attempt to reframe factual issues as legal ones. According to Labcorp, the Board erroneously required Labcorp's proposed combinations to be perfect, rather than merely desirable, which is all the case law requires. *See* Labcorp Br. 30–32. Specifically, Labcorp argues that the Board's

analysis of Bianchi (or its "DNA Leakage" rationale) is legally flawed because it "fixated on the fact that even the *potential* for only 1% leakage [in Bianchi] would have been 'contrary to' the goals of Chiu." *Id.* at 33. According to Labcorp, the Board's focus on "a minuscule amount of maternal DNA" leakage as opposed to the benefits of cell stabilization disclosed in Bianchi amounts to legal error by demanding "the most desirable combination," *id.* at 32–33 (quoting *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004)), and ignores that "simultaneous advantages and disadvantages . . . do[] not necessarily obviate motivation to combine," *id.* at 34 (quoting *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006)).

The Board did not apply an improperly heightened motivation-to-combine standard in its analysis of Bianchi. It evaluated the disclosures of Bianchi and found that a person of ordinary skill in the art "would have been dissuaded from adding Bianchi's paraformaldehyde [to the cffDNA detection method of Chiu] because the [person of ordinary skill in the art] would have expected Bianchi's paraformaldehyde to create gaps in the cell membranes, providing a means for maternal DNA to escape into the sample." *01054 Decision*, at *14. In reaching that conclusion, the Board evaluated the testimony of both experts and analyzed the teachings of Bianchi and Chiu, which ultimately led it to disagree with Labcorp's view. *See, e.g.*, *id.* at *15 ("We credit [Ravgen's expert]'s opinion that adopting Bianchi's approach to treating cells with paraformaldehyde creates a means for cellular DNA to escape."); *id.* ("As [Labcorp's expert] concedes, 'DNA leaking out of cells' is something 'Chiu tells us you do not want [] to happen.'"). The Board recognized that Bianchi "most preferably" retains "99% or greater" of the DNA in the cell but found that a person of ordinary skill in the art "would realize that releasing 1% of cellular DNA in a sample in Chiu would have a negative effect on Chiu's fetal cell-free DNA analyses." *Id.* At their core, those are

factual—not legal—determinations. *See Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1360 (Fed. Cir. 2017) ("The prior art, skill, and knowledge of an ordinary artisan may also provide reasons not to combine which would likewise be a question of fact."). The Board therefore did not require an improperly heighted standard for obviousness by rejecting Labcorp's positions; rather, it found that Labcorp failed to "provide persuasive argument or evidence to explain why creating holes in the cell membranes . . . would have been seen by the [person of ordinary skill in the art] as acceptable." *01054 Decision*, at *15.

Simply put, Labcorp's "disagreement with the Board's interpretations of [Bianchi] does not amount to a demonstration that the Board somehow failed to use the proper analysis." *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1347 (Fed. Cir. 2021).

Labcorp makes similar arguments with respect to the Board's "DNA damage" rationale and the standard for obviousness applied by the Board. According to Labcorp, the Board legally erred because it improperly relied on generic concerns of DNA damage, failed to consider if a person of ordinary skill in the art would have pursued the invention despite those concerns, and did not follow our precedent on what constitutes teaching away. Labcorp Br. 34–40. Again, we disagree with Labcorp's attempt to recast factual issues as legal ones.

The Board did not impermissibly rely on generic concerns of formaldehyde's potential to damage DNA, as Labcorp asserts. *See* Labcorp Br. 36. Labcorp compares the Board's analysis to that in *Auris Health, Inc. v. Intuitive Surgical Operations, Inc.*, 32 F.4th 1154 (Fed. Cir. 2022), where the Board impermissibly relied on "vague expert testimony that 'there was great skepticism for performing telesurgery.'" *Id.* at 1159. However, that is not the case here where the concerns relied on by the Board

were specific to the claimed invention. *Id*. ("[*S*]*pecific* evidence of industry skepticism related to a *specific* combination of references *might* contribute to finding a lack of motivation to combine."). The claims recite a method for "determining the sequence of a locus of interest on *free fetal DNA* isolated from a sample," '277 patent, col. 472, ll. 66–67 (emphasis added), and the industry's concerns were specific to "formaldehyde's potential effects on DNA, and cell-free fetal DNA in particular," *01054 Decision*, at *16; *see, e.g.*, *id.* at *19 ("Rao discloses that formaldehyde released from formaldehyde donors was known to 'irreversibly cross link[] nucleic acids.'"). As such, it is clear from the Board's analysis that it did not rely on general "industry skepticism," but rather relied on concerns specific to the combination of references. *See Auris Health*, 32 F.4th at 1159.

Similarly, the Board did not fail to consider whether a person of ordinary skill would have pursued the invention despite any concerns of formaldehyde's potential to damage DNA. Rather, it acknowledged the high level of skill in the art, *see 01054 Decision*, at *5, considered Labcorp's arguments relating to that high level of skill, and rejected them, *see, e.g.*, *id.* at *18 ("[I]nasmuch as [Labcorp] is suggesting a [person of ordinary skill in the art] might simply 'tailor' the processing conditions for using formaldehyde effectively, [Labcorp]'s argument fails."). And as with the Board's DNA Leakage rationale, Labcorp's "disagreement with the Board's interpretations . . . does not amount to a demonstration that the Board somehow failed to use the proper analysis." *Eli Lilly*, 8 F.4th at 1347.

Finally, with respect to Labcorp's arguments associated with the Board's analysis of Bianchi, the Board did not ignore our precedent on teaching away. *See* Labcorp Br. 38–40. The Board did not rely on a teaching away, but found that, on the balance of the evidence, "the literature would have dissuaded a [person of ordinary skill in the art] from using formaldehyde or paraformaldehyde in the

[Chiu] modified method." *01054 Decision*, at *17. Even if evidence does not "rise to the level of teaching away," it is still proper for the Board to consider evidence that "suggests reasons that a skilled artisan would be discouraged from pursuing such a combination." *Arctic Cat Inc.*, 876 F.3d at 1363. For the foregoing reasons, we find Labcorp's arguments that the Board legally erred in its analysis of the DNA Leakage rationale unpersuasive.

B

Next, Labcorp argues that the Board legally erred by failing to consider Bianchi and Rao for everything they teach. With respect to Bianchi, Labcorp argues that the Board ignored the teaching of Bianchi that "99% or greater" of the DNA should remain in the cells. Labcorp Br. 42–43. With respect to Rao, Labcorp argues that the Board ignored Rao's teaching that paraformaldehyde is "frequently used for fixing and stabilizing tumor cells in blood" despite its shortcomings and that handling those concerns would be "readily apparent to one skilled in cell biology." *Id.* at 43–44 (citing Rao, p. 3, ll. 16–18, p. 7, ll. 30–33). Again, we disagree.

Contrary to Labcorp's arguments, the Board did not ignore the identified teachings. The Board "acknowledge[d] that Bianchi prefers that greater amounts of DNA stay in the cells," *01054 Decision*, at *15, and cited the exact passage that Labcorp now asserts was ignored, *see id.* (quoting Bianchi's "most preferably 99% or greater" teaching). Similarly, the Board explicitly cited Rao's teaching that paraformaldehyde is "frequently used for fixing and stabilizing tumor cells in blood." *Id.* at *9. And, although less explicit, the Board's consideration of Rao's teaching that using paraformaldehyde in a concentration effective to stabilize cells without causing damage "would be readily apparent to one skilled in cell biology," was clear, *see* Reply Br. 17 (quoting Rao, p. 3, ll. 16–18) (emphasis in Reply Br. omitted), because the Board considered and

rejected Labcorp's related argument that a person of ordinary skill could "simply 'tailor' the processing conditions for using formaldehyde effectively," *01054 Decision*, at *18. However, even if the Board's consideration of these teachings were not so clear, "we have said numerous times, failure to explicitly discuss every fleeting reference or minor argument does not alone establish that the Board did not consider it." *Yeda Rsch. v. Mylan Pharms. Inc.*, 906 F.3d 1031, 1046 (Fed. Cir. 2018).

C

In one final attempt to gain *de novo* review, Labcorp argues that the Board engaged in improper *post hoc* claim construction. According to Labcorp, the Board read into the claims additional limitations prohibiting DNA damage and requiring a certain degree of cell stabilization. Labcorp Br. 46, 49–51. Relatedly, Labcorp argues that the Board improperly evaluated whether a person of ordinary skill in the art would have incorporated a feature of Bianchi and Rao, *i.e.*, formaldehyde, into the requirements of Chiu rather than the requirements of the claims. Reply Br. 7–8, 21 (citing *Axonics, Inc. v. Medtronic, Inc.*, 73 F.4th 950 (Fed. Cir. 2023)). We disagree.

During the IPR proceedings, neither party identified terms in need of construction, and the Board found it unnecessary to expressly construe any terms. *01054 Decision*, at *6. Nor do we see any implicit claim construction by the Board, *post hoc* or at any time. Instead of requiring a certain degree of cell stabilization, as Labcorp unpersuasively charges, the Board properly relied on the claims' recitation of a method for "determining the sequence of a locus of interest on free fetal DNA isolated from a sample." '277 patent, col. 472, ll. 66–67. Consistent with this claim requirement, the Board focused its motivation to combine inquiry on issues specific to cffDNA. *See, e.g.*, *01054 Decision*, at *16 ("A key question presented in this case is whether a [person of ordinary skill in the art]

would have been concerned with formaldehyde's potential effects on DNA, and cell-free fetal DNA in particular.").

In fact, the parties' arguments focused on those exact issues, Bianchi's disclosure of cell permeabilization, and the potential for formaldehyde compounds to damage DNA. *See id.* at *10–12 (summarizing the parties' motivation to combine arguments). The Board's analysis, which considered the contours of those arguments and found no motivation to combine, does not amount to reading unclaimed requirements into the claims. *See, e.g.*, *id.* at *15 (finding Ravgen's expert's testimony persuasive that a person of ordinary skill in the art "would realize that releasing 1% of cellular DNA in a sample in Chiu would have a negative effect on Chiu's fetal cell-free DNA analyses."); *id.* at *17 ("[W]e have a dearth of evidence suggesting formaldehyde's use in a sample where *cell-free* DNA is the analyte, and no sufficient, persuasive evidence or technical reasoning to explain why a [person of ordinary skill in the art] would not have been concerned with potential damage to the cffDNA.").

Similarly, the Board did not err by focusing its obviousness inquiry on the context or the requirements of the prior art rather than the claims. *But see Axonics*, 73 F.4th at 958 (finding that the Board erred by limiting its obviousness analysis to the context of a specific facial nerve addressed by the prior art when the claims were not limited to that specific facial nerve). Here, as discussed above, the Board focused its obviousness analysis on the context of cffDNA, which is the context of the claims and also the context of Chiu. *See* '277 patent, col. 472, ll. 66–67 ("determining the sequence of a locus of interest on free fetal DNA"); *see* Chiu at 1608, J.A. 17639 ("[I]t is the objective of this study to investigate the effects of different blood-processing protocols on the quantitative analysis of total and fetal DNA in maternal plasma[.]"). As such, we fail to see how the Board's analysis here is analogous to the error identified in *Axonics*. *See* 73 F.4th at 958.

For those reasons, we find no legal error in the Board's motivation to combine analysis.

II

Finally, Labcorp argues that the Board's findings were not supported by substantial evidence because the Board (1) failed to account for the evidence that both justified and detracted from its decision, (2) "grossly misinterpreted Bianchi," and (3) "relied on pure conjecture." Labcorp Br. 53–58. We disagree on all three counts.

As is apparent from the discussion of the legal issues above, the Board thoroughly considered the references and expert testimony provided by both parties. Labcorp has failed to identify any factual finding by the Board that was not reasonably supported by substantial evidence. At bottom, the Board weighed the evidence both for and against a motivation to combine the references and found that Ravgen's "reasoning and evidence on those issues, separately and cumulatively, outweigh[ed] [Labcorp's] comparatively weak showing on whether a [person of ordinary skill in the art] would have combined the art in the manner proposed." *01054 Decision*, at *14. "This court does not reweigh evidence on appeal." *In re NTP, Inc.*, 654 F.3d 1279, 1292 (Fed. Cir. 2011).

CONCLUSION

We have considered Labcorp's remaining arguments and find them unpersuasive. For the forgoing reasons, we affirm the Board's decisions in IPR2021-00902 and IPR2021-01054.

AFFIRMED