Trials@uspto.gov
571-272-7822

Paper 64
Date: August 15, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARIOSA DIAGNOSTICS
Petitioner,

v.

VERINATA HEALTH, INC.
Patent Owner.

Cases IPR2013-00276 and IPR2013-00277
Patent 8,318,430 B2

Before TONI R. SCHEINER, LORA M. GREEN, and RAMA G. ELLURU, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON REMAND
35 U.S.C. § 144 and 37 C.F.R. § 42.5(a)

BACKGROUND

In IPR2013-00276, Ariosa Diagnostics, Inc. ("Petitioner" or "Ariosa") filed a Petition requesting *inter partes* review of claims 1–18 of U.S. Patent No. 8,318,430 B2 (Ex. 1001, "the '430 patent") pursuant to 35 U.S.C. §§ 311–319. IPR2013-00276, Paper 1 ("'276 Pet."). Verinata Health, Inc., ("Patent Owner" or "Verinata") filed a Preliminary Response. IPR2013-00276, Paper 10 ("'276 Prelim. Resp."). On the basis of the Petition and the Preliminary Response, we determined that Petitioner had demonstrated a reasonable likelihood of prevailing with respect to at least one of the challenged claims, and on October 25, 2013, an *inter partes* review of claims 1–18 was instituted on the asserted ground that the claims would have been unpatentable over the combined teachings of Shoemaker,[1] Dhallan,[2] and Binladen.[3] IPR2013-00276, Paper 11 ("'276 Dec."), 21. After institution of trial, Patent Owner filed a Patent Owner Response (IPR2013-00276, Paper 20, "'276 PO Resp."), to which Petitioner filed a Reply (IPR2013-00276, Paper 26, "'276 Reply").

In IPR2013-00277, Ariosa filed a Petition requesting *inter partes* review of claims 19–30 of the '430 patent (Ex. 1001) pursuant to 35 U.S.C. §§ 311–319. IPR2013-00277, Paper 1 ("'277 Pet."). Verinata filed a

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[1] Shoemaker et al., Pub. No. US 2008/0090239 A1, published Apr. 17, 2008 ("Shoemaker") (Ex. 1008).

[2] Dhallan, Patent No. US 7,322,277 B2, issued Feb. 19, 2008 ("Dhallan") (Ex. 1004).

[3] Jonas Binladen et al., *The Use of Coded PCR Primers Enables High-Throughput Sequencing of Multiple Homolog Amplification Products by 454 Parallel Sequencing,* 2 PLOS ONE 1–9 (2007) ("Binladen") (Ex. 1005).

Preliminary Response. IPR2013-00277, Paper 9 ("'277 Prelim. Resp."). On the basis of the Petition and the Preliminary Response, we determined that Petitioner had demonstrated a reasonable likelihood of prevailing with respect to at least one of the challenged claims, and on October 25, 2013, an *inter partes* review of claims 19–30 was instituted on the asserted ground that the claims would have been unpatentable over the combined teachings of Shoemaker, Dhallan, and Binladen. IPR2013-00277, Paper 10 ("'277 Dec."), 21. After institution of trial, Patent Owner filed a Patent Owner Response (IPR2013-00277, Paper 19, "'277 PO Resp."), to which Petitioner filed a Reply (IPR2013-00277, Paper 25, "'277 Reply").

Oral argument was requested by both parties in both proceedings, and a consolidated argument was held on July 16, 2014. A transcript of the oral hearing is in the record. Paper 42,[4] "Tr."

On October 23, 2014, we issued Final Written Decisions in both proceedings in accordance with 37 C.F.R. § 42.73. We concluded that Petitioner had failed to demonstrate by a preponderance of the evidence that claims 1–30 are unpatentable. IPR2013-00276, Paper 43 ("'276 Final Written Decision"), 23 (challenged claims 1–18); IPR2013-00277, Paper 42, ("'277 Final Written Decision"), 23 (challenged claims 19–30). Petitioner appealed the '276 Final Written Decision and the '277 Final Written Decision to the United States Court of Appeals for the Federal Circuit.

The Federal Circuit consolidated the appeals of the two *inter partes* review proceedings, and issued a decision on November 16, 2015. *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359 (Fed. Cir. 2015). In

[4] If a particular proceeding is not referenced, all paper numbers refer to the paper numbers in IPR2013-00276.

particular, the court noted that we may have erred by not considering Exhibit 1010, an Illumina Brochure, "even as evidence of the background understanding of skilled artisans as of January 2010, simply because the brochure had not been identified at the petition stage as one of the pieces of prior art defining a combination for obviousness." *Id.* at 1365. The court, therefore, vacated our finding of nonobviousness and remanded the case. The Federal Circuit's mandate issued on December 23, 2015.

A conference call was held on January 8, 2016, to discuss the procedure to be taken post-remand. We authorized Petitioner to file a fifteen-page brief, "limited to how we may have overlooked how Petitioner relied upon Exhibit 1010 in the record that went up to the Court of Appeals for the Federal Circuit on appeal." Paper 49, 3. We noted that we would not consider any argument or evidence that was not before the Federal Circuit on appeal. *Id.* at 4. We authorized Patent Owner to file a fifteen-page opposition. *Id.* We also authorized Petitioner authorization to file a five-page Reply.

In accordance with the Board's Order, Petitioner filed its Opening Brief on Remand on January 22, 2016. Paper 53. Patent Owner filed a Remand Opposition Brief on February 5, 2016 (Paper 56), and Petitioner filed its Reply Brief on Remand on February 24, 2016 (Paper 60).

On remand, Petitioner argues "(1) that the proper context for consideration of Ex. 1010 is the combination of references on which review was instituted, which utilized Shoemaker (not Dhallan) as the primary reference; (2) that the Petition and supporting declarations properly presented Ex. 1010 as evidence of the state of the art in which a skilled artisan would view the combination of the art of the instituted ground; and

(3) that when properly considered, this evidence demonstrates that the asserted claims are obvious." Paper 53, 1.

The Board has reviewed the record in light of the Federal Circuit's decision and the arguments of the parties. For the reasons that follow, we again conclude that Petitioner has not demonstrated by a preponderance of the evidence that the combination of Shoemaker, Dhallan, and Binladen renders challenged claims 1–30 of the '430 patent unpatentable under 35 U.S.C. § 103(a).

ANALYSIS

A. The '430 Patent

The '430 patent discloses a method for determining the presence or absence of fetal aneuploidy—a condition in which a fetus carries an abnormal number of chromosomes—by determining the relative amounts of non-random polynucleotide sequences from a chromosome suspected of being aneuploid, and from a reference chromosome or a chromosome control region, in a cell-free sample from a pregnant woman. Ex. 1001, 1:23–27, 2:10–11, 13:9–12, 19:18–19. The '430 patent further discloses determining simultaneously the presence or absence of fetal aneuploidy in pooled, indexed, cell-free samples from a plurality of pregnant women, using massively parallel sequencing. *Id.* at 1:23–25, 1:66–67.

Briefly, cell-free samples (e.g., maternal serum or plasma) containing both maternal and fetal nucleic acid fragments are obtained from a plurality of pregnant women. *Id.* at 1:41–44. In each sample, non-random polynucleotide sequences from a chromosome suspected of being aneuploid, and non-random sequences from a reference chromosome or chromosome control region, are enriched selectively and indexed (i.e., tagged for later

identification as originating from a particular sample). *Id.* at 22:9–15. The enriched, indexed samples are pooled, and the enriched, indexed nucleic acids are sequenced by massively parallel sequencing to produce sequence reads. *Id.* The number of sequence reads from the chromosome suspected of being aneuploid, and the number of sequence reads from the reference chromosome or a chromosome control region, are counted, and the two numbers are compared to determine whether there is an abnormal level of DNA associated with the chromosome suspected of being aneuploid. *Id.* at 1:45–48, 17:53–59. As discussed above, indexing allows results from different samples to be distinguished. Ex. 1001, 22:10–15.

B. Illustrative Claims

Of challenged claims 1–30, claims 1 and 19 are independent, are illustrative of the claimed subject matter, and are reproduced below:

> 1. A method for determining a presence or absence of a fetal aneuploidy in a fetus for each of a plurality of maternal blood samples obtained from a plurality of different pregnant women, said maternal blood samples comprising fetal and maternal cell-free genomic DNA, said method comprising:
>
> (a) obtaining a fetal and maternal cell-free genomic DNA sample from each of the plurality of maternal blood samples;
>
> (b) selectively enriching a plurality of non-random polynucleotide sequences of each fetal and maternal cell-free genomic DNA sample of (a) to generate a library derived from each fetal and maternal cell-free genomic DNA sample of enriched and indexed fetal and maternal non-random polynucleotide sequences, wherein each library of enriched and indexed fetal and maternal non-random polynucleotide sequences includes an indexing nucleotide sequence which identifies a maternal blood sample of the plurality of maternal blood samples, wherein said plurality of non-random polynucleotide sequences comprises at least 100 different non-random polynucleotide sequences selected from a first

chromosome tested for being aneuploid and at least 100 different non-random polynucleotide sequences selected from a reference chromosome, wherein the first chromosome tested for being aneuploid and the reference chromosome are different, and wherein each of said plurality of non-random polynucleotide sequences is from 10 to 1000 nucleotide bases in length,

(c) pooling the libraries generated in (b) to produce a pool of enriched and indexed fetal and maternal non-random polynucleotide sequences;

(d) performing massively parallel sequencing of the pool of enriched and indexed fetal and maternal non-random polynucleotide sequences of (c) to produce sequence reads corresponding to enriched and indexed fetal and maternal non-random polynucleotide sequences of each of the at least 100 different non-random polynucleotide sequences selected from the first chromosome tested for being aneuploid and sequence reads corresponding to enriched and indexed fetal and maternal non-random polynucleotide sequences of each of the at least 100 different non-random polynucleotide sequences selected from the reference chromosome;

(e) based on the indexing nucleotide sequence, for each of the plurality of maternal blood samples, enumerating sequence reads corresponding to enriched and indexed fetal and maternal non-random polynucleotide sequences selected from the first chromosome tested for being aneuploid and sequence reads corresponding to enriched and indexed fetal and maternal non-random polynucleotide sequences selected from the reference chromosome; and

(f) for each of the plurality of maternal blood samples, determining the presence or absence of a fetal aneuploidy comprising using a number of enumerated sequence reads corresponding to the first chromosome and a number of enumerated sequence reads corresponding to the reference chromosome of (e).

19. A method for determining a presence or absence of a fetal aneuploidy in a fetus for each of a plurality of maternal blood

samples obtained from a plurality of different pregnant women, said maternal blood samples comprising fetal and maternal cell-free genomic DNA, said method comprising:

(a) obtaining a fetal and maternal cell-free genomic DNA sample from each of the plurality of maternal blood samples;

(b) selectively enriching a plurality of non-random polynucleotide sequences of each fetal and maternal cell-free genomic DNA sample of (a) to generate a library derived from each fetal and maternal cell-free genomic DNA sample of enriched and indexed fetal and maternal non-random polynucleotide sequences, wherein each library of enriched and indexed fetal and maternal non-random polynucleotide sequences includes an indexing nucleotide sequence which identifies a maternal blood sample of the plurality of maternal blood samples, wherein said plurality of non-random polynucleotide sequences comprises at least 100 different non-random polynucleotide sequences selected from at least one chromosome region tested for being aneuploid and at least 100 different non-random polynucleotide sequences selected from at least one chromosome control region, wherein the at least one chromosome region tested for being aneuploid and the at least one chromosome control region are different, and wherein each of said plurality of non-random polynucleotide sequences is from 10 to 1000 nucleotide bases in length,

(c) pooling the libraries generated in (b) to produce a pool of enriched and indexed fetal and maternal non-random polynucleotide sequences;

(d) performing massively parallel sequencing of the pool of enriched and indexed fetal and maternal non-random polynucleotide sequences of (c) to produce sequence reads corresponding to enriched and indexed fetal and maternal non-random polynucleotide sequences of each of the at least 100 different non-random polynucleotide sequences selected from the at least one chromosome region tested for being aneuploid and sequence reads corresponding to enriched and indexed fetal and maternal non-random polynucleotide sequences of each of

> the at least 100 different non-random polynucleotide sequences selected from the at least one chromosome control region;
>
> (e) based on the indexing nucleotide sequence, for each of the plurality of maternal blood samples, enumerating sequence reads corresponding to enriched and indexed fetal and maternal non-random polynucleotide sequences selected from the at least one chromosome region tested for being aneuploid and sequence reads corresponding to enriched and indexed fetal and maternal non-random polynucleotide sequences selected from the at least one chromosome control region; and
>
> (f) for each of the plurality of maternal blood samples, determining the presence or absence of a fetal aneuploidy comprising using a number of enumerated sequence reads corresponding to the at least one chromosome region tested for being aneuploid and a number of enumerated sequence reads corresponding to the at least one chromosome control region of (e).

C. The Final Written Decisions

In both the '276 Final Written Decision and the '277 Final Written Decision, we reviewed the teachings of Shoemaker, Dhallan, and Binladen. '276 Final Written Decision, 8–10; '277 Final Written Decision, 8–10. After summarizing the teachings of those references, we noted that upon consideration of the Petition, as well as the Declarations of Drs. Morton and Nussbaum, Petitioner had failed to demonstrate the unpatentability of the challenged claims by a preponderance of the evidence. '276 Final Decision, 16; '277 Final Written Decision, 16. In particular, we noted that "[a]lthough the Petition and accompanying Declarations point to disparate elements of the three references, and attempt to map them to elements of the challenged claims, virtually no effort is made to explain how or where the references differ from the challenged claims, how one of ordinary skill in the art would go about combining their disparate elements, or what modifications one of

ordinary skill in the art would necessarily have made in order to combine the disparate elements." '276 Final Decision, 16.[5] We concluded, therefore, that the Petition and accompanying Declarations failed to provide "an 'articulated reason[] with some rational underpinning to support the legal conclusion of obviousness.'" *Id.* (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

As to Exhibit 1010, we noted that we were not "persuaded by the belated attempt in the Reply and Dr. Morton's Second Declaration to bolster Petitioner's initial obviousness challenge by reference to technical advances, e.g., massively parallel sequencing ("MPS"), that one of ordinary skill in the art would have been aware of 'in the years between the filing of *Dhallan* and the earliest claimed priority date.'" *Id.* at 17. In particular, we noted that the testimony of Dr. Morton in her Second Declaration (Ex. 1042 ¶¶ 42–43), "in effect, replaces the tagging and sequencing techniques of Dhallan and Binladen with the Illumina indexing kit and sequencing platform, but neither Petitioner nor Dr. Morton explains why Exhibit 1010 could not have been presented as part of the asserted ground of unpatentability in the first instance with the Petition." *Id.* at 19. We, thus, exercised our discretion to accord that aspect of the testimony of Dr. Morton little weight. *Id.*

[5] We determine there is no need to cite to the papers and exhibits in both proceedings given the identity of the issues in both proceedings addressed here. *See, e.g.*, *Ariosa*, 805 F.3d at 1360 n.1 (noting the "board's decisions are the same in all respects material to this opinion. Instead of providing duplicative citations, we cite only the decision in IPR2013-00276, which we call simply '*Ariosa*.'").

D. The Decision of the Federal Circuit

On appeal to the Federal Circuit, Petitioner argued that we "erred in refusing to consider Exhibit 1010 for what it showed about the background knowledge that a skilled artisan would have possessed, particularly about DNA indexing, in January 2010." *Ariosa*, 805 F.3d at 1365. The Federal Circuit noted that our language in the Final Written Decision, "on its face," supported Petitioner's assertion that we declined to consider Exhibit 1010 as evidence of what the understanding of the ordinary artisan would have been at the relevant time period "simply because the brochure had not been identified at the petition stage as one of the pieces of prior art defining a combination for obviousness." *Id.* According to the Federal Circuit, if that was what we in fact meant to say, we erred, as "[a]rt can legitimately serve to document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness." *Id.* (citing *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362–63 (Fed. Cir. 2013)). The Federal Circuit stated that Petitioner was in fact using Exhibit 1010 in that manner. *Id.*

The Federal Circuit noted, however, that it was unclear whether we declined to give much weight to Exhibit 1010 on a legally proper ground. *Id.* at 1366. Specifically, according to the Federal Circuit:

> The Board might have been saying only that the development of the argument invoking Exhibit 1010 in the Petitions was not adequate. This court in *Randall* did not dispense with the need for parties to provide adequately developed explanations when relying on background knowledge based on cited art; the adequacy of the challenger's explanation in that regard was unquestioned in *Randall*. 733 F.3d at 1360. And a PTO regulation provides: "[t]he Board may exclude or give no weight to the evidence where a party has failed to state its relevance."

> 37 C.F.R. § 42.104(b)(5). In the present case, other than stating that massively parallel sequencing was known by 2008, the Petitions and supporting declarations say little about the relevance of Exhibit 1010, such as how a skilled artisan would have used what it showed about background knowledge in combining or modifying the prior-art references or how it tended to show that a skilled artisan would have had a reasonable expectation of success in achieving the suggested combination and modification.

Id.

As the Federal Circuit could not discern whether we had given Exhibit 1010 little weight for a legally proper reason, or on an erroneous legal reason, it vacated and remanded the Final Written Decisions. *Id.* at 1366–68. In doing so, the Federal Circuit stated that it was unwilling to draw its own conclusions about whether Exhibit 1010 would have filled the "explanatory gap" of Petitioner's obviousness challenge, given the complexity of the subject matter. *Id*.

Petitioner argued also on appeal that we erred in failing to consider certain embodiments of Dhallan that do not require a restriction-enzyme digestible primer. *Id.* at 1367. The Federal Circuit noted that it saw "no error in the Board's rejection of Ariosa's reliance, in its Reply submissions, on previously unidentified portions of a prior-art reference to make a meaningfully distinct contention." *Id.* Specifically, the Federal Circuit acknowledged that "[n]ot until Dr. Morton's Reply declaration did Ariosa identify specific embodiments of Dhallan that do not use restriction-enzyme digestible primers." *Id.* Thus, the Federal Circuit concluded that we did not err in determining that those portions of Dhallan that do not require a restriction-enzyme digestible primer were identified for the first time by

Ariosa in its Reply, and that we did not err in declining to rely upon those embodiments in the obviousness analysis. *Id.* at 1368.

Finally, Petitioner also argued on appeal that we erred in not sufficiently considering the teachings of Shoemaker in the obviousness analysis. *Id.* The Federal Circuit noted in response that we had addressed Shoemaker throughout our analysis, but as the case was being remanded, remarked that we "may decide whether its treatment of Shoemaker should be left as is, supplemented, or revised." *Id.*

E. Patentability of Claims

On remand, Petitioner argues that the "level of skill in the art, as evidenced by Ex. 1010, would be brought to bear in the context of the combination of Shoemaker, Dhallan and Binladen." Paper 53, 5. That combination, Petitioner asserts, starts with the MPS detection of Shoemaker, which is performed on the Illumina Genome analyzer, to determine fetal aneuploidy, and thus, modifies the method of incorporating multiplexing as taught by Binladen. *Id.*

Petitioner contends that there were two challenges presented in the Petition, and the one on which trial was instituted was based on the aneuploidy detection technique of Shoemaker, not Dhallan. *Id.* That challenge, Petitioner contends, "involves modification of Shoemaker's detection method to use cell-free DNA as taught in Dhallan and indexing of individual samples as exemplified by Binladen." *Id.* at 6. As set forth in the claim chart in the Petition, "the massively parallel sequencing method relied upon in the instituted combination is MPS on the Illumina Genome Analyzer as discussed in Shoemaker." *Id.* (quoting '276 Pet. 46 (discussing element (d) of claim 1)). That was recognized, Petitioner asserts, in the Decision on

Institution. *Id.* at 7 (quoting '276 Dec. 18). Petitioner contends further that the Federal Circuit recognized that distinction when it "noted that the Petitions presented multiple combinations based on Dhallan and that the second of those combinations relied on Dhallan only for the use of cell-free DNA." *Id.* at 8 (citing Ex. 1050,[6] 8; *Ariosa*, 805 F.3d at 1363).

Moreover, Petitioner contends, the "petition and accompanying declarations properly referenced Ex. 1010 as evidence of the level of skill in the art." Paper 53, 8 (citing '276 Pet. 41–48; Ex. 1003 ¶¶ 19–23). Petitioner argues further that the Federal Circuit also recognized that the Illumina Brochure (Ex. 1010), could be used as evidence of the level of skill in the art. *Id.* at 9 (quoting Ex. 1050, 11–12; *Ariosa*, 805 F.3d at 1365). Petitioner asserts, the "Federal Circuit decision thus recognizes that the Petition presented the Illumina multiplexing kit as evidence that indexing (*i.e.*, multiplexing) could have been executed on the Illumina Genome Analyzer with a commercially-available kit." *Id.* at 9–10.

According to Petitioner, Patent Owner, in its Response, "constructed a straw man by advancing as its primary argument that Binladen's tagging or indexing method could not be combined with Dhallan's sequencing methods." *Id.* at 10 (citing '276 PO Resp. 50–52). That argument, Petitioner argues, "has nothing to do with the sequencing technique used in the ground on which trial was actually instituted, *i.e.*, Shoemaker's MPS sequencing method performed on the Illumina Genome Analyzer." *Id.* Petitioner argues that we were apparently misled by that argument, as the Final Written Decision "says nothing about whether a skilled artisan would

[6] Exhibit 1050 is the slip opinion of the Federal Circuit's decision in *Ariosa*.

have had difficulty performing indexing on the Illumina Genome Analyzer used in Shoemaker," but instead focuses on "the compatibility of Binladen's indexing technique with Dhallan's detection technique involving restriction digestible enzymes." *Id.* (citing '276 Final Written Decision 12–17). According to Petitioner, that incompatibility is "irrelevant as it does not address the combination on which trial was instituted." *Id.*

Thus, Petitioner contends, "[u]nder a proper assessment of Petitioner's argument, including a skilled artisan's knowledge of the commercial availability of multiplexing kits as shown in Ex. 1010, Petitioner has established that the challenged claims are obvious." *Id.* at 11. Petitioner argues that as explained in the Petition, "a skilled artisan would have considered it obvious to modify Shoemaker's MPS (performed on the Illumina Genome Analyzer) to use cell-free DNA (taught by Dhallan) and multiplexing (taught by Binladen)." *Id.* (citing Pet. 41). The Illumina Brochure, Ex. 1010, demonstrates that the ordinary artisan "could perform multiplexing on the Illumina Genome Analyzer by ordering a kit from Illumina." *Id.* (citing Pet. 11; Ex. 1003 ¶¶ 21–23).

Of note, Petitioner asserts, Patent Owner and its declarants "did not argue that there was anything difficult about modifying MPS to include indexing at the time of filing." *Id.* at 13. Rather, Patent Owner argued "that 'neither the petition nor the declarations of Ariosa's experts provide explanation of **how** the references could be modified or combined to arrive at the '430 patent claimed methods.'" *Id.* (citing PO Resp. 13). However, according to Petitioner, "one skilled in the art would not attempt to bodily incorporate Binladen's specific indexes into the Illumina Genome Analyzer, especially when an off-the-shelf multiplexing kit was available from

Illumina." *Id.* at 14 (citing *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 421 (2007) for the proposition that "a person of ordinary skill has common sense and is not a mere automaton"). Petitioner contends "[t]he Nussbaum declaration [Ex. 1003] and Ex. 1010 clearly and indisputably showed that Shoemaker's MPS technique could have been modified with ease to include the indexing suggested by Binladen. Indeed, from a technical perspective nothing could be easier than ordering an off-the-shelf kit." *Id.* at 14–15.

Patent Owner responds:

> Although Ariosa successfully caused the Federal Circuit to accept the possibility that the Board might not have properly considered Exhibit 1010, the Federal Circuit nevertheless recognized that the Board may simply have found that "the development of the argument invoking Exhibit 1010 in the Petitions was not adequate." The Federal Circuit explained that this "inadequate-explanation" reading of the Board's original decision is consistent with the Board's fundamental finding that Ariosa broadly failed to develop its obviousness theory and that, even in her reply declaration, Dr. Morton did not adequately address how Exhibit 1010 would have supported Ariosa's obviousness theory.

Paper 56, 2 (citations omitted). Patent Owner asserts, therefore, that we "properly considered Exhibit 1010." *Id.*

We conclude that we did not improperly fail to consider the Illumina Brochure (Ex. 1010) as evidence of the level of skill in the art. Instead, when the challenge over Shoemaker, Dhallan, and Binladen as presented in the Petitions is considered in view of the Illumina Brochure, the Petitions fail to demonstrate the unpatentability of the challenged claims by a preponderance of the evidence for the reasons set forth in the Final Written Decisions.

As to the challenge over Shoemaker, Dhallan, and Binladen, the Petition states:

> A scientist in this field would have known that Dhallan could be enhanced through use of the PCR amplification techniques utilizing sample indices and massively parallel sequencing of pooled samples as discussed in Binladen. Professors Nussbaum and Morton explain in their declarations that a skilled artisan would also have readily understood that Shoemaker's methods for determining the presence of fetal abnormalities could be carried out with the use of cell-free DNA described in Dhallan and the multiplexed detection techniques taught in Binladen. *(Nussbaum Declaration ¶¶ 109-165; Morton Declaration ¶¶98-129)*

'276 Pet. 40–41.

Petitioner, however, provided no further explanation of the combination in the Petition, such as a reason with rational underpinning as to why the ordinary artisan would have combined the references to arrive at the method of the challenged claims, but only presented a claim chart demonstrating where the limitations of each challenged claim could be found in the cited prior art.

As noted by the Final Written Decision ('276 Final Written Decision 11), we acknowledged that Dr. Morton testified:

> [A] skilled artisan would read Dhallan in the context of the state of the art in indexed PCR amplification techniques as discussed in Binladen. A skilled artisan reading Shoemaker would understand that the disclosed methods for determining the presence of fetal abnormalities could be carried out with the Dhallan/Binladen techniques. It is my view that the state of the art as reflected by Shoemaker, Dhallan and Binladen makes obvious the techniques described in claims 1–18 of the '430 patent.

Ex. 1002 ¶ 98.

We also acknowledged ('276 Final Written Decision 11) the following testimony of Dr. Nussbaum:

> [T]his combination discloses each element of Claims 1–18 of the '430 patent and [I] believe that one skilled in the art would have been motivated to combine these techniques, as the combination would clearly result in an enhanced productivity and increased throughput of sample analysis. The sequencing and multiplexing technology of Binladen would have made the procedures of Shoemaker and Dhallan less expensive, faster and more efficient because one could sequence indexed samples from many different patients in a single sequencing run instead of laboriously performing a single sequencing run for the DNA samples from each patient.

Ex. 1003 ¶ 109.

Although the Declarations provided more explanation of why a skilled artisan would have had reason to combine the identified references than the Petition, as we noted in the Final Written Decision:

> [T]here is no mention in the Petition or the Declarations of any differences between the claimed subject matter and the prior art, beyond a single statement that "Dhallan does not teach indexing" (Ex. 1002 ¶ 104). Moreover, nowhere is it explained how one of ordinary skill in the art would go about combining the disparate elements of the references, nor is it explained what modifications one of ordinary skill in the art would necessarily have made in order to combine them.

'276 Final Written Decision 11–12.

In particular, although Petitioner now argues that "if one starts with the Shoemaker's MPS performed on the Illumina Genome Analyzer as the base technique, it is readily apparent from the Illumina multiplexing kit brochure that modifying Shoemaker's MPS technique to include indexing required nothing more than ordering a kit" (Paper 53, 11), Petitioner does not explain where it made that argument in the Petition, or in any of its

papers. Petitioner points us to paragraphs 21 to 23 of Dr. Nussbaum's Declaration (Paper 53, 11–12), but it does not point us to where in the Petition it relied on those paragraphs in its challenge of the claims over Shoemaker, Dhallan, and Binladen. *Cf. DeSilva v. DiLeonardi*, 181 F.3d 865, 866-67 (Fed. Cir. 1999) ("A brief must make all arguments accessible to the judges, rather than ask them to play archaeologist with the record.").

Petitioner states also that the "Federal Circuit specifically noted this testimony in its decision" (Paper 12 (citing Ex. 1050, 13)), but as noted by the Federal Circuit:

> In the present case, other than stating that massively parallel sequencing was known by 2008, the Petitions and supporting declarations say little about the relevance of Exhibit 1010, such as how a skilled artisan would have used what it showed about background knowledge in combining or modifying the prior-art references or how it tended to show that a skilled artisan would have had a reasonable expectation of success in achieving the suggested combination and modification.

Ex. 1050, 13; *Ariosa*, 805 F.3d at 1366.

Thus, although the Illumina Brochure may be evidence of the level of skill in the art, Petitioner has not explained how we overlooked how it relied on that brochure in its Petition and in the Declarations of Drs. Nussbaum and Morton, such that the brochure remedies the deficiencies of the challenge over Shoemaker, Dhallan, and Binladen as discussed in our Final Written Decisions. In fact, as Petitioner recognizes (Paper 53, 7), we specifically cited those portions of Shoemaker that rely on the Illumina System in our Institution Decision. '276 Dec. 18 (citing Shoemaker, Ex. 1008 ¶ 157, which states that the "above embodiment can also be modified to provide for genotyping by hybridizing the nucleic acid tags to bead arrays as are commercially available by Illumina.").

As the Supreme Court pointed out in *KSR*, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Rather, the Court stated:

> [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements *in the way the claimed new invention does* . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

Id. at 418-419 (emphasis added); *see also id.* at 418 (requiring a determination of "whether there was an apparent reason to combine the known elements *in the fashion claimed* by the patent at issue") (emphasis added).

Moreover, paragraphs 21 to 23 of Dr. Nussbaum's Declaration do not convince us otherwise. The Declaration merely notes that Illumina "offered a commercially available kit for production and analysis of indexed libraries from different samples of origin," such that a molecular geneticist "would have had the ability to order a commercially available kit for production of enriched and indexed libraries, which I could have analyzed on a commercially-available massively parallel sequencing platform sold by the same vendor." Ex. 1003 ¶¶ 21, 23. As noted by the Federal Circuit (*Ariosa*, 805 F.3d at 1366), however, Dr. Nussbaum does not explain how that kit would have been used in the combination of Shoemaker, Dhallan, and Binladen, nor how it provides a reasonable expectation of achieving the method of the challenged claims.

Petitioner, in its Opening Brief on Remand (Paper 53, 6) points us also to the following section of the claim chart discussing element (d) of challenged claim 1[7]:

(d) performing massively parallel sequencing of the pool of enriched and indexed fetal and maternal non-random polynucleotide sequences of (c) to produce sequence reads . . . selected from the first chromosome tested for being aneuploid and sequence reads corresponding to enriched and indexed fetal and maternal non-random polynucleotide sequences . . . selected from the reference chromosome;	"The amplified DNA region(s) can be analyzed by sequencing methods." *(Shoemaker ¶15; see also the discussion of the Illumina Genome Analyzer at ¶157)* "In step 410, pooled genomic DNA/amplicons are analyzed to measure, e.g., allele abundance of genomic DNA regions (e.g. STRs amplified). In some embodiments such analysis involves the use of capillary gel electrophoresis (CGE). In other embodiments, such analysis involves sequencing or ultra deep sequencing." *(Shoemaker ¶122)* "The amplification on the bead results in each bead carrying at least one million, at least 5 million, or at least 10 million copies of the original amplicon coupled to is. Finally, the beads are placed into a highly parallel sequencing by synthesis machine which generates over 400,000 reads (-100 bp per read) in a single 4 hour run." *(Shoemaker ¶127)* *See Shoemaker ¶¶114, 147, 159.* "In embodiments, alleles of multiple loci of interest are sequenced and their relative amounts quantitated and expressed as a ratio. In one embodiment, the sequence of alleles of one to tens to hundreds to thousands of loci of interest on a single chromosome on template DNA is determined. In another embodiment, the sequence of alleles of one to tens to hundreds to thousands of loci of interest on multiple chromosomes is determined." *(Dhallan, 7:9-16)*

[7] Petitioner's claim chart as to this element of challenged claim 19 in IPR2013-00277 is virtually identical to the claim chart of this element of challenged claim 1 in IPR2013-00276, and, thus, we see no need to address claim 19 separately from claim 1 on remand.

	"Any method that provides information on the sequence of a nucleic acid can be used including but not limited to… DNA sequencing, Sanger dideoxy sequencing, DNA sequencing gels, capillary electrophoresis on an automated DNA sequencing machine…" *(Dhallan, 36: 6-14)* "We use conventional PCR with 59-nucleotide tagged primers to generate homologous DNA amplification products from multiple specimens, followed by sequencing through the high-throughput Genome Sequence 20™ DNA Sequencing System (GS20, Roche/454 Life Sciences)." *(Binladen, 1:Background:4-6*) *see also Figure 1.* See Declarations of Prof. Nussbaum at ¶¶130-133 and Prof. Morton at ¶110.

That section of the claim chart relies on paragraphs 130 to 133 of Dr. Nussbaum's Declaration and paragraph 110 of Dr. Morton's Declaration.

Dr. Morton testified:

> The twelfth element of claim 1 of the '430 patent is disclosed in Shoemaker, Dhallan and Binladen. Claim 1 recites, "(d) performing massively parallel sequencing . . . . Shoemaker discloses massively parallel sequencing of enriched and indexed non-random polynucleotide sequences at, *e.g.*, ¶15, ...
>
> Dhallan teaches massively parallel sequencing . . . .
>
> Binladen teaches indexing of samples in the background . . . .

Ex. 1002 ¶ 110.

Similarly, Dr. Nussbaum testified:

> **(d) performing massively parallel sequencing . . . .**
>
> 130) Claim 1(d): Step (c) of claim 1 is disclosed in the combination of Shoemaker, Dhallan and Binladen. Shoemaker teaches various sequencing platforms, including massively parallel sequencing, *e.g.*, at [0127] . . .

> 131) Dhallan teaches that various forms of sequencing can be used for determining the sequence of the selected polynucleotide regions analyzed . . . .
>
> 132) Dhallan further states at Col. 36, lines 6-14 that "[a]ny method that provides information on the sequence of a nucleic acid can be used including but not limited to . . . DNA sequencing, Sanger dideoxy sequencing, DNA sequencing gels, capillary electrophoresis on an automated DNA sequencing machine . . ."
>
> 133) Binladen teaches indexing of samples for assignment of a PCR product to a particular sample to enable accurate sequencing and assignment of homologous DNA sequences from multiple sources in single high-throughput GS20 run.

Ex. 1003 ¶¶ 129–133.

Notably, neither the claim chart nor the Declarations of Drs. Morton and Nussbaum provide a reason, with rational underpinning, as to why the ordinary artisan would have combined the cited teachings to arrive at element (d) of claim 1, even in view of Shoemaker's teaching of massively parallel sequencing methods, which may be performed on the Illumina Genome Analyzer, as taught by the Illumina brochure. *Kahn*, 441 F.3d at 977.

Thus, when the combination of Shoemaker, Dhallan, and Binladen is considered in view of the state of the art as evidenced by the Illumina Brochure, Ex. 1010, Petitioner did not establish a reason to combine to the identified asserted references. As noted in our Final Written Decisions:

> Although the Petition and accompanying Declarations point to disparate elements of the three references, and attempt to map them to elements of the challenged claims, virtually no effort is made to explain how or where the references differ from the challenged claims, how one of ordinary skill in the art would go about combining their disparate elements, or what modifications one of ordinary skill in the art would necessarily have made in

> order to combine the disparate elements. What is lacking in the Petition and accompanying Declarations is an "articulated reason[] with some rational underpinning to support the legal conclusion of obviousness." *Kahn*, 441 F.3d at 988. The inadequacy of the obviousness analysis in the Petition and accompanying Declarations is readily apparent when the disparate elements of the references are scrutinized closely, as in Patent Owner's response, and we decline to search through the record and piece together those teachings that might support Petitioner's position.

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As noted above, the Federal Circuit also observed that we had addressed Shoemaker throughout our analysis, but as they were remanding the case, noted that we "may decide whether [our] treatment of Shoemaker should be left as is, supplemented, or revised." *Ariosa*, 805 F.3d at 1368. For the reasons we already discussed as to the deficiencies of the obviousness challenge over Shoemaker, Dhallan, and Binladen, and as the Federal Circuit determined that we had addressed Shoemaker throughout our analysis, we determine that there is no need to revisit the teachings of Shoemaker on remand.

As we conclude we did not improperly decline to consider the Illumina Brochure (Ex. 1010) as evidence of the level of skill in the art, and that we properly considered the teachings of Shoemaker, we need not address Petitioner's remaining arguments as to the obviousness of the challenged claims over the combination of Shoemaker, Dhallan, and Binladen in its Opening Brief on Remand.

F. Conclusion

We conclude, taking into the account the decision of the Court of Appeals for the Federal Circuit in *Ariosa*, that Petitioner has failed to

demonstrate the unpatentability of challenged claims 1–30 by a preponderance of the evidence.

ORDER

Accordingly, it is

ORDERED that Petitioner has failed to demonstrate the unpatentability of claims 1–30 by a preponderance of the evidence; and

FURTHER ORDERED that this is a final written decision of the Board under 35 U.S.C. § 318(a). Parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

PETITIONER:

Greg Gardella
cpdocketgardella@oblon.com

Scott McKeown
cpdocketmckeown@oblon.com

Dianna DeVore
DDeVore@convergentlaw.com

Sarah Brashears
sbrashears@covergentlaw.com

PATENT OWNER:

Michael Rosato
mrosato@wsgr.com

Maya Skubatch
mskubatch@wsgr.com

Steven Parmelee
sparmelee@wsgr.com