United States Court of Appeals for the Federal Circuit

ILLUMINA, INC., SEQUENOM, INC.,
Plaintiffs-Appellants

v.

ARIOSA DIAGNOSTICS, INC., ROCHE SEQUENCING SOLUTIONS, INC., ROCHE MOLECULAR SYSTEMS, INC.,
Defendants-Appellees

2019-1419

Appeal from the United States District Court for the Northern District of California in No. 3:18-cv-02847-SI, Senior Judge Susan Y. Illston.

OPINION ISSUED: March 17, 2020
OPINION MODIFIED: August 3, 2020*

EDWARD R. REINES, Weil, Gotshal & Manges LLP, Redwood Shores, CA, argued for plaintiffs-appellants. Also represented by CHRISTOPHER SHAWN LAVIN, DEREK C. WALTER; ZACHARY TRIPP, Washington, DC.

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* This opinion has been modified and reissued following a petition for rehearing filed by Defendants-Appellees.

DARALYN JEANNINE DURIE, Durie Tangri LLP, San Francisco, CA, argued for all defendants-appellees. Defendant-appellee Ariosa Diagnostics, Inc. also represented by DAVID FLOYD MCGOWAN, LAURA MILLER.

ROBERT J. GUNTHER, JR., Wilmer Cutler Pickering Hale and Dorr LLP, New York, NY, for defendants-appellees Roche Sequencing Solutions, Inc., Roche Molecular Systems, Inc. Also represented by OMAR KHAN, CHRISTOPHER R. NOYES; THOMAS SAUNDERS, Washington, DC.

Before LOURIE, MOORE, and REYNA, *Circuit Judges*.

Opinion for the court filed by *Circuit Judge* LOURIE.

Dissenting opinion filed by *Circuit Judge* REYNA.

LOURIE, *Circuit Judge*.

Illumina, Inc. and Sequenom, Inc. (collectively, "Illumina") appeal from a decision of the United States District Court for the Northern District of California that claims 1–2, 4–5, and 9–10 of U.S. Patent 9,580,751 (the "'751 patent") and claims 1–2 and 10–14 of U.S. Patent 9,738,931 (the "'931 patent") are invalid under 35 U.S.C. § 101 as directed to an ineligible natural phenomenon. *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 356 F. Supp. 3d 925 (N.D. Cal. 2018) ("*Decision*"). Because we conclude that the claims are directed to patent-eligible subject matter, we reverse.

BACKGROUND

"In 1996, Drs. Dennis Lo and James Wainscoat discovered cell-free fetal DNA in maternal plasma and serum, the portion of maternal blood samples that other researchers had previously discarded as medical waste." *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1373 (Fed. Cir. 2015). They applied for a patent, and, in 2001, they obtained U.S. Patent 6,258,540, which claimed a method

for detecting the small fraction of paternally inherited cell-free fetal DNA in the plasma and serum of a pregnant woman. *Id.* In 2015, we held that the claims of that patent were invalid under 35 U.S.C. § 101 because they were directed to "matter that is naturally occurring"—*i.e.*, the natural phenomenon that cell-free fetal DNA exists in maternal blood. *Id.* at 1376.

The present case involves two patents that are unrelated to the patent held invalid in *Ariosa*, but rather claim priority from a European patent application filed in 2003. The '751 and '931 patents at issue in this case, which are related to each other and have largely identical specifications, begin by acknowledging the natural phenomenon that was at issue in *Ariosa*: "[I]t has been shown that in the case of a pregnant woman extracellular fetal DNA is present in the maternal circulation and can be detected in maternal plasma . . . ." '751 patent col. 1 ll. 23–25. The patents then identify a problem that was the subject of further research on cell-free fetal DNA in maternal blood:

> [T]he major proportion (generally >90%) of the extracellular DNA in the maternal circulation is derived from the mother. This vast bulk of maternal circulatory extracellular DNA renders it difficult, if not impossible, to determine fetal genetic alternations [sic] . . . from the small amount of circulatory extracellular fetal DNA.

Id. col. 1 ll. 42–50. In simple terms, the problem that the inventors encountered was that, although it was known that cell-free fetal DNA existed in the mother's bloodstream, there was no known way to distinguish and separate the tiny amount of fetal DNA from the vast amount of maternal DNA.

The inventors of the '751 and '931 patents attempted to find a solution to that problem. First, they made a discovery:

> An examination of circulatory extracellular fetal DNA and circulatory extracellular maternal DNA in maternal plasma has now shown that, surprisingly, the majority of the circulatory extracellular fetal DNA has a relatively small size of approximately 500 base pairs or less, whereas the majority of circulatory extracellular maternal DNA in maternal plasma has a size greater than approximately 500 base pairs.

Id. col. 1 ll. 54–61. To arrive at that discovery, the inventors examined five pregnancies and found that cell-free fetal DNA fragments "were almost completely of sizes smaller than 500 base pairs." '751 patent col. 4 ll. 50–53. Moreover, the inventors found that 70% of all DNA fragments smaller than 300 base pairs were fetal. *Id.*

Having made that discovery regarding the relative size distributions of cell-free fetal and maternal DNA fragments in a pregnant mother's bloodstream, the inventors used their discovery to develop a solution to the identified problem of distinguishing the fetal DNA from the maternal DNA:

> This surprising finding forms the basis of the present invention according to which separation of circulatory extracellular DNA fragments which are smaller than approximately 500 base pairs provides a possibility to enrich for fetal DNA sequences from the vast bulk of circulatory extracellular maternal DNA.

Id. col. 2 ll. 1–6.

The claims of the '751 and '931 patents are directed to that solution. Specifically, they claim methods of preparing a fraction of cell-free DNA that is enriched in fetal DNA. The methods of preparation include size discrimination of the DNA based on size parameters that the inventors selected to balance the need to remove enough longer

maternal DNA fragments to enrich the sample but also leave behind enough shorter fetal DNA fragments to allow for testing. As explained in the patent, "depending on the downstream application" of the enriched mixture, the size parameter is not fixed at either 500 or 300 base pairs but can be even smaller. *See* '751 patent col. 4 ll. 57–59.

Claim 1 of the '751 patent, the only independent claim, includes an inventor-chosen size parameter of 500 base pairs to allow for selective removal of longer DNA fragments from the mixture:

> 1. A method for preparing a deoxyribonucleic acid (DNA) fraction from a pregnant human female useful for analyzing a genetic locus involved in a fetal chromosomal aberration, comprising:
>
> (a) extracting DNA from a substantially cell-free sample of blood plasma or blood serum of a pregnant human female to obtain extracellular circulatory fetal and maternal DNA fragments;
>
> (b) producing a fraction of the DNA extracted in (a) by:
>
> (i) size discrimination of extracellular circulatory DNA fragments, and
>
> (ii) selectively removing the DNA fragments greater than approximately 500 base pairs,
>
> wherein the DNA fraction after (b) comprises a plurality of genetic loci of the extracellular circulatory fetal and maternal DNA; and
>
> (c) analyzing a genetic locus in the fraction of DNA produced in (b).

'751 patent col. 7 l. 54–col. 8 l. 57. In contrast, claim 1 of the '931 patent imposes a different size parameter, namely, 300 base pairs:

> 1. A method, comprising:

> (a) extracting DNA comprising maternal and fetal DNA fragments from a substantially cell-free sample of blood plasma or blood serum of a pregnant human female;
>
> (b) producing a fraction of the DNA extracted in (a) by:
>
> (i) size discrimination of extracellular circulatory fetal and maternal DNA fragments, and
>
> (ii) selectively removing the DNA fragments greater than approximately 300 base pairs,
>
> wherein the DNA fraction after (b) comprises extracellular circulatory fetal and maternal DNA fragments of approximately 300 base pairs and less and a plurality of genetic loci of the extracellular circulatory fetal and maternal DNA fragments; and
>
> (c) analyzing DNA fragments in the fraction of DNA produced in (b).

'931 patent col. 7 l. 58–col. 8 l. 63.

Dependent claims in each patent place further limitations on the size discrimination and selective removal processes recited in step (b) of the method claims. For example, dependent claim 7 of the '751 patent recites that "the size discrimination in (b) comprises centrifugation," and claim 8 further limits it to "density gradient centrifugation." '751 patent col. 9 ll. 1–4. Likewise, dependent claims 4–10 of the '931 patent recite that step (b) can comprise "chromatography," "electrophoresis," "centrifugation," and/or "nanotechnological means." '931 patent col. 9 ll. 1–14.

Illumina filed suit against Ariosa Diagnostics, Inc., Roche Sequencing Solutions, Inc., and Roche Molecular Systems, Inc. (collectively, "Roche") alleging infringement of the '751 and '931 patents. Roche moved for summary judgment that the asserted claims are invalid under 35

U.S.C. § 101. The district court granted Roche's motion for summary judgment, holding that the claims of the '751 and '931 patents are directed to ineligible subject matter. *Decision*, 356 F. Supp. 3d at 935. The court entered judgment in favor of Roche, and Illumina appealed. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

We review a grant of summary judgment according to the law of the regional circuit. *Kaneka Corp. v. Xiamen Kingdomway Grp. Co.*, 790 F.3d 1298, 1303 (Fed. Cir. 2015) (citing *Halo Elecs., Inc. v. Pulse Elecs., Inc.*, 769 F.3d 1371, 1377 (Fed. Cir. 2014)). In the Ninth Circuit, a grant of summary judgment is reviewed *de novo*. *Leever v. Carson City*, 360 F.3d 1014, 1017 (9th Cir. 2004) (citing *Hargis v. Foster*, 312 F.3d 404, 409 (9th Cir. 2002)). Summary judgment is appropriate when "there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56.

I

Section 101 provides that "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor . . . ." 35 U.S.C. § 101. Given the expansive terms of § 101, "Congress plainly contemplated that the patent laws would be given wide scope"; the legislative history likewise indicated that "Congress intended statutory subject matter to 'include anything under the sun that is made by man.'" *Diamond v. Chakrabarty*, 447 U.S. 303, 308–09 (1980) (internal citation omitted).

The Supreme Court has held that § 101 "contains an important implicit exception. '[L]aws of nature, natural phenomena, and abstract ideas' are not patentable." *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 70 (2012) (alteration in original) (quoting *Diamond v. Diehr*, 450 U.S. 175, 185 (1981)). These exceptions exist

because monopolizing the basic tools of scientific work "might tend to impede innovation more than it would tend to promote it." *Id.* at 71. However, the Supreme Court has advised that these exceptions must be applied cautiously, as "too broad an interpretation of this exclusionary principle could eviscerate patent law." *Id.*

Laws of nature and natural phenomena are not patentable, but applications and uses of such laws and phenomena may be patentable. A claim to otherwise statutory subject matter does not become ineligible by its use of a law of nature or natural phenomenon. *See Diehr*, 450 U.S. at 187; *Parker v. Flook*, 437 U.S. 584, 590 (1978). On the other hand, adding "conventional steps, specified at a high level of generality," to a law of nature or natural phenomenon does not make a claim to the law or phenomenon patentable. *Mayo*, 566 U.S. at 82.

To distinguish claims to patent-eligible applications of laws of nature and natural phenomena from claims that impermissibly tie up such laws and phenomena, we apply the two-part test set forth by the Supreme Court. First, we examine whether the claims are "directed to" a law of nature or natural phenomenon. *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 573 U.S. 208, 217 (2014). If—and only if—they are, then we proceed to the second inquiry, where we examine whether the limitations of the claim apart from the law of nature or natural phenomenon, considered individually and as an ordered combination, "'transform the nature of the claim' into a patent-eligible application." *Id.* (quoting *Mayo*, 566 U.S. at 78).

II

This is not a diagnostic case. And it is not a method of treatment case. It is a method of preparation case.

Under *Mayo*, we have consistently held diagnostic claims unpatentable as directed to ineligible subject matter. *See Athena Diagnostics, Inc. v. Mayo Collaborative*

Servs., LLC, 927 F.3d 1333, 1352 (Fed. Cir. 2019) (Moore, J., dissenting from denial of rehearing *en banc*) ("Since *Mayo*, we have held every single diagnostic claim in every case before us ineligible."); *see also, e.g., Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 915 F.3d 743 (Fed. Cir. 2019); *Cleveland Clinic Found. v. True Health Diagnostics LLC*, 859 F.3d 1352 (Fed. Cir. 2017); *Cleveland Clinic Found. v. True Health Diagnostics LLC*, 760 F. App'x 1013 (Fed. Cir. 2019). In contrast, we have held that method of treatment claims are patent-eligible. *See Endo Pharm. Inc. v. Teva Pharm. USA, Inc.*, 919 F.3d 1347 (Fed. Cir. 2019); *Natural Alternatives Int'l, Inc. v. Creative Compounds, LLC*, 918 F.3d 1338 (Fed. Cir. 2019); *Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd.*, 887 F.3d. 1117 (Fed. Cir. 2018). The claims in this case do not fall into either category, and we consider the claims under the *Alice*/*Mayo* test.

Here, it is undisputed that the inventors of the '751 and '931 patents discovered a natural phenomenon. But at step one of the *Alice*/*Mayo* test, "it is not enough to merely identify a patent-ineligible concept underlying the claim; we must determine whether that patent-ineligible concept is what the claim is 'directed to.'" *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1050 (Fed. Cir. 2016). The focus of the dispute in this case is whether the claims of the '751 and '931 patents are "directed to" the natural phenomenon, *i.e.*, whether they claim the discovered natural phenomenon itself versus eligible subject matter that exploits the discovery of the natural phenomenon.

As an initial matter, there are differences between the district court and the parties about how to articulate the natural phenomenon that the inventors discovered. The district court appeared to find that the relevant natural phenomenon is either the "testable quantity" of fetal DNA or "test results" obtained from that fetal DNA. *Decision*, 356 F. Supp. 3d at 933. Roche's articulation of the natural phenomenon was a moving target throughout its briefing

and at oral argument, but appears to be the "size distribution" of fetal to maternal cell-free DNA in a mother's blood reflected in Table 1 of the specification, with a particular focus on the number "500 base pairs" as the critical dividing line between the two. *See* Appellee's Br. 14, 18, 21; Oral Arg. 27:58, 28:35, 29:16. And Illumina asserts more simply that the inventors' discovery was that "fetal cell-free DNA tends to be shorter than maternal cell-free DNA." Appellant's Br. 24; *see also id.* at 8 ("[I]n a sample of cell-free DNA from a pregnant woman, the DNA that arises from the fetus is smaller on average than the DNA that arises from the mother.").

We take note of Roche's inability—despite its status as the party challenging the validity of the patents—to clearly identify the natural phenomenon that forms the basis of its challenge. But, ultimately, we find that the parties' respective articulations reflect distinctions without differences. For simplicity, we adopt Illumina's articulation of the natural phenomenon, *i.e.*, that cell-free fetal DNA tends to be shorter than cell-free maternal DNA in a mother's bloodstream. We thus turn to the crucial question on which this case depends: whether the claims are "directed to" that natural phenomenon. We conclude that the claims are *not* directed to that natural phenomenon but rather to a patent-eligible method that utilizes it.

The claims in this case are directed to methods for preparing a fraction of cell-free DNA that is enriched in fetal DNA. The methods include specific process steps—size discriminating and selectively removing DNA fragments that are above a specified size threshold—to increase the relative amount of fetal DNA as compared to maternal DNA in the sample. '751 patent col. 7 ll. 63–67. The size thresholds in the claims—500 base pairs in the '751 patent and 300 base pairs in the '931 patent—are not dictated by any natural phenomenon, particularly because the size distributions of fetal and maternal cell-free DNA overlap each other (*i.e.*, there are maternal DNA fragments shorter than

300 base pairs). The claimed size thresholds are human-engineered parameters that optimize the amount of maternal DNA that is removed from the mixture and the amount of fetal DNA that remains in the mixture in order to create an improved end product that is more useful for genetic testing than the original natural extracted blood sample.

Moreover, the claimed methods achieve more than simply observing that fetal DNA is shorter than maternal DNA or detecting the presence of that phenomenon. The claims include physical process steps that change the composition of the mixture, resulting in a DNA fraction that is different from the naturally occurring fraction in the mother's blood. The dependent claims further illustrate the concrete nature of the claimed process steps. For example, claims 7–8 of the '751 patent and claims 8–9 of the '931 patent require that the size discrimination step comprise "centrifugation," and specifically "density gradient centrifugation." '751 patent col. 9 ll. 1–4; '931 patent col. 9 ll. 9–12. Other dependent claims in the '931 patent comprise other discrimination and separation means, such as "high performance liquid chromatography" (claims 4–5), "capillary electrophoresis" (claims 6–7), or "nanotechnological means" (claim 10). These dependent claims are supported by the specification's description of the physical means by which the size discrimination and selective removal step of the claims can be achieved:

> The size separation of the extracellular DNA in said serum or plasma sample can be brought about by a variety of methods, including but not limited to: chromatography or electrophoresis such as chromatography on agarose or polyacrylamide gels, ion-pair reversed-phase high performance liquid chromatography [], capillary electrophoresis in a self-coating, low-viscosity polymer matrix [], selective extraction in microfabricated electrophoresis devices [], microchip electrophoresis on reduced viscosity polymer matrices [], adsorptive membrane

> chromatography [] and the like; density gradient centrifugation []; and methods utilising [sic] nanotechnological means such as microfabricated entropic trap arrays [] and the like.

'931 patent col. 2 l. 61–col. 3 l. 18 (citations omitted); *see also id.* col. 4 ll. 15–22 ("3. The gel was electrophoresed at 80 Volt for 1 hour. 4. The Gel [sic] was cut into pieces corresponding to specific DNA sizes . . . ."). As described by the specification, the inventors used these concrete process steps, not merely to observe the presence of the phenomenon that fetal DNA is shorter than maternal DNA, but rather to exploit that discovery in a method for preparation of a mixture enriched in fetal DNA.

Roche insists that the claims in this case are no more eligible than the claims at issue in *Ariosa*. We disagree. In *Ariosa*, the relevant independent claims were directed to a method "for detecting a paternally inherited nucleic acid" (claims 1 and 24) or a method "for performing a prenatal diagnosis" (claim 25). *See Ariosa*, 788 F.3d at 1373–74. The only operative steps in the claims were "amplifying" (*i.e.,* making more of) the cell-free fetal DNA and then "detecting [it]," "subjecting [it] . . . to a test," or "performing nucleic acid analysis on [it] to detect [it]." *Id.* We found those claims ineligible because, like the invalid diagnostic claims at issue in *Mayo*, *Athena*, and *Cleveland Clinic*, they were directed to detecting a natural phenomenon after a sample has been prepared or extracted. In essence, the inventors in *Ariosa* discovered that cell-free fetal DNA exists, and then obtained patent claims that covered a method directed to starting with a sample that contains cell-free fetal DNA and seeing that that the cell-free fetal DNA exists.

Here, in contrast, the claims are directed to more than just the correlation between a DNA fragment's size and its tendency to be either fetal or maternal, a correlation which is not even mentioned in the claims. The claims do not cover a method for detecting whether a cell-free DNA

fragment in a previously-prepared sample is fetal or maternal based on the natural size distribution of cell-free DNA fragments; rather, the claimed methods exploit that natural size distribution *during* the sample preparation steps to remove some maternal DNA from the mother's blood. Even the "analyzing" step of the claims is *not* directed to analyzing the discovered natural phenomenon, but to analyzing something else entirely, namely, "fetal chromosomal aberrations." *See* '751 patent col. 7 ll. 55–56, col. 8 ll. 56–57, col. 9 ll. 5–8; '931 patent col. 9 ll. 17–24. Thus, the claims in this case are different from the claims that we held invalid in *Ariosa*.

Roche also argues, based on the Supreme Court's decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, that "a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated." 569 U.S. 576, 580 (2013). But the claims here are not directed to the cell-free fetal DNA itself. The Supreme Court in *Myriad* expressly declined to extend its holding to method claims reciting an innovative process used to isolate DNA. *See id.* at 595–96. The Court stated:

> It is important to note what is *not* implicated by this decision. First, there are no method claims before this Court. Had Myriad created an innovative method of manipulating genes while searching for the BRCA1 and BRCA2 genes, it could possibly have sought a method patent. But the processes used by Myriad to isolate DNA were well understood by geneticists at the time of Myriad's patents, were well understood, widely used, and fairly uniform insofar as any scientist engaged in the search for a gene would likely have utilized a similar approach, and are not at issue in this case.

Id. (internal quotation marks omitted). Thus, in *Myriad*, the claims were ineligible because they covered a gene that

the inventors isolated but did not invent, rather than an innovative process for isolating a gene.

Here, we encounter the opposite situation, *i.e.*, the claims do not cover separated cell-free fetal DNA itself but rather a process for selective removal of non-fetal DNA to enrich a mixture in fetal DNA. That process includes size parameters that the inventors engineered to balance the practicalities of the specific problem that they were facing, namely, removing enough cell-free maternal DNA to enrich the mixture while leaving enough cell-free fetal DNA to allow for testing. Thus, the Supreme Court's decision in *Myriad* is not on point in this case where the inventors claimed to have conceived and reduced to practice, not the separated DNA, but a method that uses unconventional size parameters to perform the separation.

In our view, *CellzDirect*, while not directly on point, is instructive. In *CellzDirect*, the inventors discovered the natural phenomenon "that some fraction of hepatocytes are capable of surviving multiple freeze-thaw cycles." 827 F.3d at 1045. Having made that discovery, they patented an "improved process of preserving hepatocytes," that comprises freezing hepatocytes, thawing the hepatocytes, removing the non-viable hepatocytes, and refreezing the viable hepatocytes. *Id*. We found that their claimed invention was patent-eligible because it was "not simply an observation or detection of the ability of hepatocytes to survive multiple freeze-thaw cycles. Rather, the claims are directed to a new and useful method of preserving hepatocyte cells." *Id.* at 1048.

The inventors in *CellzDirect* did not invent hepatocytes or impart to hepatocytes an ability to survive cycles of freezing and thawing. *Id*. at 1045. Rather, they discovered that hepatocytes naturally have that ability, and they exploited that phenomenon in a patent-eligible method. So too here, the inventors of the '751 and '931 patents obviously did not invent cell-free fetal DNA or the relative size

distribution of fetal and maternal cell-free DNA in maternal blood. And, like in *CellzDirect*, the inventors used their discovery to invent a method of preparing a fraction of DNA that includes physical process steps with human-engineered size parameters to selectively remove some maternal DNA in blood to produce a mixture enriched in fetal DNA.

Roche argues that the techniques for size discriminating and selectively removing DNA fragments that are used to practice the invention were well-known and conventional. And we recognize, of course, that the inventors of the '751 and '931 patents did not invent centrifugation, chromatography, electrophoresis, or nanotechnology.[1] But conventional separation technologies can be used in unconventional ways. And Roche, the party challenging the validity of the patents and thus bearing the burden of proof on its § 101 challenge, has presented no evidence that thresholds of 500 base pairs and 300 base pairs were conventional for separating different types of cell-free DNA fragments. Thus, the claims are directed to a human-engineered method rather than the natural size distributions of cell-free DNA. Moreover, while such conventionality considerations may be relevant to the inquiry under *Alice*/*Mayo* step two, or to other statutory considerations such as obviousness that are not at issue before us in this case, they do not impact the *Alice*/*Mayo* step one question whether the claims themselves are directed to a natural phenomenon. Again, *CellzDirect* is instructive, where we acknowledged that the inventors had not invented the well-known processes of "freezing" and "thawing," but only in

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[1] We note, without deciding, that Illumina argues that claim 11 of the '931 patent requires the use of microarrays, which it claims was a methodology not previously used with cell-free DNA. Appellant's Br. 40.

the context of the *Alice*/*Mayo* step two inquiry. 827 F.3d at 1050–51.

Rather than focusing on what the inventors of the '751 and '931 patents did not invent, we focus our *Alice*/*Mayo* step one analysis on what the inventors *did* purport to invent and what they claimed in their patents: methods for preparing a fraction of cell-free DNA by the physical process of size discriminating and selectively removing DNA fragments longer than a specified human-engineered threshold. Those methods are "directed to" more than merely the natural phenomenon that the inventors discovered. Accordingly, we conclude at step one of the *Alice*/*Mayo* test that the claims are not directed to a patent-ineligible concept, and we need not reach step two of the test.

III

In *Ariosa*, we recognized that the inventors had made a discovery with implications that would allow what had previously been discarded as medical waste to be used as a tool for determining fetal characteristics. 788 F.3d at 1373. We acknowledged the profound impact that the discovery had on the field of prenatal medicine, including that it "created an alternative for prenatal diagnosis of fetal DNA that avoids the risks of widely-used techniques that took samples from the fetus or placenta." *Id.* Nevertheless, under guidance from the Supreme Court, we determined that the discovery of that natural phenomenon, no matter how significant it was to the medical field, was not itself patentable, and neither was a method for detecting it. *Id.* at 1379–80.

The invention in this case is the product of further research on cell-free fetal DNA. This time, the inventors discovered that, not only does the fetal DNA exist in the bloodstream of a pregnant mother, but it has characteristics that make it distinguishable, and therefore separable, from the maternal DNA. Again, regardless how

groundbreaking this additional discovery may have been, the inventors were not entitled to patent the natural phenomenon that cell-free fetal DNA tends to be shorter than cell-free maternal DNA. "Groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry." *Myriad*, 569 U.S. at 591. Thus, they could not claim a method directed to the natural phenomenon, *e.g.*, a method for determining whether a fragment of cell-free DNA is fetal or maternal based on its length. And they did not attempt to patent such a method.

The inventors here patented methods of preparing a DNA fraction. The claimed methods utilize the natural phenomenon that the inventors discovered by employing physical process steps and human-engineered size parameters to selectively remove larger fragments of cell-free DNA and thus enrich a mixture in cell-free fetal DNA. Though we make no comment on whether the claims at issue will pass muster under challenges based on any other portion of the patent statute, under § 101 the claimed methods are patent-eligible subject matter.

CONCLUSION

We conclude that the claims of the '751 and '931 patents are directed to patent-eligible subject matter under 35 U.S.C. § 101. We therefore reverse the district court's grant of summary judgment and remand for further proceedings.

REVERSED AND REMANDED

United States Court of Appeals for the Federal Circuit

ILLUMINA, INC., SEQUENOM, INC.,
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v.

ARIOSA DIAGNOSTICS, INC., ROCHE SEQUENCING SOLUTIONS, INC., ROCHE MOLECULAR SYSTEMS, INC.,
Defendants-Appellees

2019-1419

Appeal from the United States District Court for the Northern District of California in No. 3:18-cv-02847-SI, Senior Judge Susan Y. Illston.

REYNA, *Circuit Judge*, dissenting.

The claims, written description, and legal precedent converge to a conclusion that the '751 and '931 patents[1] cover patent ineligible subject matter. The asserted claims are directed to a natural phenomenon, the patents' sole claimed advance is the discovery of that natural

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[1] U.S. Patent Nos. 9,580,751 and 9,738,931. The patents contain nearly identical written descriptions and claims. For economy, this opinion will reference only the '751 patent.

phenomenon, and the application of the natural phenomenon utilizes routine steps and conventional procedures that are well known in the art.

The patents in this appeal proclaim a surprising discovery that has advanced the medical arts in an area of great need. Without doubt, scientists are entitled to great credit and recognition for such a discovery. But, under U.S. patent law, they are not entitled to a patent.

DISCUSSION

I. The Claims are Directed to a Natural Phenomenon

At the time of the invention, skilled artisans were aware that cell-free fetal DNA ("cff-DNA") existed; that cff-DNA could be detected in a sample of a pregnant woman's blood or serum; and that cff-DNA was useful for reliably analyzing fetal genetic markers (for detecting certain diseases and disorders). '751 patent at col. 1 ll. 22–34. But for some genetic markers found in the genomes of both the mother and the fetus, skilled artisans faced a problem: the relatively small amount of cff-DNA compared to the amount of maternal extracellular DNA in the mother's blood made it difficult to identify and analyze genetic alterations in the fetus. *Id.* at col. 1 ll. 41–50.

The patent informs us that the problem was overcome when the inventors made a "surprising" discovery. *Id.* at col. 1 ll. 54–61. The inventors discovered that cff-DNA tends to be shorter than cell-free maternal DNA in a mother's blood. *See* '751 patent at col. 1 ll. 54–67; *see also* Maj. Op. at 3–4, 8. The written description explains that the majority of cff-DNA in the mother's blood plasma "has a relatively small size of approximately 500 base pairs or less, whereas the majority of circulatory extracellular maternal DNA in maternal plasma has a size greater than approximately 500 base pairs." *Id.* at col. 1 ll. 54–61. The written description states that "[t]his surprising finding

forms the basis of the present invention." *Id.* at col. 2 ll. 1–2 (emphasis added).

As explained in detail below, it is to this precise surprising discovery of size discrepancy of cff-DNA in a mother's blood—an undisputed natural phenomenon—that the claims at issue are directed. These claims, thus, do not escape *Alice* step one.

A. The Claimed Method Steps Involve a Natural Phenomenon

The first step of the *Alice* test requires that we determine whether the claims at issue are "directed to" a natural phenomenon. *Alice Corp. Pty. Ltd. v. CLS Bank Intern*, 573 U.S. 208, 217–18 (2014). To make this determination, the Supreme Court has analyzed whether the claims "involved" patent-ineligible subject matter. *Id.* at 219; *see also id.* at 218–20 (citing *Gottschalk v. Benson*, 409 U.S. 63, 71–72 (1972), *and Bilski v. Kappos*, 561 U.S. 593, 599 (2010)). In *Alice*, the Court determined that the claims were directed to an abstract idea because the claims "involve" the abstract idea of "intermediated settlement," a concept the Court deemed a "fundamental economic practice." *Alice*, 573 U.S. at 219. Like in *Alice*, the claims here are directed to a natural phenomenon because they *involve* a fundamental natural phenomenon, that cff-DNA tends to be shorter than cell-free maternal DNA in a mother's blood, to produce a "mixture" of naturally-occurring substances.

For example, the preamble of claim 1 of the '751 patent informs us that the patent claims a method for preparing a DNA "fraction" from a pregnant human female that can be used for diagnostic purposes.[2] The remainder of claim 1

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[2] Claim 1 recites:

recites the method steps for producing the fraction and analyzing it. Each step involves the DNA taken from the blood plasma or serum of a pregnant human female. The DNA itself is not changed or altered.

The first step is achieved by (a) *extracting* DNA from a substantially cell-free sample of blood plasma or blood serum taken from a pregnant female. That sample is then

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> A method for preparing a deoxyribonucleic acid (DNA) fraction from a pregnant human female useful for analyzing a genetic locus involved in a fetal chromosomal aberration, comprising:
>
> (a) extracting DNA from a substantially cell-free sample of blood plasma or blood serum of a pregnant human female to obtain extracellular circulatory fetal and maternal DNA fragments;
>
> (b) producing a fraction of the DNA extracted in (a) by:
>
> (i) size discrimination of extracellular circulatory DNA fragments, and
>
> (ii) selectively removing the DNA fragments greater than approximately 500 base pairs, wherein the DNA fraction after (b) comprises a plurality of genetic loci of the extracellular circulatory fetal and maternal DNA; and
>
> (c) analyzing a genetic locus in the fraction of DNA produced in (b).

'751 patent at col. 7 ll. 54-67, col. 8 ll. 53-57; *cf.* '931 patent at col. 7 ll. 58-67, col. 8 ll. 57-63 (claim 1).

used to (b) produce a "fraction" of the DNA extracted in the first step (a). The fraction is produced via (i) *size discrimination* of the extracellular circulatory DNA fragments, and (ii) *selective removal* of DNA fragments greater than approximately 500 base pairs. Claim 1 states that after the extraction, size discrimination, and selection and removal steps are completed, the fraction comprises "a plurality of genetic loci of the extracellular circulator fetal and maternal DNA." '751 patent at col. 8 ll. 53–55. The Majority describes the resulting fraction as "a mixture enriched in fetal DNA." Maj. Op. at 12. But this mixture is made of the same natural substances present in the original sample.

In sum, the claimed method begins with extracting a sample of blood plasma or serum from a pregnant mother that consists wholly of various naturally occurring substances, including cff-DNA. '751 patent at col. 7. ll. 58–61. The claimed method separates those naturally occurring substances by size, leaving a "fraction" of the original sample that is predominantly cff-DNA. *Id.* at col. 7 ll. 63–67, col. 8 ll. 53–55. The claimed method ends with analyzing the components of the "fraction," which contains cff-DNA. *Id.* at col. 8 ll. 56–57. The substances present throughout the process are naturally occurring substances, and the claimed method steps do not alter those substances. Thus, under the Supreme Court's step-one analysis, the claimed method steps "involve" natural phenomenon and are, therefore, directed to a natural phenomenon.[3]

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[3] The dependent claims add detail such as techniques for conducting each method step and the detection of specific chromosomal aberrations. For example, claim 7 of the '751 patent specifies centrifugation for the size discrimination step and claim 10 specifies for the detection of a fetal chromosomal aberration causing Down Syndrome. '751 patent at col. 9 ll. 1-2, 7-8.

B. The Claimed Advance is a Natural Phenomenon

My conclusion that the method steps are directed to a natural phenomenon is bolstered by our precedent that looks to the "claimed advance" for determining whether a claim is directed to patent ineligible subject matter. *E.g.*, *Athena*, 915 F.3d 743, 750 (Fed. Cir. 2019) (Lourie, J.); *Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1375 (Fed. Cir. 2016); *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015).

In *Ariosa*, we concluded that the claims were directed to a natural phenomenon relying, in part, on the patent's disclosure that the natural phenomenon was a "surprising and unexpected finding." 788 F.3d at 1376 (citation and quotation omitted). In *Athena*, we concluded that the claimed advance was "only in the discovery of the natural law" by relying, in part, on the patent's disclosure that the inventors "surprisingly found" the natural law. 915 F.3d at 751 (citation and quotation omitted). In *Cleveland Clinic*, we concluded that the claims were directed to a natural law relying, in part, on the patent's disclosure that "the inventions are 'based on the discovery'" of the natural law. 859 F.3d at 1360–61 (citation omitted).

Here, the claimed advance is the inventors' "surprising[]" discovery of a natural phenomenon—that cff-DNA tends to be shorter than cell-free maternal DNA in a mother's bloodstream. *See* '751 patent at col. 1 ll. 54–61. Like in *Ariosa* and *Athena*, the patent's written description identifies only the natural phenomenon as the "surprising finding." *Id.* at col. 1 l. 54–col. 2 l. 6. And the patent explains that the natural phenomenon "forms the basis of the present invention," like the patent in *Cleveland Clinic*. *Id.* at col. 2 ll. 1–6. It is undisputed that the surprising discovery is a natural phenomenon. *See* Maj. Op. at 3–4, 9. The claimed advance is, therefore, the discovery of the natural phenomenon.

The conclusion that the claimed advance is the discovery of a natural phenomenon is supported by the fact that the claimed method steps begin and end with a naturally occurring substance. *See Ariosa*, 788 F.3d at 1376. In *Ariosa*, we found ineligible process claims directed to a method of detecting paternally inherited cff-DNA. *Id.* The claimed method steps began with a naturally occurring blood sample and ended with cff-DNA, itself a naturally occurring substances. *Id.* In this case, as in *Ariosa*, the inventors did not create or alter via the claimed method steps any of the genetic information encoded in the cff-DNA in the claimed method steps. *Id.*

The Majority avoids our claimed advance precedent by reasoning that these claims belong in a distinct category of process claims for "method[s] of preparation."[4] *See* Maj. Op. at 8. But characterizing the claims as a "method of preparation" does not render inapplicable this court's precedent including *Athena*, *Roche Molecular*, *Cleveland Clinic*, *Genetic Techs.*, and *Ariosa.*[5] *Id.* Our precedent does not support such cherry picking. A "method of preparation" is treated no differently than any other process claim under our law. The statute provides that the term "process" in § 101 encompasses all "process, art or method"

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[4] *Cf. Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1050 (Fed. Cir. 2016) (reciting in claim 1's preamble "[a] method of producing a desired preparation").

[5] *Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 915 F.3d 743 (Fed. Cir. 2019); *Roche Molecular Sys., Inc. v. Cepheid*, 905 F.3d 1363 (Fed. Cir. 2018); *Cleveland Clinic Found. v. True Health Diagnostics LLC*, 859 F.3d 1352 (Fed. Cir. 2017); *Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369 (Fed. Cir. 2016); *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015).

claims. 35 U.S.C. § 100(b). It makes no distinction based on how the process or method is characterized.

Here, the Majority fails to adequately address the claimed advance inquiry. *E.g.*, Maj. Op. at 8–13. Yet, the Majority maintains that the claimed methods are not directed to the natural phenomenon—under the *Alice*/*Mayo* step-one inquiry—because they "include physical process steps" that "achieve more than simply observing that fetal DNA is shorter than maternal DNA or detecting the presence of that phenomenon." Maj. Op. at 11. The problem with this approach is that it conflates the *Alice*/*Mayo* step-one analysis with the step-two analysis by focusing on whether and how the claimed "physical process steps" transform the invention into more than an observation of the natural phenomenon. *See Alice*, 573 U.S. 217–18. The Supreme Court describes step two of the 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.* (emphasis added) (quoting *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66, 72–73 (2012)).

The Majority also suggests that the claimed advance is an improvement in "size discriminat[ion]" and "selective[] remov[al]" techniques. *See* Maj. Op. at 9–11. The Majority reasons that the inventors used "specific process steps" of "size discriminating and selectively removing DNA fragments that are above a specified size threshold" and that these "concrete process steps . . . exploit [the natural phenomenon] in a method for preparation of a mixture enriched in fetal DNA." *Id.* at 9–10, 12. But whether the claimed method steps are specific and concrete is not the point of analysis for the "directed to" inquiry or for determining the claimed advance at step one. *See Athena*, 915 F.3d at 752 (concluding that the claims' specific and concrete nature "does not disturb our conclusion at step one").

The claimed advance suggested by the Majority, an improvement in the underlying DNA-processing technology, is not supported by the claims or the written description. As discussed below, the written description identifies the claimed method steps as well-known or performed using commercially available tools or kits. *See* '751 patent at col. 2 l. 49–col. 3 l. 18, col. 3 ll. 49–50, col. 3 l. 65–col. 4 l. 13, col. 5 ll. 45–50. Where a written description identifies a technology as well-known or performed using commercially available tools or kits, that technology cannot logically constitute a claimed advance. *Ariosa,* 788 F.3d at 751; *see also Athena*, 915 F.3d at 751 (identifying the claimed "immunological assay techniques [as] known per se in the art" and therefore not the claimed advance); *Cleveland Clinic*, 859 F.3d at 1361 (relying on the patent's disclosure of "commercially available testing kits" for detecting the natural law).

Table 1, below, highlights the commercially available tools and kits that are identified in the written description as used to perform each claimed method step.

Table 1: Performance of Claimed Method Steps

Claimed Method Step	Commercially Available Tool or Kit
Claim 1(a), "extracting DNA"	QIAgen Maxi kit ('751 patent at col. 3 ll. 49–50)
Claim 1(b)(i), "size discrimination"	Invitrogen 1% agarose gel ('751 patent at col. 3 ll. 66–67) New England Biolabs 100 base pair ladder (*id.* at col. 4 ll. 4–5)
Claim 1(b)(ii), "selectively removing"	Lamda Hind III digest ('751 patent at col. 4 ll. 5–6) QIAEX Gel Extraction kit (*id.* at col. 4 ll. 10–12)
Step (c), "analyzing a genetic locus"	Applied Biosystems (ABI) 7000 Sequence Detection System ('751 patent at col. 4 ll. 14-38) TaqMan System and TaqMan Minor Groove Binder (*id.* at col. 4 ll. 19–38)

The Majority turns to attorney argument to save these claims. It reasons that Roche "has presented no evidence that thresholds of 500 base pairs and 300 base pairs were conventional for separating different types of cell-free DNA

fragments." Maj. Op. at 15. But whether a claim is directed to patent ineligible subject matter depends on the claims and the written description, and not attorney argument. The absence, or silence, of conventionality of an aspect of an invention in the written description does not render that aspect *un*conventional. There is nothing in the patent itself to indicate that size selection based on 500 and 300 base pairs was an unconventional human engineered parameter or that this aspect of the invention is the claimed advance. This explains why the Majority's repeated statements concerning human engineered parameters are unsupported by citations to the specification. *See* Maj. Op. at 10, 14–17. The claimed DNA-processing technologies do not, therefore, constitute the claimed advance. *See Cleveland Clinic*, 859 F.3d at 1361.

The Majority relies on *CellzDirect*. *See* Maj. Op. at 14–15. But *CellzDirect* is distinct from this case. In *CellzDirect*, the inventors created a new and useful cryopreservation technique comprising multiple free-thaw cycles. 827 F.3d at 1048. The claimed invention went beyond applying a known laboratory technique to a newly discovered natural phenomenon and, instead, created an entirely new laboratory technique. *Id.* Unlike in *CellzDirect*, the claimed method steps here are not new, nor are the claimed techniques used in a new or unconventional way. The method steps do not recite or recognize the creation of a new laboratory technique. The Majority recognizes that the inventors "did not invent centrifugation, chromatography, electrophoresis, or nanotechnology"—the claimed techniques described in the written description. Maj. Op. at 15.

The Majority further reasons that the claimed method steps of size discrimination and selective removal "change the composition of the mixture, resulting in a DNA fraction that is different from the naturally-occurring fraction in the mother's blood." *Id.* at 9–10. On this basis, the Majority concludes that the claimed method in the patent "achieves more than simply observing that fetal DNA is

shorter than maternal DNA, or detecting the presence of that phenomenon." *Id.*

The Majority's position is declaratory, but not logical. That the claimed process changes the *composition* of a sample of naturally occurring substances, but does not alter the naturally occurring substances themselves, is not sufficient to render the claimed process patent eligible. *See Genetic Techs.*, 818 F.3d at 1374 (holding ineligible the claimed process for using PCR to amplify genomic DNA in a sample before detecting it); *Ariosa*, 788 F.3d at 1373 (holding ineligible the claimed process for using PCR to amplify cff-DNA in a sample before detecting it).

Here, the claimed method steps of size discrimination and selective removal do not alter the naturally occurring substances in the sample of blood plasma or serum from a pregnant mother. Importantly, the majority correctly understands that the patent does not claim the fraction in terms of chemical composition, as a naturally occurring substance that has been chemically altered by the method steps. *Cf. Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 593 (2013) ("Myriad's claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA.").

The Majority also suggests that the claimed methods are not directed to the natural phenomenon because the "correlation" that "a DNA fragment's size and its tendency to be either fetal or maternal" is not recited in the claim. Maj. Op. at 12–13. Neither our precedent nor that of the Supreme Court imposes such a requirement. Requiring a recitation of the natural phenomenon leads to the "draftsman's art" problem, where a claim drafter has written a claim that is devoted to an ineligible concept, but the drafter managed to avoid reciting the ineligible concept itself. It was this recognition of "the draftsman's art" that motivated the Supreme Court to adopt the step-two,

inventive concept inquiry. *Mayo*, 566 U.S. at 72 (citing *Parker v. Flook*, 437 U.S. 584, 593 (1978)); *see also Diamond v. Diehr*, 450 U.S. 175, 188–89 (1981).

The Majority's category-based approach also allows claim draftsmanship to evade § 101's safeguard at the step-one inquiry. In *Myriad*, the Court concluded that the claims at issue were "concerned primarily" with a patent-ineligible product of nature and recognized that "separating [a] gene from its surrounding genetic material is not an act of invention." 569 U.S. at 591. Here, the separation of genetic material from its surroundings is plainly the focus of the claims at issue. Yet, the Majority distinguishes *Myriad* on the sole ground that these claims have been drafted as method claims rather than composition of matter claims. In any event, whether a patent claim recites a process or a composition of matter does not impact the step-one, "directed to" inquiry because this inquiry applies equally to composition of matter and process claims.[6] I see no principled reason why under the facts of this case *Myriad* should or should not apply simply because this case presents a method claim and not a composition of matter claim. Regardless of whether the asserted claims are to a composition of matter or a "method of preparation," the purpose of § 101 remains the same: to safeguard against

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[6] *E.g.*, *Myriad*, 569 U.S. at 591 (analyzing the "focus" of the relevant composition of matter claims), *Mayo*, 566 U.S. at 72-73 (analyzing the "focus" of the relevant process claims); *Bilski*, 561 U.S. at 609–13 (analyzing whether the process claims involved an abstract idea); *Diehr*, 450 U.S. at 192 (analyzing whether the process claims were "drawn to" a mathematical formula or a patent-eligible process applying that formula); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 132 (1948) (analyzing eligibility of "product claims").

claims that monopolize a law of nature, natural phenomenon, or abstract idea. *See Alice*, 573 U.S. at 216.

II. The Claims Do Not Survive Step Two

Step two of the *Alice* inquiry is a search for other elements that transform ineligible claims into significantly more than a patent upon the natural law or phenomenon. *See Mayo*, 566 U.S. at 72–73. *Mayo* made clear that transformation into a patent eligible application requires "more than simply stat[ing] the law of nature while adding the words 'apply it.'" *Id.* at 72.

In step two, we ask: "[w]hat else is there in the claims before us?" *Id.* at 78. This question is a lifeline, one that is limited to "additional features" of the claim that transforms the nature of the claim into a patent-eligible application. *Id.* at 77; *Ariosa*, 788 F.3d at 1377.

For method claims that encompass natural phenomena, the method steps are the additional features that must be new and useful. *See Parker v. Flook*, 437 U.S. 584, 591 (1978) ("The process itself, not merely the mathematical algorithm, must be new and useful."). We must assess whether the additional features are new and useful within the field generally, not in the context of their particular application to the newly discovered phenomenon. *See Roche Molecular*, 905 F.3d at 1372; *see also Athena*, 915 F.3d at 754.

The method steps under review do not transform the nature of the claims into patent-eligible applications. The three claimed method steps of (a) extracting DNA, (b) producing a fraction of DNA by size discrimination, and (c) analyzing a genetic locus are not new, either alone or in combination. As illustrated above in Table 1, the written description indicates that the laboratory techniques of the claimed method are commercially available. And the written description explains that step (b)'s requirement of producing a fraction by size discrimination "can be brought

about by a variety of methods." '751 patent at col. 2 ll. 49–51.

Contrary to the majority's belief, that the size discrimination and selective removal method steps were applied for the first time to the newly discovered natural phenomenon does not render those steps transformative, new and useful, under the *Alice*/*Mayo* step-two inquiry. *See Roche Molecular*, 905 F.3d at 1372; *see also Athena*, 915 F.3d at 754. In *Roche Molecular*, we held that the method claims at issue, which involved PCR amplification of DNA, did not contain an inventive concept even though the inventors were the first to use PCR to detect the claimed natural phenomenon. 905 F.3d at 1372. We reasoned that the claims did not contain an inventive concept because they did not "disclose any 'new and useful' improvement to PCR protocols or DNA amplification techniques in general." *Id. see also Athena*, 915 F.3d at 754 (noting that "to supply an inventive concept, the sequence of claimed steps must do more than adapt a conventional assay to a newly discovered natural law").

Like in *Roche Molecular*, the claimed method steps here do not disclose any new and useful improvement to DNA separation techniques. And they do not disclose an unconventional assay to apply the newly discovered natural phenomenon. As noted above in the step-one discussion, the Majority reasons that Roche has presented "no evidence that thresholds of 500 base pairs and 300 base pairs were conventional for separating different types of cell-free DNA fragments." Maj. Op. at 15. But, like in *Roche*, the addition of these so-called thresholds—which are claimed as approximations conforming to the natural phenomenon—are nothing more than an adaptation of commercially available DNA separation techniques to the natural phenomenon.

The dependent claims also fail to transform the nature of the claims because they too rely on the same

commercially available, routine, and conventional techniques as claim 1, only they provide more specificity on which techniques to use (e.g., '751 patent, claim 7, identifying "density gradient centrifugation" for the size discrimination method).

For example, the written description describes two examples where experiments illustrate the application of the natural phenomenon. '751 patent at col. 3 l. 30–col. 6 l. 46. The results of Example 1, as captured in Table 1, demonstrate that "DNA fragments originating from the fetus were almost completely of sizes smaller than 500 base pairs with around 70% being of fetal origin for sizes smaller than 300 base pairs." *Id.* at col. 4 l. 50–col. 5 l. 7. The results of Example 2 demonstrate that fetal alleles for "D21S11," a genetic marker found in the human chromosome related to Down Syndrome, could be detected in cell-free DNA samples from which fragments greater than 500 base pairs or 300 base pairs had been removed. The patent explains that both experiments were conducted using known laboratory techniques and commercially available testing kits. *E.g., id.* at col. 3 ll. 49–50, col. 3 l. 65–col. 4 l. 13, col. 5 ll. 45–50; *see also id.* at col. 2 l. 61–col. 3 l. 18.

Simply appending routine, conventional steps to a natural phenomenon, specified at a high level of generality, is not enough to supply an inventive concept. Thus, the claims of the patent in this appeal that are directed to patent ineligible subject matter are not transformed into significantly more than a patent upon the natural law or phenomenon. *See Mayo*, 566 U.S. at 72–73.

III. Preemption

The Supreme Court has made clear that the principle of preemption is the basis for the judicial exceptions to patentability. *Alice*, 573 U.S. at 216–17. As *Mayo* emphasized, "there is a danger that the grant of patents that tie up the[] use [of laws of nature] will inhibit future innovation premised upon them." 566 U.S. at 86.

Here, the claims are drafted in a manner that tie up future innovations premised upon the natural phenomenon because no skilled artisan would be entitled to rely on the natural phenomenon to isolate cff-DNA. That a skilled artisan could isolate or enrich cff-DNA using some unclaimed technique is not dispositive for preemption. *See Athena Diagnostics, Inc. v. Mayo Collaborative Servs.*, 927 F.3d 1333, 1351 (Fed. Cir. 2019) (Chen, J., concurring in the denial of the petition for rehearing en banc) ("That claims 7 and 9 do not preempt all ways of observing the law of nature isn't decisive, as none of the steps recited therein add anything inventive to the claims."). As in *Athena*, the only claimed advance here is the discovery of the natural phenomenon, and as drafted, these claims significantly preempt use of that natural phenomenon.

CONCLUSION

Much of what we are as humans has its source in our respective DNA, including particular genetic aberrations. The development of medical and scientific procedures to detect and diagnose genetic aberrations, like those involved in the patents in this appeal, count among the great discoveries of modern medicine. Such procedures may qualify for a patent, but DNA itself, or a segment of DNA that discloses an aberration, like the entirety of the human genome, does not.

I dissent because while I do not doubt that process claims that are directed to natural phenomenon could be patent eligible subject matter, this is not such a case.