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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ROLAND STOUGHTON, RAVI KAPUR, MEHMET TONER, RONALD DAVIS, and BARB ARIEL COHEN[1]

Appeal 2018-006149
Application 13/863,992
Technology Center 1600

Before JEFFREY N. FREDMAN, TAWEN CHANG, and DAVID COTTA, *Administrative Patent Judges*.

CHANG, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a method of determining a likelihood of aneuploidy in a fetus, which have been rejected as being directed to a judicial exception to patent-eligible subject matter without significantly more. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] Appellants states that, although "[a]ssignments from the inventors have not yet been recorded in this application, . . . the inventors are under an obligation to assign to Verinata Health Inc. . . . , The General Hospital Corporation . . . , and GPB Scientific LLC." (Br. 2.)

STATEMENT OF THE CASE

According to the Specification, certain methods currently available for prenatal tests, such as amniocentesis and chorionic villus sampling (CVS), are "potentially harmful to the mother and to the fetus." (Spec. ¶ 2.) The Specification states that "[t]he presence of fetal cells within the blood of pregnant women offers the opportunity to develop a prenatal diagnostic that . . . eliminates the risk of today's invasive diagnosis." (*Id.* ¶ 5.) However, the Specification explains that, because "fetal cells represent a small number of cells against the background of a large number of maternal cells in the blood," prenatal tests based on analyses of maternal blood may be "time consuming and prone to error." (*Id.*) Further according to the Specification, [t]he methods of the present invention allow for the detection of fetal cells and fetal abnormalities when fetal cells are mixed with a population of maternal cells, even when the maternal cells dominate the mixture." (*Id.* ¶ 4.)

Claims 1–4, 9–15, 17, 20–24, 26–28, 32, 33, and 36 are on appeal.[2] Claim 1 is illustrative and reproduced below:

> 1. A method of determining a likelihood of a presence or absence of a fetal aneuploidy in a fetus using a maternal blood sample derived from a pregnant human female comprising fetal and maternal DNA, the method comprising:
>
> (a) selectively amplifying a plurality of single nucleotide polymorphism (SNP) sites of a first chromosome selected from the group consisting of chromosomes 13, 18, 21, X, and Y in the maternal blood sample comprising fetal and maternal DNA;
>
> (b) sequencing the amplified plurality of SNP sites of the fetal and maternal DNA of (a) and determining abundances of

[2] Claims 29–31, 34, 35, and 37 have been cancelled. (Amendment under 37 C.F.R. § 41.33(b)(1) (Mar. 16, 2018); Office Communication (May 14, 2018).)

sequence reads of alleles at the plurality of SNP sites, wherein the sequencing comprises sequencing millions of molecules in parallel;

(c) selectively amplifying the plurality of SNP sites of the first chromosome in a maternal-only sample comprising maternal DNA, wherein the maternal-only sample is essentially free of fetal DNA;

(d) sequencing the amplified plurality of SNP sites of the first chromosome of the maternal DNA of (c) and determining abundances of sequence reads of alleles at the plurality of SNP sites, wherein the sequencing of step (d) comprises sequencing millions of molecules in parallel;

(e) creating models corresponding to a plurality of fetal ploidy states based on the abundances of sequence reads of alleles at the plurality of SNP sites of (d);

(f) comparing the abundances of sequence reads of alleles at the plurality of SNP sites of (b) to the models and selecting from the models a model that provides a best fit to the abundances of sequence reads of alleles at the plurality of SNP sites of (b); and

(g) determining the likelihood of the presence or absence of a fetal aneuploidy of the first chromosome using the selected model.

(Br. 21–22 (Claims App.).)

The Examiner rejects claims 1–4, 9–15, 17, 20–24, 26–28, 32, 33, and 36 under 35 U.S.C. § 101 as being directed to a judicial exception (i.e., a law of nature, a natural phenomenon, or an abstract idea) without significantly more.[3] (Ans. 3.)

[3] The Examiner withdrew the rejection of claims 32, 33, and 36 under 35 U.S.C. ¶ 112, first paragraph. (Ans. 14.) The Examiner also rejects claims 29–31, 34, 35, and 37 under 35 U.S.C. § 101 as being directed to a judicial exception without more, as well as under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. (*Id.* at 3, 9.) However, as discussed above, claims 29–31, 34, 35, and 37 have been cancelled. *See supra* n. 2.

DISCUSSION

Issue

The Examiner finds that the claims on appeal are directed to "an abstract idea of a correlation between the likelihood of fetal aneuploidy and the number of sequencing reads of SNPs obtained in maternal plus fetal DNA and maternal-only samples." (Ans. 7.) The Examiner further finds that the claims do not include additional elements that amount to significantly more than the judicial exception, because the claims "do not provide improvement to another technology," "do not effect a transformation of a particular article to a different state or thing," and "do not add specific limitations other than what was well-understood, routine and conventional in the field." (*Id.* at 8, emphasis omitted.)

Appellants contend that the Examiner has not established that the claims are directed to an abstract idea. (Br. 10.) Appellants contend that the claims are in fact directed to a patent-eligible improvement in fetal aneuploidy detection. (*Id.* at 7–8.) Appellants contend that the claims do not preempt the field of fetal aneuploidy detection. (*Id.* at 8–9). Appellants further contend that the claims are patent-eligible because they contain additional elements that, when considered separately or in an ordered combination, are not conventional, well-understood, or routine and "make the claims amount to significantly more than a judicial exception." (*Id.* at 10–14.)

Appellants do not separately argue the claims. We therefore limit our analysis to claim 1 as representative. The issues with respect to this rejection are (1) whether claim 1 is directed to a patent-ineligible concept (i.e., a law of nature, a natural phenomenon, or an abstract idea) and, if so,

(2) whether claim 1 contains elements that, individually or as an ordered combination, transform the nature of the claim into a patent-eligible application.

Analysis

Unless otherwise noted, we adopt the Examiner's findings of fact and reasoning regarding the Examiner's rejection of claim 1 under 35 U.S.C. § 101 (Final Act. 2–12, 18–20, 22–24; Ans. 3–4, 7–8, 20–28) and agree that claim 1 is unpatentable as being directed to a judicial exception without significantly more. Only those arguments timely made by Appellants in the Appeal Brief (no Reply Brief was submitted) have been considered; arguments not so presented in the Brief are waived. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2015); *see also Ex parte Borden*, 93 USPQ2d 1473, 1474 (BPAI 2010) (informative) ("Any bases for asserting error, whether factual or legal, that are not raised in the principal brief are waived."). We highlight the following points for emphasis.

We analyze this case under the framework set forth by the Supreme Court in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66 (2012), and applied by our reviewing court in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015). As the *Ariosa* court explained:

> In *Mayo* . . . , the Supreme Court set forth a framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts. First, we determine whether the claims at issue are directed to a patent-ineligible concept. . . . If the answer is yes, then we next consider the elements of each claim both individually and "as an ordered combination" to determine

> whether additional elements "transform the nature of the claim" into a patent-eligible application. . . . The Supreme Court has described the second step of this analysis as a search for an "inventive concept"—i.e., an element or combination of elements that is "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself."

Id. at 1375.

Whether Claim 1 Is Directed to Patent-Ineligible Concept

We begin with the first step of the *Mayo* test, namely whether a claim is "directed to" a patent-ineligible concept. On January 7, 2019, the Director of the USPTO issued the "2019 Revised Patent Subject Matter Eligibility Guidance" ("Revised Guidance"), which provides further details regarding how the Patent Office analyzes patent-eligibility questions under 35 U.S.C. § 101. 84 Fed. Reg. 50–57 (Jan. 7, 2019). Under the Revised Guidance, the first step of the *Mayo* test (i.e., Step 2A of the Revised Guidance) is "a two-pronged inquiry." *Id.* at 54. In prong one, we evaluate whether the claim recites a judicial exception, such as laws of nature, natural phenomena, or abstract ideas. *Id.* If the claim recites a judicial exception, the claim is further analyzed under prong two, which requires "evaluat[ion of] whether the claim recites additional elements that integrate the exception into a practical application of that exception." *Id.* The Revised Guidance explains that, "[i]f the recited exception is integrated into a practical application of the exception, then the claim is eligible at Prong Two of . . . Step 2A [of the Revised Guidance]." *Id.*

Prong One of Step 2A of Revised Guidance

With respect to the first prong of Step 2A of the Revised Guidance, we agree with the Examiner that claim 1 recites a patent-ineligible law of

nature or natural phenomenon, specifically, the correlation between (1) "the abundances of sequence reads of alleles at . . . SNP sites" of certain chromosomes in a maternal blood sample comprising fetal and maternal DNA as compared to a "maternal-only sample . . . essentially free of fetal DNA" and (2) "the likelihood of the presence or absence of a fetal aneuploidy" of the chromosomes. (Br. 21–22 (Claims App.), claim 1, steps (b) and (d)–(g); *see also* Spec. ¶¶ 6–11 (explaining that "invention relates to methods for detecting a fetal abnormality by determining the ratio of the abundance of one or more maternal alleles to . . . paternal alleles" or by comparing "a ratio of the abundance of the maternal alleles in [a] first genomic region to . . . [a] second genomic region" to the ratio in a control sample); *see also id.* ¶¶ 107, 110–112, 113, 121.)

In *Mayo*, the Supreme Court found that a claim was directed to a natural law, where the claim required administering a drug and determining the levels of a metabolite following administration and where the level of metabolite was indicative of a need to increase or decrease the dosage of the drug. *See Mayo Collaborative Services v. Prometheus Labs., Inc.*, 566 U.S. 66, 74 (2012). In *Ariosa*, the Federal Circuit found that a method for performing a prenatal diagnosis was directed to matter that is naturally occurring, where the method comprised "obtaining a non-cellular fraction of [a maternal] blood sample[,] amplifying a paternally inherited nucleic acid from the . . . fraction[,] and performing nucleic acid analysis on the amplified nucleic acid to detect paternally inherited fetal nucleic acid." *Ariosa*, 788 F.3d at 1374, 1376. In particular, the *Ariosa* court reasoned that both the existence of cell-free fetal DNA (cffDNA) in maternal blood and paternally inherited cffDNA are natural phenomena. *Id.* at 1376.

Here, similar to the claims in *Mayo* that correlate a physiological parameter of a subject to the need to increase or decrease dosage of a drug, claim 1 recites correlating genetic parameters (i.e., abundances of sequence reads of alleles at certain SNP sites of different samples) to the likelihood of the presence or absence of a condition (i.e., fetal aneuploidy). Likewise, claim 1 recites "determining the likelihood of the presence or absence of a fetal aneuploidy of [a] chromosome" (i.e., performing a prenatal diagnosis as in *Ariosa*) comprising, among other things, amplifying certain nucleic acid from a maternal blood sample containing fetal DNA—the existence of which is a natural phenomenon as explained in *Ariosa*—and then performing nucleic acid analysis. Under the reasoning set forth in *Mayo* and *Ariosa*, therefore, claim 1 recites a patent-ineligible natural law or natural phenomenon.

Claim 1 further recites mathematical concepts and/or mental steps in steps (e)–(g), namely "creating models corresponding to a plurality of fetal ploidy states based on the abundances of sequence reads of alleles at . . . SNP sites of [maternal-only sample . . . essentially free of fetal DNA]," "comparing the abundances of sequence reads of alleles at . . . SNP sites of [fetal and maternal DNA] to the models and selecting . . . a model that provides a best fit," and "determining the likelihood of the presence or absence of a fetal aneuploidy of the [selected] chromosome using the selected model." (Br. 21–22 (Claims App.), claim 1, steps (e)–(g).)

For instance, the Specification provides examples of "model[s] for SNP data in the context of fetal diagnosis" where the presence or absence of aneuploidy is determined by mathematical equations that may take into account factors such as "efficiencies of amplification, hybridization, and

readout common to the alleles" at a particular locus k, "amplification differences between different primer pairs," "fraction of fetal cells in the mixture," and "unit data contributions" of maternal and paternal alleles at locus k. (Spec. ¶¶ 115–119.) Furthermore, creating such models, selecting a model that provides a best fit, and determining the likelihood of the presence or absence of fetal aneuploidy based on the model are all activities that may be performed in the human mind and thus also fall within the "mental step" category of abstract ideas.

Appellants contend that "[t]he Examiner has not cited an appropriate court decision that supports the identification of the subject matter recited in the claim language as an abstract idea." (Br. 10.) We are not persuaded. As discussed above, claim 1 recites a diagnostic method based on a natural law or natural phenomenon as well as a mathematical concept and/or mental step. *Mayo* and *Ariosa* both held that such diagnostic methods are, without more, directed to patent-ineligible subject matter. Similarly, both Supreme Court and Federal Circuit case law make clear that mental steps and mathematical concepts as such are abstract ideas. *See, e.g., Bilski v. Kappos*, 561 U.S. 593, 611 (2010) (explaining that "[t]he concept of hedging . . . reduced to a mathematical formula . . . is an unpatentable abstract idea"); *Parker v. Flook*, 437 U.S. 584, 594 (1978) (stating that "the discovery of [a mathematical formula] cannot support a patent unless there is some other inventive concept in its application"); *SAP America, Inc. v. InvestPic, LLC*, 898 F.3d 1161, 1163 (Fed. Cir. 2018) (holding that claims to a "series of mathematical calculations based on selected information" are directed to an abstract idea); *In re BRCA1 & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755, 763 (Fed. Cir. 2014) (holding that "comparing BRCA

sequences and determining the existence of alterations" is a patent-ineligible abstract idea).

Prong Two of Step 2A of Revised Guidance

The second prong of Step 2A asks whether the claims as a whole integrates the judicial exception into a practical application of the exception. Revised Guidance, 84 Fed. Reg. at 54. We find that claim 1 does not recite additional elements that integrate the recited law of nature, mathematical concept, and/or mental steps into a practical application.

In particular, the only elements of claim 1 that are not either a statement of the natural law, a mathematical concept, or a mental step are (1) "selectively amplifying a plurality of . . . SNP . . . sites of a first chromosome selected from the group consisting of chromosomes 13, 18, 21, X, and Y in the maternal blood sample comprising fetal and maternal DNA" (Appeal Br. 21 (Claims App.), claim 1, step (a)), (2) "selectively amplifying the plurality of SNP sites of the first chromosome in a . . . maternal-only sample . . . essentially free of fetal DNA" (*id.* at step (c)), and (3) "sequencing the amplified plurality of SNP sites" from the two samples wherein the sequencing comprises "sequencing millions of molecules in parallel" (*id.* at steps (b), (d)).

These steps, however, merely collect the data (i.e., the abundance of sequence reads) needed for determining the likelihood of fetal aneuploidy. Similar to the step of "determining the level of [relevant metabolite] in [a] subject," which the Supreme Court found in *Mayo* to be insufficient to transform a law of nature into a patent-eligible application of the law, 566 U.S. at 77, they are insignificant pre-solution activities that do not serve to integrate a judicial exception into a practical application. 84 Fed. Reg. at 55.

Appellants contend that, "[c]onsidered as a whole and in light of the specification, the instant claims are directed to a noninvasive technological process that improves the field of fetal aneuploidy detection by reducing the risk of induced abortion." (Br. 7.) In particular, Appellants contend that "[t]he claimed invention improves on . . . amniocentesis and chorionic villus sampling (CVS), which tend to be dangerously invasive, insufficiently sensitive, and limited to late in pregnancy." (*Id.*) Similarly, Appellants contend that "[t]he steps of the claims . . . reduce the amount of sequence information generated relative to sequence information generated by whole genome amplification, improving the cost effectiveness of fetal aneuploidy detection." (*Id.*)

We are not persuaded. We agree that a judicial exception may be integrated into a practical application where "[a]n *additional* element reflects . . . an improvement to [a] technology or technical field" when the claim is considered as a whole. 84 Fed. Reg. 55 (emphasis added) (explaining that "additional elements" refers to "claim features, limitations, and/or steps that are recited in the claim beyond the identified judicial exception).

In this case, however, the improvement that Appellants point to are the natural law and/or the mathematical concepts themselves. That is, the alleged improvement (over amniocentesis, CVS, and whole genome amplification) is the discovery of the correlation between fetal aneuploidy and the abundance of sequence reads of alleles at SNPs of maternal blood samples with and without fetal DNA, and/or the mathematical models based

on the abundances of these sequence reads.[4] Such an improvement does not suffice to render claim 1 patent-eligible.

In *Ariosa*, for example, our reviewing court rejected a similar argument by appellant Sequenom that its claimed methods are "patent eligible applications of a natural phenomenon, specifically a method for detecting paternally inherited cffDNA," because the court found that "[t]he only subject matter new and useful . . . was the discovery of the presence of cffDNA in maternal plasma or serum." *Ariosa*, 788 F.3d 1377; *see also Assoc. for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 591 (2013) (explaining that "[g]roundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry"); *Flook*, 437 U.S. at 591 (explaining that, to be patentable, "[t]he process itself, not merely the mathematical algorithm, must be new and useful").

Appellants compare the claims to those in *Rapid Litig. Mgmt. v. CellzDirect Inc.*, 827 F.3d 1042 (Fed. Cir. 2016), where "the process steps were focused on manipulating hepatocytes to achieve [a] desired outcome [of multi-cryopreserved viable hepatocytes] in accordance with the natural ability of the cells to survive multiple freeze-thaw cycles, rather than simply observing or detecting the ability of hepatocytes to survive multiple freeze-thaw cycles." (Br. 8.) Appellants argue that, similarly, the claims on appeal "are drawn to a process that involves numerous steps that manipulate DNA

[4] For instance, we note that Dhallan, which similarly teaches a correlation between (1) ratio for alleles at a locus of interest and (2) presence or absence of a chromosomal abnormality, also requires sequencing "only the desired bases or loci of interest" rather than sequencing the entire genome. Dhallan, US 2004/0137470, published July 15, 2004, ¶ 202.

in blood samples to achieve the desired outcome of creating an improved and noninvasive technological process that detects fetal aneuploidy." (*Id.*)

We are not persuaded. As explained by the *CellzDirect* court, while "[t]he inventors [in *CellzDirect*] certainly discovered the cells' ability to survive multiple freeze-thaw cycles, . . . that is not where they stopped, nor is it what they patented." *CellzDirect*, 827 F.3d at 1048. Instead, the inventors in *CellzDirect* "employed their natural discovery to create a new and improved way of preserving hepatocyte cells for later use." *Id.* Once again, in this case Appellants arguably discovered the natural correlation between fetal aneuploidy and the abundance of sequence reads of alleles at SNPs of maternal blood samples with and without fetal DNA. Unlike the claims in *CellzDirect*, however, claim 1 not directed to a method of *using* the natural correlation: While the end result of the method in *CellzDirect* is a preparation of multi-cryopreserved hepatocytes, the end result of the method of claim 1 is a diagnosis, i.e., a statement of the correlation itself.[5]

Finally, citing *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 837 F.3d 1299, 1315 (Fed. Cir. 2016), Appellants contend that the claims are not directed to a patent-ineligible law of nature or abstract idea because they do

[5] Appellants contend that, although the last step of claim 1 is to "determin[e] the likelihood of the presence or absence of a fetal aneuploidy of the first chromosome using the selected model," a skilled artisan would understand that the invention is in fact directed to "*detecting* fetal aneuploidy . . . ." (Br. 10.) We are not persuaded. Assuming for the sake of argument that Appellants' claims recite a method for "detecting" fetal aneuploidy rather than "determining a likelihood of a presence or absence of a fetal aneuploidy," such a method does not do more than "state the law of nature while adding the words 'apply it,'" which would not suffice to "transform unpatentable law of nature into patent-eligible application of such law." *Mayo*, 566 U.S. at 72.

not preempt "the field of fetal aneuploidy detection" or "the alleged, narrower judicial exception of an 'abstract idea of a correlation between the likelihood of fetal aneuploidy and the number of sequencing reads of SNPs obtained in maternal plus fetal DNA and maternal-only samples.'" (Br. 8–9.) Appellants contend that fetal aneuploidy may be detected via non-claimed processes such as amniocentesis and CVS. (*Id.* at 9.) Appellants likewise contend that the allegedly abstract correlation may be determined using chromosomes or maternal samples not recited in the claims and without "sequencing millions of molecules in parallel" as required by, e.g., independent claims 1 and 27. (*Id.*)

We are not persuaded. "While preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility." *Ariosa*, 788 F.3d at 1379. In *Ariosa*, for instance, our reviewing court held various dependent claims to be invalid as directed to patent-ineligible subject matter, even though these claims are limited to specific techniques of amplifying and detecting nucleic acid. *See id.* at 1374, 1378 (finding invalid dependent claims requiring amplification of nucleic acid by polymerase chain reaction or detection of nucleic acid via a sequence specific probe because they are "focused on the use of the natural phenomenon in combination with well-understood, routine, and conventional activity").

Whether Claim 1 Amounts to "Significantly More"

Having determined that claim 1 is directed to a patent-ineligible law of nature, we next consider whether claim 1 recites "an element or combination of elements that is 'sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible

concept] itself.'" *Ariosa*, 788 F.3d at 1375 (citation omitted). We agree with the Examiner that it does not. (Ans. 7–8, 21–27.)

As discussed above, the only elements of claim 1 that are not either a statement of the natural law, a mathematical concept, or a mental step, involve the data gathering steps of "selectively amplifying a plurality of . . . SNP . . . sites" of one of the recited chromosomes in maternal blood samples either comprising fetal DNA or essentially free of fetal DNA, and then "sequencing the amplified plurality of SNP sites" from the two samples wherein the sequencing comprises "sequencing millions of molecules in parallel." (Appeal Br. 21 (Claims App.), claim 1, steps (a)–(d).)

The Examiner finds, and we agree, that these "data collection steps are well-understood, common and routine in the art." (Ans. 21.) For instance, as the Examiner points out, the Specification teaches that amplifying and sequencing DNA are known to those skilled in the art, and prior art also teaches amplifying and sequencing DNA for purposes of detecting chromosomal abnormalities in a fetus. (*Id.* at 21–28; *see also* Dhallan Abstract (describing non-invasive method for detecting fetal chromosomal abnormalities by determining sequence of alleles of a locus of interest and quantitating a ratio for the alleles), ¶ 208 ("[a]ny method that provides information on the sequence of a nucleic acid" may be used to determine the sequence of a locus of interest, including among others DNA sequencing), ¶ 46 (wherein loci of interest is suspected of containing an SNP and wherein loci of interest can be amplified), ¶¶ 48–49, 59–60, 64–65, 67–70, 72–73 (amplifying alleles of locus of interest), ¶¶ 46, 62, 64–65, 67–70 (describing methods of amplification), ¶ 204 (any number of loci of interest can be analyzed and processed).)

Appellants do not dispute that amplifying and sequencing DNA, including sequencing millions of molecules in parallel, are routine and conventional techniques in DNA analysis. (*See, e.g.,* Tr. 10:12–11:3.) However, Appellants contend that the Examiner has not established that "at least sequencing millions of molecules and using both a maternal blood sample comprising fetal and maternal DNA and a maternal-only sample essentially free of fetal DNA" was conventional, well-understood, and routine *in the field of fetal aneuploidy detection*, which Appellants contend to be the subject of the invention and thus the relevant field of art for determining whether additional claim elements are well-known, routine, and conventional. (Br. 10–11; Tr. 13:4–19.)

We are not persuaded. Appellants improperly rely on the patent-ineligible natural law or phenomenon in their arguments for patent eligibility. As the Supreme Court has explained, in determining patent eligibility of a claim that recites a natural law or mathematical formula, "th[e] case must . . . be considered as if the principle or mathematical formula were well known." *Flook*, 437 U.S. at 592. Thus, the relevant question in step 2 of the *Mayo* test is not whether, e.g., sequencing millions of molecules in parallel is well-known, routine, and conventional *in the field of fetal aneuploidy detection*;[6] rather, it is whether such a technique is well-

[6] As evidenced by Dhallan, the prior art in fact does teach using similar DNA amplification and sequencing steps in detecting fetal aneuploidy. (*See, e.g.,* Dhallan Abstract (describing non-invasive method for detecting fetal chromosomal abnormalities by determining sequence of alleles of a locus of interest and quantitating a ratio for the alleles), ¶ 208 ("[a]ny method that provides information on the sequence of a nucleic acid" may be used to determine the sequence of a locus of interest, including among others DNA sequencing), ¶ 46 (wherein loci of interest is suspected of containing an SNP

known, routine, and conventional *for sequencing DNA and determining abundances of sequence reads of alleles*. We agree with the Examiner that they are. Appellants' argument that using samples comprising fetal and maternal DNA as well as maternal-only samples is not routine in fetal aneuploidy detection is flawed for the same reason: the correlation between the likelihood of fetal aneuploidy and the abundances of SNP sequence reads in the two different samples is the recited natural law and cannot form the basis for patent eligibility.

The Federal Circuit's analysis in *Ariosa* also supports the rejection. The claims in that case included methods for "detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female," comprising the steps of, e.g., "amplifying a paternally inherited nucleic acid" from the sample using methods such as PCR. *Ariosa*, 788 F.3d at 1373–74. The claims also included "[a] method for performing a prenatal diagnosis on a maternal blood sample." *Id.*

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and wherein loci of interest can be amplified), ¶¶ 48–49, 59–60, 64–65, 67–70, 72–73 (amplifying alleles of locus of interest), ¶¶ 46, 62, 64–65, 67–70 (describing methods of amplification), ¶ 204 (any number of loci of interest can be analyzed and processed).) Citing the USPTO's May 4, 2016 Memorandum on subject matter eligibility, Appellants contend that "'mere knowledge of the particular laboratory technique or use of the particular laboratory techniques by a few scientists is not sufficient to make the use of the particular laboratory technique routine or conventional in the relevant field.'" (Br. 11.) While this is true, Dhallan nevertheless supports the finding that DNA amplification and sequencing are well-known, routine, and conventional techniques in the field of DNA analysis and diagnostics, regardless of the specific purpose for which DNA is analyzed.

In applying the second step of the *Mayo* test, the Federal Circuit acknowledged that the discovery of the presence of cell-free fetal DNA in maternal plasma or serum is new and useful. *Id*. at 1377. Thus, while techniques like PCR may have been well-understood, routine, and conventional in amplifying and detecting DNA generally, it presumably was not well-understood, routine, and conventional for the specific purposes of "detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female." Nevertheless, and despite appellant Sequenom's argument that before its patent "*no one* was using the plasma or serum of pregnant mothers to amplify and detect paternally-inherited cffDNA," the Federal Circuit found the claims in *Ariosa* to be patent-ineligible, because "[t]he method at issue here amounts to a general instruction to doctors to apply routine, conventional techniques when seeking to detect [cell-free fetal DNA (cffDNA)]." *Id.* at 1377, 1379.

Similarly, in this case, there is no dispute that amplifying and sequencing SNP sites is conventional, well-understood, and routine in DNA analysis. What is allegedly new is only the discovery that the likelihood of fetal aneuploidy correlates to the abundance of sequence reads of SNPs in maternal plus fetal DNA versus maternal-only samples. Thus, as in *Ariosa*, "[t]he method at issue here amounts to a general instruction to doctors to apply routine, conventional techniques when seeking to [determine the likelihood of fetal aneuploidy]." *Id.* at 1377.

Appellants argue that the pending claims are not analogous to the claims at issue in *Ariosa* because the pending claims are not directed to determining the presence of a nucleic acid but rather to an improved method of fetal aneuploidy detection. (Br. 12.) We are not persuaded. As discussed

above, the claims at issue in *Ariosa* also included claim 25, which recites "[a] method for preforming a prenatal diagnosis" similar to Appellants' claim to "[a] method of determining a likelihood of a presence or absence of a fetal aneuploidy." 788 F.3d at 1374. Neither do Appellants provide any persuasive explanation why a diagnostic method is necessarily more patent eligible than a method for detecting the presence of a nucleic acid.[7]

Appellants contend that the claims at issue are analogous to the patent eligible claim 3 in Example 29 of USPTO's May 2016 Subject Matter Eligibility Examples: Life Sciences ("May 2016 Examples"), which is set forth below:

> 3. A method of diagnosing julitis in a patient, said method comprising:
> a. obtaining a plasma sample from a human patient;
> b. detecting whether JUL-1 is present in the plasma sample by contacting the plasma sample with a porcine anti-JUL-1 antibody and detecting binding between JUL-1 and the porcine antibody; and
> c. diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is detected.

(Br. 11; May 2016 Examples 10.)

Appellants contend that "[t]he example indicates that use of a porcine anti-JUL antibody 'in <u>veterinary therapeutics</u> was known to most scientists <u>in the field</u>'" and further contend that, therefore, claim 3 must have been

[7] To the extent Appellant's argument is based on the statement in *Ariosa* that "[u]sing methods like PCR to amplify and detect cffDNA was well-understood, routine and conventional activity in 1997" (Br. 12), we are not persuaded. As discussed above, although "the preparation and amplification of DNA sequences in plasma or serum were well-understood, routine, conventional," there appears to be no disagreement that the discovery of the presence of cffDNA in maternal plasma or serum was new as of the time of Sequenom's invention. *Ariosa*, 788 F.3d at 1377.

patent-eligible because "[t]he use of the porcine anti-JUL antibody in the claimed field is unconventional." (Br. 11.)

We are not persuaded. The analysis with respect to Example 29 explains that claim 3 is patent eligible because "there is no evidence that porcine antibodies were routinely or conventionally used *to detect human proteins such as JUL-1*." (May 2016 Examples 13 (emphasis added).) In contrast, as discussed above, the Specification and Dhallan show that amplifying and sequencing DNA from blood samples are well-known, routine and conventional techniques. Unlike claim 3 of Example 29, therefore, pending claim 1 does not include significantly more than the judicial exceptions recited therein.

Indeed, Example 29 supports the Examiner's rejection of the claims on appeal. The analysis accompanying the example explains that claim 2 of Example 29, which detects whether JUL-1 is present by detecting binding between JUL-1 and an anti-JUL-1 antibody, is patent-ineligible because detecting a protein using an antibody to that protein is a routine and conventional technique. (*Id.* at 9–10, 12.) In other words, claim 2 was patent-ineligible, despite the fact that it would not have been routine and conventional to use the anti-JUL-1 antibody "in the field of julitis diagnosis" because the correlation between the presence of JUL-1 protein and the presence of julitis in the patient was not previously known.

Appellants contend that "[t]he pending claims are also patent eligible because the ordered combination of the elements in the instant claims was not conventional, well-understood, and routine *in fetal aneuploidy detection*." (Br. 12 (emphasis added).) Appellants contend that "a patent eligible 'process' includes a 'new use of a known process, machine,

manufacture, composition of matter, or material'" and that the Examiner "attest[ed] to [the] nonconventional nature [of the claims]" by withdrawing earlier anticipation and obviousness rejections. (*Id.* at 12–13.)

We are not persuaded. The additional elements as a combination merely use well-understood, routine, and conventional techniques to gather the data necessary to apply the recited judicial exception(s). Thus, they add no meaningful limitations to the exception not already present when the elements are considered separately. To the extent Appellants' argument is that the combination of elements is not well-understood, routine, and conventional *in fetal aneuploidy detection*, we are not persuaded for the reasons discussed above.

Neither are we persuaded by Appellants' apparent argument that claim 1 must be patent eligible because the Examiner withdrew earlier rejections based on prior art. A claim may recite a "[g]roundbreaking, innovative, or even brilliant discovery" — and thus be nonobvious — and nevertheless fail to satisfy the § 101 inquiry. *Myriad*, 569 U.S. at 591. As the Supreme Court explained in the context of mathematical algorithms,

> [t]he process itself, not merely the mathematical algorithm, must be new and useful. Indeed, the novelty of the mathematical algorithm is not a determining factor at all. Whether the algorithm was in fact known or unknown at the time of the claimed invention, as one of the "basic tools of scientific and technological work," it is treated as though it were a familiar part of the prior art.

Parker v. Flook, 437 U.S. 584, 591–592 (1978).

Finally, Appellants contend that claim 1 is patent eligible under the second step of the *Mayo* inquiry because it recites "specific meaningful limitations" such as a specific type of disease, nucleic acid, samples, loci of

interest, sequencing, chromosomes, requirements for creating models, and comparison step. (Br. 13.)

We are not persuaded. As already discussed, limitations that merely recite a judicial exception or insignificant pre-solution activities performed using well-known, routine, and conventional techniques are insufficient to transform a claim into a patent-eligible application of the judicial exception. Likewise, limiting a claim to a particular technological environment (e.g., specific type of disease, chromosomes, etc.) is, without more, insufficient to transform the claim into a patent-eligible application of the judicial exception. *Bilski*, 561 U.S. at 610–611 (explaining that "the prohibition against patenting abstract ideas 'cannot be circumvented by attempting to limit the use of [the abstract idea] to a particular technological environment'") (citation omitted).

Accordingly, we affirm the Examiner's rejection of claim 1. Claims 2–4, 9–15, 17, 20–24, 26–28, 32, 33, and 36, which are not separately argued, fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

SUMMARY

For the reasons above, we affirm the Examiner's decision rejecting claims 1–4, 9–15, 17, 20–24, and 26–28, 32, 33, and 36.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED