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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARIOSA DIAGNOSTICS,
Petitioner,

v.

VERINATA HEALTH, INC.,
Patent Owner.

Case IPR2013-00276
Patent 8,318,430 B2

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

SCHEINER, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

A. Background

Ariosa Diagnostics, Inc. ("Petitioner") 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. Paper 1 ("Pet."). Verinata Health, Inc., ("Patent Owner") filed a Preliminary Response. Paper

10. On the basis of the Petition and the Preliminary Response, the panel 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, Dhallan, and Binladen. Paper 11 ("Dec.").[1]

After institution of trial, Patent Owner filed a Patent Owner Response (Paper 20, "PO Resp."), to which Petitioner filed a Reply (Paper 26). Oral argument was requested by both parties, and was held on July 16, 2014. A transcript of the oral hearing is included in the record. Paper 42, "Tr."

Both parties presented witness testimony via declaration during the course of the proceeding. Petitioner presented the Declarations of Dr. Cynthia Casson Morton (Ex. 1002, "Morton Decl.") and Dr. Robert Nussbaum (Ex. 1003, "Nussbaum Decl.") with the Petition.[2] Patent Owner presented the Declaration of Dr. Atul J. Butte (Ex. 2003, "Butte Decl.") with its Patent Owner's Response. Finally, with its Reply, Petitioner presented the Second Declaration of Dr. Morton. Ex. 1042 ("Second Morton Decl.").

The Board has jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision, issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73, addresses issues and arguments raised during trial. For the reasons discussed below, we determine that Petitioner has not met its burden to

[1] Patent Owner did not address this asserted ground in its Preliminary Response.

[2] All references to Exhibits 1002 and 1003 are to the replacement Declarations filed on March 31, 2014, unless otherwise indicated.

prove, by a preponderance of the evidence, that claims 1–18 of the '430 patent are unpatentable.

B. Related Matters

The '430 patent is the subject of a civil action, *Verinata Health, Inc. v. Ariosa Diagnostics, Inc.*, Case No. 3:12-cv-05501-S1 (N.D. Cal.), filed October 25, 2012. Paper 39. Furthermore, concurrent with the instant Petition, Petitioner filed another petition challenging claims 19–30 of the '430 patent, IPR2013-00277.

C. 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.

D. Illustrative Claim

Of challenged claims 1–18, claim 1 is the only independent claim. Claim 1, reproduced below, is illustrative.

> 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).

E. The Prior Art

Petitioner relies on the following prior art:

Shoemaker	US 2008/0090239 A1	Apr. 17, 2008	(Ex. 1008)
Dhallan	US 7,332,277 B2	Feb. 19, 2008	(Ex. 1004)

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) (Ex. 1005) ("Binladen").

F. Grounds of Unpatentability Instituted for Trial

The Board instituted *inter partes* review based on the following ground of unpatentability:

Claims 1–18 under 35 U.S.C. §103(a) as unpatentable over the combination of Shoemaker, Dhallan, and Binladen.

II. ANALYSIS

A. Claim Construction

In the Decision on Institution, the panel construed several claim terms (Dec. 7–11), all of which appear in claim 1: (1) "selectively enriching a plurality of non-random polynucleotide sequences;" (2) "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;" (3) "sequence reads corresponding to enriched and indexed fetal and maternal non-random polynucleotide sequences;" (4) and "reference chromosome." We determine it is not necessary to depart from those claim constructions for purposes of this decision.

B. Principles of Law

To prevail in its challenge to the patentability of the claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 18 (1966). An invention "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. Moreover, a rejection on the ground of obviousness must include "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The obviousness analysis "should be made explicit" and it "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." *KSR*, 550 U.S. at 418.

We analyze the instituted grounds of unpatentability in accordance with those principles.

C. Alleged Obviousness over Shoemaker, Dhallan, and Binladen

Petitioner asserts that claims 1–18 of the '430 patent are unpatentable under 35 U.S.C. § 103(a) as having been obvious over the combination of Shoemaker, Dhallan, and Binladen. Petitioner asserts that the combination of Shoemaker, Dhallan, and Binladen teaches all the limitations of the claimed subject matter (Pet. 40–55), and relies, initially, on the Declaration of Dr. Morton (Ex. 1002), as well as the Declaration of Dr. Nussbaum (Ex. 1003), for a rationale to combine those elements. Patent Owner disagrees with Petitioner's assertions (PO Resp. 4–55) and relies on the Declaration of Dr. Butte (Ex. 2003) as evidence that it would not have been obvious for one of ordinary skill in the art to combine the teachings of the references relied on.

1. Shoemaker (Exhibit 1008)

Shoemaker discloses detection and genetic analysis of fetal cells in a blood sample from a pregnant woman—a maternal blood sample—which contains both fetal and maternal cells. Ex. 1008 ¶¶ 13, 71. Genetic analysis of the fetal cells may include determination of the presence or absence of fetal aneuploidy, such as trisomy of chromosome 21, 18, or 13. Ex. 1001 ¶¶ 71, 107, 108. Multiple samples may be obtained from the same individual at different times during the course of the pregnancy (*id.* ¶ 108), but Shoemaker does not disclose pooling the multiple samples with each other, or pooling samples from other individuals. Nor does Shoemaker disclose analyzing a cell-free sample.

Specifically, Shoemaker's method involves enriching fetal cells in the maternal blood sample and distributing them among an array of discrete, addressable locations, e.g., the wells of a microtiter plate, such that each well

contains either one fetal cell, or none at all. *Id.* ¶¶ 107–110. Genomic regions, i.e., loci, of interest are chosen "on a chromosome suspected of trisomy and on a control chromosome," and the loci are amplified and tagged with locator elements (short nucleic acid sequences incorporated into amplification primers). *Id.*¶¶ 114–118. The locator elements "make[] it possible to pool the amplicons from all the discrete locations following the amplification step and analyze the amplicons in parallel." *Id.* ¶¶ 118, 119. After the amplicons are analyzed—i.e., sequenced—the locator elements of the tags are used to sort the sequence reads into "bins" which correspond to the individual wells of the microtiter plate (and thus, the cell(s) in that well), and the sequence reads from the bins are used to determine allele abundance, which in turn, is used to determine aneuploidy. *Id.* ¶¶ 138, 140.

2. Dhallan (Exhibit 1004)

Dhallan discloses non-invasive detection of chromosomal abnormalities, including fetal aneuploidy, in cell-free maternal blood samples. Ex. 1004, 5:63–6:14. Dhallan does not disclose indexing the samples, or pooling samples from multiple individuals.

Briefly, Dhallan's method involves amplifying loci of interest with multiple primer sets. Ex. 1004, 47:63-65, 48:64. Loci of interest may be single nucleotide polymorphisms (SNPs). *Id.* at 25:1-10. The primers may be "designed such that one or both primers of the primer pair contain a sequence in the 5' region for one or more restriction endonucleases (restriction enzyme)." *Id.* at 37: 51-54. Following amplification, restriction digestion of the primer(s) allows creation of a 5' overhang proximal to a locus of interest, and the sequence of the locus of interest is analyzed by incorporating fluorescently-labeled nucleotides to fill in the 5' overhang. Ex.

1004, 7:61–8:8, 19:7–11, 45:43–46, 53:29–31. Hundreds or thousands of loci of interest on multiple chromosomes are sequenced simultaneously, their relative amounts are quantitated, and expressed as a ratio. *Id.* at 7:9–16.

3. Binladen (Exhibit 1005)

Binladen discloses simultaneous sequencing of homolog amplification products from the mitochondrial DNA of thirteen mammalian species, including humans. Ex. 1005, 1, 3.

Binladen's method involves generating homologous DNA amplification products with 5'-nucleotide tagged primers from multiple specimens using conventional PCR, followed by high-throughput sequencing on a parallel sequencing platform. Each DNA sequence is subsequently traced back to its individual source through 5'-tag-analysis. *Id.* at 1, 3, 5.

4. Analysis

Petitioner's position, supported by the Morton and Nussbaum Declarations, is that the method of claim 1 would have been obvious because "a scientist in this field would have known that Dhallan could be enhanced through the use of the PCR amplification techniques utilizing sample indices and massively parallel sequencing of pooled samples as discussed in Binladen" and because "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" (Pet. 40–41 (citing Ex. 1002 ¶ 98, Ex. 1003 ¶ 109)).

Specifically, Dr. Morton explains that:

> [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.

Similarly, Dr. Nussbaum explains that:

> [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.

In addition, Petitioner provides a claim chart detailing where various elements of the challenged claims can be found in Shoemaker, Dhallan, and Binladen. Pet. 41–55. For each element or clause of the claims, the claim chart purportedly identifies where some aspect of that element or clause is disclosed by one or more of the references. The Morton Declaration and the Nussbaum Declaration closely correspond to Petitioner's claim chart in this respect. Ex. 1002 ¶¶ 99–112, Ex. 1003 ¶¶ 110–165. However, there 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.

Patent Owner argues that "[Petitioner] and its experts fail to address the claims as a whole and instead dissect the claims into artificially disembodied 'techniques,' which they interpret in a vacuum and attempt to map into the disclosures of Shoemaker, Dhallan and Binladen." PO Resp. 8. Patent Owner contends "[t]his piecemeal approach is presented in the Petition in the form of a claim chart listing quotes from Shoemaker, Dhallan and Binladen" and "[a] similar piecemeal approach is performed by Drs. Morton and Nussbaum in their declarations." PO Resp. 8 (citing Pet. 41–55, Ex. ¶¶ 98–129, Ex. 1003 ¶¶ 109–165).

Moreover, Patent Owner argues that Petitioner's failure to explain how one of ordinary skill in the art would "combine the disparate parts of these unrelated references in a functional manner" is particularly relevant to this *inter partes* review because "a person of ordinary skill in the art could not actually combine the methods disclosed in the cited references and . . . would not even attempt the proposed combination." PO Resp. 2.

Specifically, Patent Owner argues that Binladen's tagging method would not have been combinable with Dhallan's use of restriction digestible primers. Patent Owner contends "the methods disclosed in Dhallan critically rely on restriction digestible primers [for amplification] followed by cleaving the primer sequence by enzyme digestion" (PO Resp. 50). As

explained by Dr. Butte, Dhallan's "'primers are designed such that one or both primers of the primer pair contain [a]sequence in the 5' region for one or more restriction endonucleases (restriction enzyme)'" (Ex. 2003 ¶ 215 (quoting Ex. 1004, 37:50–53)), and the primers are "designed so that digestion occurs proximal to the SNP site" (Ex. 2003 ¶ 217 (citing Ex. 1004, 38:8–5, 38:24–26, Fig. 1A)). Following amplification, restriction digestion allows creation of a 5' overhang, and the SNP sequence is analyzed by incorporating fluorescently-labeled nucleotides to fill in the 5' overhang. Ex. 2003 ¶¶ 218, 219 (citing Ex. 1004, 7:61–8:8, 19:7–11, 45:43–46, 53:29–31). Dr. Butte explains that Dhallan's "particular primer design approach is necessary for Dhallan's goal of limiting sequence identification to one or a few nucleotides." *Id.* ¶ 217 (citing Ex. 1004, 38:8–5, 38:24–26, Fig. 1A). Binladen, however, teaches the use of tags that are vulnerable to restriction enzymes because they have restriction enzyme sites. *Id.* ¶ 222. Thus, contends Patent Owner, "Binladen['s] tags could not be incorporated in the methods described in Dhallan because they would be incompatible with the restriction digestible primers critical to the process of Dhallan" and "would simply be cleaved off by the restriction enzyme" (*id.* at 52 (citing Ex. 2003 ¶¶ 222–224)). In support, Dr. Butte testifies that "[o]ne of ordinary skill in the art would recognize that the Binladen tags could not be incorporated in the methods described in Dhallan because they would be incompatible with the restriction digestible primers critical to the process of Dhallan." Ex. 2003 ¶ 222.

In addition, Patent Owner argues that a skilled artisan would not have combined the references because Binladen's high error rate is unsuitable for detecting fetal aneuploidy. Patent Owner argues that "determination of fetal

aneuploidy requires not only accurate sequence determination but also highly precise quantification methods" because "a mistake leading to either false negative . . . or false positive . . . can be devastating." PO Resp. 45–46. Patent owner contends "Binladen discloses generating a limited amount of sequences with a large and unpredictable number of sequencing errors" (*id.* at 46 (emphasis omitted)), as well as "unpredictable variation in sequence distribution . . . specifically attribute[d] to tag composition" (*id.* at 47). Thus, Patent Owner contends, one of ordinary skill in the art would recognize that "the tags and corresponding methods of Binladen would simply be unsuitable for use in methods for determining fetal aneuploidy." *Id.* at 49 (citing Ex. 2003 ¶ 207). In Dr. Butte's opinion, "one of ordinary skill . . . would not have considered utilizing the Binladen tags in a fetal aneuploidy determination method" because of the large number of sequencing errors, an observed bias in sequence read distribution, and unpredictable variation in sequence distribution, attributed by Binladen to the composition of the tags. Ex. 2003 ¶¶ 200–203. Dr. Butte asserts that "high sequencing error rates and inaccuracies in sequence abundance (which may correlate to chromosome numbers) would be unacceptable" in determining fetal aneuploidy, which "requires not only accurate sequence determination but also highly precise quantification methods." *Id.* ¶ 199.

On cross-examination, Dr. Morton was unable to recall describing "a synthesis of how to put [Shoemaker, Dhallan, and Binladen] together" anywhere in her Declaration (Ex. 2005, 85:12–16), but expressed the opinion that the three references, taken together, provide "the path to do what is presented here" (*id.* at 84:17–19). Dr. Morton testified:

> [W]hen you combine . . . what's presented in the three references . . . you recognize from Dhallan that you have the presence of fetal DNA in the maternal circulation, and that in Binladen, you can index samples from different individuals and combine them for sequence analysis, and then you can figure out the sequence for that particular individual based on the indexing.
>
> And that in Shoemaker, you can do a similar analysis, except that you're using individual cells instead of -- as the source of DNA, instead of the source being a particular individual, a pregnant woman that has a mixture of fetal and maternal sequences in the same sample. Instead, in Shoemaker, you're combining single fetal cells and indexing those, and then you can actually deconvolute the sequence in each one of those. So in I feel that taken together, the three of them actually show me the path to do what is presented here.

Id. at 84:1–19.

Nevertheless, Dr. Morton conceded that certain aspects of Dhallan and Binladen would not be compatible, and "different methods" would have been required to implement the claimed method. Ex. 2005, 97:16. For example, Dr. Morton conceded that one "would do a different process to incorporate the tags" (*id.* at 97:6–7), and Binladen's "tagging would not be the way that that was done, because the method of inserting the tag, the way it's done now was not known at that time" (*id.* at 100:10–13).

In response to Patent Owner's contentions regarding the unsuitability of Binladen's tags due to a high rate of sequencing errors and variation in sequence distribution, Dr. Morton asserts that "Binladen proposes 'primer design guidelines'" and "one of ordinary skill . . . would be able to easily apply the teachings of Binladen to optimize the tags to decrease the error rate and increase the accuracy of putative sample tags." Ex. 1042 ¶¶ 27, 29. We are not persuaded. We note Dr. Morton's earlier testimony, in which

she asserted that, unlike detection of fetal nucleic acids "known *a priori* to be physically absent in the mother" (e.g., Y chromosome sequences), "[d]etection of cell-free fetal nucleic acid sequences that are present in both the fetus and the pregnant mother presents different technical challenges, as does the detection of fetal aneuploidies" and "is currently possible only through the use of highly precise methods for quantification by, e.g., amplification of the fetal and maternal nucleic acids in the sample followed by single molecule sequencing." Ex. 1002 ¶¶ 22, 23.

Having considered the Petition, and the Declarations of Drs. Morton and Nussbaum that accompanied it, we conclude that Petitioner has failed to prove by a preponderance of the evidence that claims 1–18 would have been unpatentable over Shoemaker, Dhallan, and Binladen. 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. *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 archeologist with the record.").

To the extent Petitioner's Reply and Dr. Morton's Second Declaration are responsive to specific points raised by Dr. Butte in his Declaration concerning the combinability of Binladen or Shoemaker with Dhallan, we are not persuaded. As discussed above, Dr. Morton acknowledged on cross-examination that Binladen's indexing (i.e., tagging) scheme could not be used with Dhallan's restriction-digestible amplification primers. Dr. Morton, in her Second Declaration, contends that Dhallan also teaches a number of amplification and/or detection methods which do not require the use of restriction digestible primers" (Ex. 1042 ¶¶ 17, 18), but those portions of Dhallan were not identified or discussed in the Petition or the accompanying Declarations. Moreover, although Dr. Morton asserts that "one of ordinary skill in the art would use basic common sense and not utilize the embodiments of Dhallan where restriction sites are added to the primers" (*id.* ¶ 32 (emphasis omitted)), Dr. Morton still does not explain how these other methods would be combined with Binladen or Shoemaker.

Nor are we 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" (Reply 8, 9). For example, Exhibit 1010 was introduced briefly in Dr. Nussbaum's Declaration as disclosing "a commercially available kit for production and analysis of indexed libraries from different samples of origin" "designed to be used with Illumina's multiplexed

sequencing platform, the Illumina Genome Analyzer™" (Ex. 1003 ¶ 21). In her Second Declaration, Dr. Morton asserts:

> It is my opinion that one of ordinary skill in January 2010 would not only be aware of the use of next generation, massively parallel sequencing [*e.g.*, Ex. 1033; Ex. 1036; Ex. 1011; Ex. 1045], but would have been aware of the commercially-available indexing kit available through Illumina, Inc. in 2008 [Ex. 1010] that allowed for sequencing of 96 different samples on a single flow cell. Thus, not only was barcoding or sample indexing known in the art as evidenced by both Binladen and Shoemaker, but as early as 2008 Illumina, Inc. offered a sample indexing kit that was compatible with the Genome Analyzer, the same sequencing system used in generating the data reported in the '430 patent. [Ex. 1001 at col. 18:52-540].
>
> It is my opinion that one of ordinary skill in January 2010 would be motivated to index individual samples and pool them for sequencing to maximize sequencing capacity and to minimize sequencing cost. For example, the Illumina, Inc. product flyer from 2008 [Ex. 1010] states, "[h]arnessing this sequencing power in a multiplexed fashion increases experimental throughput while reducing time and cost."

Ex. 1042 ¶¶ 42–43 (brackets in original).[3]

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[3] Exhibit 1010, submitted with the Nussbaum Declaration, Exhibits 1033 and 1036, submitted with the Morton Declaration, and Exhibits 1011 and 1045, submitted with Dr. Morton's Second Declaration, are as follows:

> *Multiplexed Sequencing with the Illumina Genome Analyzer System*, Illumina Inc. (2008) (Ex. 1010).
>
> Rossa W.K. Chiu et al., *Noninvasive Prenatal Diagnosis of Fetal Chromosomal Aneuploidy by Massively Parallel Genomic Sequencing of DNA in Maternal Plasma*, 105 PNAS 20458–20462 (2008) (Ex. 1033).
>
> Rossa W.K. Chiu et al., *Noninvasive Pre-natal Diagnosis by Single Molecule Counting Technologies*, 25 Trends in Genetics 324–331 (2009) (Ex. 1036).

This testimony, 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.[4] Therefore we accord this aspect of Dr. Morton's testimony no weight.

5. Conclusion

Having considered Petitioner's and Patent Owner's positions, as well as their supporting evidence, we determine that Petitioner has not met its burden of showing, by a preponderance of the evidence, that claims 1–18 of the '430 patent are unpatentable as having been obvious over Shoemaker, Dhallan, and Binladen.

D. Patent Owner's Motion to Exclude

Patent Owner, by its Motion to Exclude, seeks to exclude Petitioner's Replacement Exhibit 1002, Replacement Exhibit 1003, Exhibits 1014–1040, portions of Exhibit 1041, Paragraphs 3–46 of Exhibit 1042, Exhibit 1011, Exhibit 1045, and Exhibit 1046. Paper 30 ("Mot.").

H. Christina Fan et al., *Noninvasive Diagnosis of Fetal Aneuploidy by Shotgun Sequencing DNA from Maternal Blood*, 105 PNAS 16266–16271 (2008) (Ex. 1011).

Lo et al. US 2009/0029377 A1 Jan. 29, 2009 (Ex. 1045)

[4] "A reply may only respond to arguments raised in the corresponding . . . patent owner response." 37 C.F.R. § 42.23(b). That is, "[r]eply evidence . . . must be responsive and not merely new evidence that could have been presented earlier to support the movant's motion." Rules of Practice for Trials before the Patent Trial and Appeal Board, 77 Fed. Reg. 48,612, 48,620 (Aug. 14, 2014).

As the movant, Patent Owner has the burden of proof to establish that it is entitled to the requested relief. *See* 37 C.F.R § 42.20(c). For the reasons discussed below, Patent Owner's Motion to Exclude is *denied*.

1. Replacement Exs. 1002, 1003, and Substitute Exs. 1014–1040

Patent Owner seeks to exclude the replacement Declarations of Drs. Morton and Nussbaum (Exs. 1002 and 1003), and substitute Exhibits 1014–1040, filed on March 31, 2014. Mot. 2–3.

Patent Owner contends that it "may incur some prejudice" because substitute Exhibits 1014–1040 were originally "buried in the record as attachments to Petitioner's expert declarations" (*id.* at 3), and are now "present[ed] in a new light as separate documents" (*id.*). Substitute exhibits 1014–1040 were included as attachments to original Exhibits 1002 and 1003 (filed on May 10, 2013), but were not in compliance with 37 C.F.R § 42.63(c). Petitioner was authorized to refile the exhibits that were already included and listed in the Declarations of Drs. Morton and Nussbaum (Exs. 1002 and 1003, originally filed on May 10, 2013), to bring the exhibits into compliance with 37 C.F.R § 42.63(c). *See* Paper 22. The substitute exhibits were merely renumbered, and the replacement Declarations amended to reflect the new numbering scheme. We regard the risk of prejudice to Patent Owner as minimal in this instance.

Accordingly, the Motion is denied with respect to the replacement Declarations of Drs. Morton and Nussbaum (Exs. 1002 and 1003), and substitute Exhibits 1014–1040.

2. Deposition Transcript of Dr. Butte (Ex. 1041); Dr. Morton's Second Declaration (Ex. 1042); Fan (Ex. 1011); (Lo Ex. 1045); (Daines Ex. 1046)

Patent Owner argues that portions of Exhibit 1041 relied on by Petitioner on pages 1, 2, 4, 5, and 14 of its Reply (Paper 26) should be excluded under Federal Rule of Evidence 403[5] because "Petitioner's citations to portions of Ex. 1041 omit portions 'that in fairness ought to be considered at the same time,' and inaccurately characterized the testimony so as to be misleading and unfairly prejudicial to [Patent Owner]." Mot. 4, 6.

Patent Owner also seeks to exclude paragraphs 3–46 of Dr. Morton's Second Declaration. Essentially, Patent Owner contends

> Dr. Morton's second declaration is replete with attempted remedial testimony related to a *prima facie* case of obviousness that should have been submitted with the Petition. It is packed with terms such as "person of ordinary skill," "motivation to combine references," "references considered as a whole," "reasonable expectation of success," and the "relevant field." None of these phrases or subjects appear in her first declaration or in the Petition.

Id. at 7.

Patent Owner further seeks to exclude Exhibits 1011 and 1045 as "new evidence used to belatedly address knowledge of the person of ordinary skill in the art during the relevant time period" and "outside the scope of the Petition." *Id.* at 4, 13. Patent Owner seeks to exclude Exhibit 1046 as "a belated identification of challenge." *Id.* at 13.

[5] As stated in 37 C.F.R. § 42.62, the Federal Rules of Evidence generally apply in an *inter partes* review.

Nevertheless, the Board, sitting as a non-jury tribunal with administrative expertise, is well-positioned to determine and assign appropriate weight to evidence presented. *Gnosis S.P.A. v. S. Alabama Medical Science Foundation*, Case IPR2013-00118, slip op. at 43 (PTAB June 20, 2014) (Paper 64). *See also Donnelly Garment Co. v. NLRB*, 123 F.2d 215, 224 (8th Cir. 1941) ("One who is capable of ruling accurately upon the admissibility of evidence is equally capable of sifting it accurately after it has been received."). In an *inter partes* review, we regard it as the better course to have a complete record of the evidence to facilitate public access, as well as appellate review. *See id.* ("If the record on review contains not only all evidence which was clearly admissible, but also all evidence of doubtful admissibility, the court which is called upon to review the case can usually make an end of it, whereas if evidence was excluded which that court regards as having been admissible, a new trial or rehearing cannot be avoided.").

To the extent the arguments made in Petitioner's Reply and Dr. Morton's Second Declaration are responsive to arguments made in Patent Owner's Response and Dr. Butte's Declaration, we have considered the arguments and found them unpersuasive. To the extent the arguments and evidence presented in Petitioner's Reply and Dr. Morton's Second Declaration are not responsive and could have been presented earlier to support Petitioner's challenge, we accord them no weight. Patent Owner's Motion to Exclude is denied.

III. CONCLUSION

We conclude that Petitioner has failed to meet its burden of proof, by a preponderance of the evidence, that claims 1–18 of the '430 patent are unpatentable under 35 U.S.C. § 103 as having been obvious over the combination of Shoemaker, Dhallan, and Binladen.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner has failed to prove by a preponderance of the evidence that claims 1–18 of U.S. Patent No. 8,318,430 are unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude is *denied*; and

FURTHER ORDERED that because this is a final written decision, 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.

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