**No. 2019-1419**

# 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.*

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

## DEFENDANTS-APPELLEES' COMBINED PETITION FOR PANEL REHEARING AND REHEARING EN BANC

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April 16, 2020

# CERTIFICATE OF INTEREST

Counsel for Defendants-Appellees Roche Molecular Systems, Inc. and Roche Sequencing Solutions, Inc. certifies the following:

1. The full name of every party or *amicus* represented by me is:

Roche Molecular Systems, Inc. and Roche Sequencing Solutions, Inc.

2. The names of the real party in interest represented by me is:

Not applicable.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Roche Holdings, Inc., Roche Holding Ltd., and Novartis AG

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are:

None.

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal:

None.

Dated: April 16, 2020

/s/ Robert J. Gunther, Jr.

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## CERTIFICATE OF INTEREST

Counsel for Defendant-Appellee Ariosa Diagnostics, Inc. certifies the following:

1. The full name of every party or *amicus* represented by me is:

Ariosa Diagnostics, Inc.

2. The names of the real party in interest represented by me is:

Not applicable.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

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4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are:

DURIE TANGRI LLP: Eneda Hoxha

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal:

None.

Dated: April 16, 2020

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Based on my professional judgment, I believe the panel decision is contrary to the following decisions: *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576 (2013); *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66 (2012); *Parker v. Flook*, 437 U.S. 584 (1978); *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948); *Roche Molecular Systems, Inc. v. Cepheid*, 905 F.3d 1363 (Fed. Cir. 2018); *Genetic Technologies 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).

Based on my professional judgment, I also believe this appeal requires an answer to the following precedent-setting question of exceptional importance:

> Whether methods of separating one naturally occurring material from another using well-known laboratory techniques are patent eligible under step one of the *Mayo*/*Alice* analysis, ***without regard to step two***, where (1) Supreme Court precedent establishes that isolated naturally occurring material is not itself patent eligible, and (2) this Court has consistently invalidated diagnostic claims reciting similar steps.

/s/ Robert J. Gunther, Jr.
ROBERT J. GUNTHER, JR.

## INTRODUCTION

In a precedential opinion, a divided panel of this Court held that using known and conventional laboratory techniques to separate certain naturally occurring DNA from other naturally occurring DNA according to their naturally occurring size differences is patent eligible at step one of the *Mayo*/*Alice* analysis without any consideration at step two of the inventiveness of the techniques used. The majority opinion conflicts with Supreme Court precedent holding that patentability requires more than mere isolation of naturally occurring compositions of matter. It is also irreconcilable with this Court's diagnostic-methods precedents. Although the claims here require both preparing a DNA sample and "analyzing" that sample, the majority treated the claims as so-called "method of preparation" claims deemed categorically patent eligible despite this Court's decisions invalidating claims with comparable preparation and analysis steps. Rehearing is urgently needed to bring the panel decision back in line with Supreme Court precedent and reconcile the conflict among this Court's decisions.

The majority's method-of-preparation analysis led it to hold at step one that the mere separation of smaller cell-free DNA from larger cell-free DNA is patent eligible as a matter of law. As the dissent noted, that holding cannot be squared with the Supreme Court's decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576 (2013). There, the Court held that "a naturally

occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated." *Id.* at 580. It further stated that "separating [a] gene from its surrounding genetic material is not an act of invention." *Id.* at 591. Just as an isolated DNA segment is itself unpatentable, so too is employing conventional techniques to isolate the DNA. And while a method involving unconventional steps for isolating a naturally occurring material might survive § 101, no such method is at issue here. More importantly, the panel did not even consider the question. By resolving this case at step one, the panel held that separation ***alone*** is enough to survive § 101. That erroneous bright-line rule is likely to create perverse outcomes, opening the door to patents on isolating natural products using routine methods.

As the dissent noted, the panel's holding also cannot be reconciled with this Court's precedent invalidating diagnostic claims. The majority sidestepped that precedent by categorizing Illumina's claims—based solely on certain claims' preambles—as "method of preparation" claims. That categorization is inapt: Illumina's claimed methods require analyzing the separated DNA, just as in other diagnostic claims. Moreover, the majority's delineation between "method of preparation" claims and "diagnostic" claims is a distinction without a difference. Many diagnostic claims include preparation steps. For example, in *Ariosa Diagnostics, Inc. v. Sequenom, Inc*., 788 F.3d 1371 (Fed. Cir. 2015)—which

involved nearly identical prenatal diagnostic technology (and the same patentee)—the Court held that claims directed to the amplification and detection of cell-free fetal DNA are not patent eligible. The amplification step there was an even more transformative sample-preparation step than the mere separation here. Yet, the panel decision, with its artificial distinction, opens the door to claim drafting that elevates form over substance.

Rehearing is required to correct the panel decision, restore consistency to this Court's diagnostic-methods decisions, and avoid confusion in the application of § 101 at the district court level.

## BACKGROUND

### I. ILLUMINA/SEQUENOM'S PATENTS

The Sequenom patents exclusively licensed to Illumina—U.S. Patent Nos. 9,580,751 ("'751 patent") and 9,738,931 ("'931 patent")—state that the inventors observed the following natural phenomenon: "Circulatory extracellular fetal DNA in the maternal circulation [is generally] smaller in size (approximately 500 base pairs or less) than circulatory extracellular maternal DNA (greater than approximately 500 base pairs)." Appx31(1:63-67). In making that finding, the inventors removed DNA fragments larger than approximately 500 base pairs from a maternal blood sample, leaving behind for analysis a sample that "is largely constituted by fetal extracellular DNA." Appx31(2:1-10). That is Illumina's

purported invention: analyzing size-separated DNA based on the discovery that the DNA's natural characteristics permit such separation. Maj. 14.

Claim 1 of the '751 patent is representative:

> 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)***.

Appx34(7:54-8:57) (emphases added). The specification states that the claimed method can be performed using "known methods" and commercially available materials, and it recites an example in which the method was performed merely to confirm the natural phenomenon that the inventors discovered. Diss. 2-3, 9-10; Appx31(2:46-48).

## II. THE PANEL DECISION

The district court granted summary judgment of invalidity under § 101, finding the claims indistinguishable from Sequenom's claims in *Ariosa Diagnostics v. Sequenom* ("*Ariosa* claims"). Appx11-14. A divided panel of this Court reversed, holding at *Mayo*/*Alice* step one that Illumina's claims are patent eligible as a matter of law.

The majority acknowledged that the inventors "discovered" the natural phenomenon that cell-free fetal DNA (cffDNA) tends to be shorter than cell-free maternal DNA, but nonetheless characterized the claims as "methods for preparing" a fraction of cell-free DNA, which the majority found distinguishable from the claims in *Ariosa* and this Court's other diagnostic-methods precedent. Maj. 8-10. The majority likewise distinguished the Supreme Court's holding in *Myriad* on the ground that Myriad Genetics claimed compositions of isolated natural products, whereas Illumina claims methods to isolate such products. *Id.* at 12. Having found the claims patent eligible at step one, the majority did not proceed to step two.

Judge Reyna dissented, explaining that the majority improperly "sidestep[ped]" this Court's precedent involving diagnostic claims by classifying Illumina's claims as "methods of preparation." Diss. 4. The dissent also disagreed with the majority's attempt to distinguish *Myriad*'s composition claims from

Illumina's method claims, as well as the majority's dismissal of *Ariosa*. Like the *Ariosa* patent, the dissent noted, Illumina's patents consistently describe the invention as a "finding," and the claims merely "separate[]" one naturally occurring substance from another. *Id.* at 7-8. At step two, the dissent observed that the claims recite what the specification describes as conventional, well-known laboratory techniques. *Id.* at 12-14.

## ARGUMENT

### I. THE PANEL DECISION IS IRRECONCILABLE WITH SUPREME COURT AND THIS COURT'S PRECEDENT

#### A. The Panel's Holding That Mere Separation Of Naturally Occurring Substances Is Patent Eligible At Step One Must Be Vacated

The panel majority held Illumina's claims patent eligible at step one merely because they "are directed to methods for preparing a fraction of cell-free DNA that is enriched in fetal DNA." Maj. 10. Put simply, the panel held that the mere separation of one natural product (smaller cell-free DNA) from another (larger cell-free DNA) is enough to survive a § 101 challenge, without regard to the inventiveness of that separation. That holding cannot stand because it runs headlong into Supreme Court precedent and leads to perverse outcomes.

### 1. Mere Separation, Standing Alone, Is Not Enough To Survive § 101

The Supreme Court has held that the separation of naturally occurring materials, standing alone, is not patent eligible. In *Myriad*, the Court reversed this Court's determination that isolated segments of DNA encoding the BRCA1 and BRCA2 genes are patent eligible. 569 U.S. at 580. In so ruling, the Court held that "a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated," even where the isolating step "severs chemical bonds" so as to "create[] a nonnaturally occurring molecule." *Id.* at 580, 593. Indeed, the Court expressly noted that ***"separating [a] gene from its surrounding genetic material is not an act of invention***." *Id.* at 591 (emphasis added).

*Myriad* is consistent with older precedent holding that merely changing the concentration of one naturally occurring substance relative to another (*e.g.*, by isolating, amplifying, or aggregating) is not patent eligible where the constituent substances are not altered and therefore "serve the ends nature originally provided and act quite independently of any effort of the patentee." *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 131 (1948); Diss. 11. Such claims are directed to nothing more than the natural products themselves.

Here, Illumina's claims separate smaller DNA fragments from larger ones in maternal blood before analyzing the smaller fragments. It is undisputed that the

claimed method does not change the molecular structure or nucleotide sequence of the separated DNA. Diss. 8. Under *Myriad*, therefore, the separated DNA fragments are themselves unpatentable. 569 U.S. at 593. Methods employing only routine steps to carry out that separation are likewise unpatentable. Routine separation merely facilitates the analysis of the separated DNA—it is indistinguishable from the natural phenomenon itself. *See Funk Bros.*, 333 U.S. at 132 ("[O]nce nature's secret of the non-inhibitive quality of certain strains … was discovered, ***the state of the art made the production of a mixed inoculant a simple step***." (emphasis added)).

The majority dismissed *Myriad* as directed to ***composition*** claims, in contrast to Illumina's ***method*** claims. Maj. 12. To support that distinction, the majority quoted dicta in *Myriad* suggesting that, "[h]ad Myriad created an innovative method of manipulating genes … it could possibly have sought a method patent." *Id.* (quoting *Myriad*, 569 U.S. at 595-596). But that passage only highlights the impropriety of the majority's holding that Illumina's claims are patent eligible ***at step one***. At most, *Myriad* suggests that, had the patentee developed an ***inventive*** method, it might have been patent eligible. But that is a question for step two. Here, the majority never considered whether the claimed

separation is innovative or unconventional because it never reached step two.[1] By stopping at step one, the majority held that mere separation of naturally occurring material is ***sufficient alone*** to survive § 101. That cannot be correct. Otherwise, claims involving mere separation would never be subject to step two, rendering them *per se* eligible. *CyberSource Corp. v. Retail Decisions, Inc.*, 654 F.3d 1366, 1374 (Fed. Cir. 2011) (rejecting the argument that a claim may be "patent-eligible per se because it recites a 'manufacture,' rather than a 'process,'" and noting that, "[r]egardless of what statutory category ('process, machine, manufacture, or composition of matter,' 35 U.S.C. § 101) a claim's language is crafted to literally invoke, we look to the underlying invention for patent-eligibility purposes").

The majority's holding that mere separation is enough to survive § 101, without regard to its inventiveness, warrants en banc review.

**2. The Panel's Contrary Holding Leads To Perverse Outcomes**

The panel's holding will lead to illogical results. As an initial matter, the majority's analysis suggests that, had Myriad's claims been drafted as methods

[1] The majority could not have reasonably found the claims patent eligible at step two. As the dissent noted (Diss. 9-10), Illumina's patents describe the claimed steps as being performed using commercially available tools and kits. Indeed, the majority acknowledged that the inventors "did not invent centrifugation, chromatography, electrophoresis, or nanotechnology." Maj. 13. Regardless, even if the panel disagreed with the district court's step-two findings, the proper remedy would have been vacatur and remand so that Roche could present the § 101 issue to the jury, not reversal. *See Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1052 (Fed. Cir. 2016).

instead of compositions, the outcome would have been different. But *Myriad* itself does not suggest as much, and the Supreme Court has long admonished that the "determination of patentable subject matter" ought not "depend simply on the draftsman's art." *Parker v. Flook*, 437 U.S. 584, 593 (1978); *see also Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 77 (2012) ("If a law of nature is not patentable, then neither is a process reciting a law of nature, unless that process has additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself."). Thus, as the dissent noted, "[w]hether the asserted claims recite a composition of matter or a 'method of preparation,' the purpose of § 101 remains the same, to safeguard against claims that monopolize a law of nature, natural phenomenon, or abstract idea." Diss. 12.

Further, the panel's holding opens the door to patents on methods that are indisputably directed to natural phenomena. Consider an instruction to filter larger material from a sample of pond water before analyzing a microorganism contained therein. The microorganism is a product of nature and would not be patentable merely because it has been separated from other natural material in the pond. *Myriad*, 569 U.S. at 593; *Funk Bros.*, 333 U.S. at 130 ("The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men."). And yet, under the panel's holding, the

mere instruction to filter the microorganism from its surroundings would be patent eligible as a "method of preparing" a filtered sample. This untenable result confirms the unsoundness of the panel decision.

### B. The Panel Decision Conflicts With This Court's Diagnostic Cases

The panel decision also conflicts with this Court's diagnostic cases. Although the majority acknowledged that the Court has "consistently held diagnostic claims unpatentable as directed to ineligible subject matter," Maj. 8, it summarily dismissed that precedent. This was error.

#### 1. Illumina's Claims Are Indistinguishable From Diagnostic Claims This Court Has Invalidated

Illumina's claims are analytically indistinguishable from diagnostic claims this Court has invalidated. The claims in *Ariosa*, for example, recited methods comprising "obtaining a non-cellular fraction," enriching the fraction for cffDNA by "amplifying a paternally inherited nucleic acid from the non-cellular fraction," and "performing nucleic acid analysis" on the enriched sample. 788 F.3d at 1373-1374, 1376. At step one, this Court observed that the claimed method "begins and ends with a natural phenomenon" and held that the claims "are generally directed to detecting the presence of a naturally occurring thing or a natural phenomenon." *Id.* at 1376. Likewise, the claims in *Genetic Technologies Ltd. v. Merial L.L.C.*, 818 F.3d 1369 (Fed. Cir. 2016), recited a "method of detecting an allele of interest" by "amplifying a sequence of non-coding region DNA" linked with the

allele and then "analyzing the non-coding region to detect the allele." *Id.* at 1374, 1376. The Court observed that the claims "involve[] no creation or alteration of DNA sequences, and do[] not purport to identify novel detection techniques." *Id.* at 1376; *see also Roche Molecular Sys., Inc. v. Cepheid*, 905 F.3d 1363, 1366-1367, 1371-1374 (Fed. Cir. 2018) (claims to methods for amplifying DNA and detecting amplification product patent ineligible).

Just as claims to amplifying and analyzing DNA are unpatentable, so too are claims to separating and analyzing such DNA. In fact, Illumina's claims hew even ***closer to nature*** than those in *Ariosa*, *Genetic Technologies*, and *Cepheid* because, while the naturally-occurring DNA in those cases was artificially multiplied in the laboratory to create new molecules, the separated DNA analyzed in Illumina's broad claims is all initially present in the maternal blood sample itself. Illumina's claims are thus directed to mere filtering for analysis, a far less transformative process than amplification.

The majority attempted to distinguish *Ariosa* on the basis that the claims there proved the natural phenomenon at issue, unlike Illumina's claims. Maj. 11-12. But the majority's premise is incorrect. Illumina's specification explains that ***the very steps recited in the claimed methods*** were performed to conclude that cffDNA is generally shorter than maternal cell-free DNA. Diss. 2-3. A claim covering the steps used to prove the existence of a natural phenomenon is directed

to the natural phenomenon itself. *Ariosa*, 788 F.3d at 1376; *Genetic Techs.*, 818 F.3d at 1375-1376; Diss. 14-15.

### 2. The Majority's Distinction Between "Method Of Preparation" Claims And "Diagnostic" Claims That Recite Preparation Steps Is Untenable

Rather than confronting this Court's diagnostic-methods precedent head-on, the majority dismissed it because, according to the majority, Illumina's claims are "method of preparation" claims rather than "diagnostic" claims. Maj. 8; Diss. 4-5. But that conclusion was based solely on the preamble of claim 1 of the '751 patent. When the claims are considered in their totality, it is evident that the majority's characterization of the claims is wrong.

Each of Illumina's claims recites a step in which the separated DNA is "analyzed," and some claims recite analysis for the purpose of detecting "fetal chromosomal aberrations," like aneuploidy and Down's Syndrome. *See* Appx34(7:54-8:57); Appx35(9:5-8); Appx42(7:58-8:64); Appx43(9:17-24). The specification confirms that the claimed analysis is performed for the purpose of detecting—*i.e.*, diagnosing—chromosomal aberrations. Appx31(2:10-18) (claimed method "permits the analysis of fetal genetic traits"). Indeed, the patents' Titles and Abstracts refer to the "***detection*** of fetal genetic traits," not the preparation of DNA. Appx28; Appx36 (emphasis added). Illumina's patents, like the *Ariosa* patent, are prenatal ***diagnostic*** patents.

That is why the majority's reliance on *Rapid Litigation Management Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042 (Fed. Cir. 2016)—despite its acknowledgment that *CellzDirect* is "not directly on point"—is misguided. Maj. 12-13. CellzDirect's claims lacked Illumina's claims' "analyzing" step and culminated in cryopreserved hepatocytes with specific properties that, in contrast to Illumina's claims, are ***not*** naturally occurring and can be used for treatment. *CellzDirect*, 827 F.3d at 1045-1049; Diss. 11. Thus, the majority's passing invocation of *CellzDirect* does not support its dismissal of this Court's diagnostic-methods precedent.

In addition, neither Supreme Court nor this Court's precedent supports the majority's artificial grouping of patent-eligible claims. As the dissent noted, "[a] 'method of preparation case' is treated no differently than any other process claim under" established § 101 law. Diss. 5; *CyberSource*, 654 F.3d at 1374.

Indeed, many of the diagnostic claims this Court has invalidated ***also*** recited method-of-preparation limitations. The *Ariosa* claims, for example, recited "obtaining a non-cellular fraction of the blood sample" and "amplifying a paternally inherited nucleic acid from the non-cellular fraction." 788 F.3d at 1374. Similarly, the claims in *Cepheid* recited a method for detecting Mycobacterium tuberculosis in a biological sample that is prepared by first amplifying DNA. 905 F.3d at 1371. The claims in *Genetic Technologies* likewise require "amplifying"

DNA prior to "analyzing the non-coding region to detect the allele." 818 F.3d at 1372, 1376. The "preparation" of the DNA samples in these cases was nothing more than pre-solution activity—*i.e.*, a starting point for analyzing DNA. *Cf. Association for Molecular Pathology v. U.S. Patent & Trademark Office*, 702 F. Supp. 2d 181, 236 (S.D.N.Y. 2010) ("[I]solation and sequencing of DNA from a human sample[] … would represent nothing more than data-gathering steps to obtain the DNA sequence information on which to perform the claimed comparison or analysis."), *aff'd in relevant part*, 689 F.3d 1303, 1334-1335 (Fed. Cir. 2012). The claims here are no different.

## II. THE PANEL DECISION FURTHER COMPLICATES § 101 LAW

If left to stand, the panel decision will further complicate this already-complicated area of law and will unnecessarily sow confusion. First, even if it were appropriate to classify patent claims into *per se* categories for purposes of the § 101 analysis (it is not), the panel decision provides no guidance about how to make that classification. As discussed above, many of the diagnostic claims that this Court has invalidated recited "preparation" steps. Under what circumstances, then, should lower courts focus on "preparation" limitations over "diagnostic" limitations? The panel decision does not say.

Because the decision provides no guidance on this point, it will encourage applicants to circumvent § 101 by drafting the preambles of their diagnostic claims

to recite "methods of preparation." In fact, that is precisely what Illumina did here. Illumina added the "method of preparation" language recited in the '751 patent claims' preambles during prosecution to overcome a § 101 rejection shortly after this Court's opinion in *CellzDirect* issued. *Compare* Appx339 ('751 Patent File History, 12/28/2015 Claim Amendment), *with* '751 Patent File History, 09/29/2016 Claim Amendment. Prior to that amendment, the preamble recited "a method for ***analyzing*** deoxyribonucleic acid," consistent with the "analyzing" limitation recited in the body of the claims. Appx339 (emphasis added); *see* Appx344. If allowed to stand, the panel decision will condone this tactic, leaving patent eligibility to impermissibly turn on "the draftsman's art." *Flook*, 437 U.S. at 593.

Second, this Court has invalidated claims that "begin and end" with natural material and claims that change the composition of a DNA mixture—*e.g.*, by amplification—without changing the underlying DNA structure or sequence. *Ariosa*, 788 F.3d at 1376; *Cepheid*, 905 F.3d at 1371; *Genetic Veterinary Scis., Inc. v. LABOKLIN GmbH & Co. KG*, 933 F.3d 1302, 1318 (Fed. Cir. 2019); *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755, 764-765 (Fed. Cir. 2014). The majority apparently believed that Illumina's claims—which begin and end with naturally occurring cffDNA and which do not change the DNA structure or sequence, *see* Diss. 8—are distinguishable from such

precedent at step one but did not explain why. How are lower courts to apply that precedent? Again, the panel decision does not say.

The panel's silence on these important questions leaves district courts, companies, and the patent bar to muddle through conflicting precedent on their own. Members of this Court have frequently noted the complexity and confusion that § 101 law has engendered. *See, e.g.*, *Interval Licensing LLC v. AOL, Inc.*, 896 F.3d 1335, 1348 (Fed. Cir. 2018) (Plager, J., concurring in part, dissenting in part) ("The law[] … renders it near impossible to know with any certainty whether the invention is or is not patent eligible. Accordingly, I also respectfully dissent from our court's continued application of this incoherent body of doctrine."). Respectfully, the last thing § 101 law needs is the additional confusion the panel's decision is bound to create.

## CONCLUSION

The petition should be granted.

Respectfully submitted,

/s/ Robert J. Gunther, Jr.

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April 16, 2020

# ADDENDUM

# United States Court of Appeals for the Federal Circuit

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

**v.**

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

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2019-1419

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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.

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Decided: March 17, 2020

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

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.

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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. Having made that discovery, they used it to develop a solution to the identified problem of distinguishing fetal DNA from maternal DNA in the mother's bloodstream:

> 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. Claim 1 is the only independent claim in each patent:

> 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.

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 bucket, 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. Those process steps change the composition of the mixture, resulting in a DNA fraction that is different from the naturally-occurring fraction in the mother's blood. Thus, the process achieves more than simply observing that fetal DNA is shorter than maternal DNA or detecting the presence of that phenomenon.

The dependent claims further illustrate the concrete nature of the claimed process steps. For example, claims 7–8 of the '751 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. In essence, the inventors in *Ariosa* discovered that cell-free fetal DNA exists, and then obtained patent claims that covered only the knowledge that it exists and a method to see that it 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. And the claims do not merely cover a method for detecting whether a cell-free DNA fragment is fetal or maternal based on its size. Rather the claimed method removes some maternal DNA from the mother's blood to prepare a fraction of cell-

free DNA that is enriched in fetal DNA. 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 a 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 . . . are not at issue in this case.

*Id.* Thus, in *Myriad*, the claims were ineligible because they covered a gene rather than a process for isolating it. Here, we encounter the opposite situation, *i.e.*, the claims do not cover cell-free fetal DNA itself but rather a process for selective removal of non-fetal DNA to enrich a mixture in fetal DNA. Thus, the Supreme Court's decision in *Myriad* is not on point.

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 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 while such 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

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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.

well-known processes of "freezing" and "thawing," but only in 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 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 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

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

**v.**

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

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2019-1419

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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.

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REYNA, *Circuit Judge*, dissenting.

The Majority holds that the asserted patents are directed to patent-eligible subject matter. I respectfully disagree and dissent. I conclude that the claims are directed to a natural phenomenon. The patents' only claimed advance is the discovery of that natural phenomenon. The claims, the written description, and the legal precedent applicable to this case all support the conclusion that the patents are ineligible.

## I. The '751 and '931 Patents[1]

At the time of the invention, skilled artisans knew that cell-free fetal DNA ("cff-DNA") existed, that it could be detected in a sample of a pregnant woman's blood or serum, and that it was useful for reliably analyzing fetal genetic markers (for detecting certain diseases and disorders). '751 patent col. 1 ll. 22–34. But for some genetic markers that are 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 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 maintains that the problem was overcome when the inventors made a "surprising" discovery. *Id.* at col. 1 ll. 54–61. The inventors discovered a natural phenomenon: that cff-DNA tends to be shorter than cell-free maternal DNA in a mother's blood. *See id.* 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 "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).

Other than the surprising discovery, nothing else in the specification or the record before us indicates there was anything new or useful about the claimed invention. In two

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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.

examples, the patent describes experiments that illustrate the natural phenomenon and a potential application. *Id.* 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 bases." *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. 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.

The claims recite nearly identical method steps. The method steps of the '751 patent separate DNA fragments greater than or equal to 500 base pairs. The method steps of the '931 patent separate DNA fragments greater than or equal to 300 base pairs.

For example, claim 1 of the '751 patent recites the following method:

> 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).

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

The dependent claims for each patent 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 col. 9 ll. 1–2, 7–8.

## II. The Claims Are Not Patent Eligible

The Majority sidesteps well-established precedent by reasoning that the claims in this case belong in a unique "bucket" reserved for patents that claim "a method of preparation."[2] *See* Maj. Op. at 8. By placing this case in that bucket and not in a "diagnostic case" bucket, the Majority summarily dismisses precedent like *Athena*, *Roche*

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[2] *Cf.*, *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1046 (Fed. Cir. 2016) (reciting in claim 1's preamble "[a] method of producing a desired preparation").

*Molecular*, *Cleveland Clinic*, *Genetic Techs.*, *Ariosa*,[3] and others. *Id.* Our precedent, however, does not support the Majority's per se grouping of claims. A "method of preparation case" is treated no differently than any other process claim under our law.

35 U.S.C. § 101 grants patent rights to "[w]hoever invents or discovers any new and useful process[4], machine, manufacture, or composition of matter, or any new and useful improvement thereof." *See Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 589 (2013). Laws of nature, natural phenomena, and abstract ideas, however, are not patent-eligible subject matter. *Id.*

To determine whether a patent claims a patent-eligible application of a natural phenomenon or impermissibly monopolizes a natural phenomenon, we apply the two-step test set forth by the Supreme Court. *Alice Corp. v. CLS Bank Int'l*, 573 U.S. 208, 217–18 (2014). In the first step, we determine whether the claims at issue are "directed to" a patent-ineligible concept. *Id.* If they are, we consider in the second step whether the additional claim elements—both individually and "as an ordered combination"—"transform the nature of the claim" into a patent-eligible application. *Id.*

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[3] *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).

[4] The term "process," as recited in § 101, encompasses all "process, art or method" claims. 35 U.S.C. § 100(b).

### A. The Claims are Directed to a Patent-Ineligible Natural Phenomenon

The claims are directed to a natural phenomenon because the patent's claimed advance is the discovery of that natural phenomenon. The Majority disregards well-established precedent for conducting the *Alice*, step one, "directed to" inquiry by failing to consider the patent's claimed advance.

The Supreme Court first articulated the "directed to" inquiry in *Alice*, 573 U.S. at 217–218. To make that determination, the Court analyzed whether the claims "involved" patent-ineligible subject matter (there, an abstract idea). *Id.* at 218–220 (citing *Gottschalk v. Benson*, 409 U.S. 63, 71–72 (1972), *and Bilski v. Kappos*, 561 U.S. 593, 599 (2010)).

In the three years following *Alice*, this court addressed numerous § 101 cases without articulating a more definite "directed to" inquiry. Instead, we performed step one of the patent-eligibility inquiry by comparing the claims at issue to the claims held eligible or ineligible in earlier Supreme Court and Federal Circuit cases. *See, e.g.*, *In re Smith*, 815 F.3d 816, 818 (Fed. Cir. 2016); *buySAFE, Inc. v. Google, Inc.*, 765 F.3d 1350, 1353 (Fed. Cir. 2014).

Since 2016, in a string of cases reciting process claims, we began conducting the "directed to" inquiry by asking whether the "claimed advance" of the patent "improves upon a technological process or [is] merely an ineligible concept." *Athena*, 915 F.3d at 750 (Lourie, J.); *Genetic Techs.*, 818 F.3d at 1375.

To determine a process's "claimed advance," we review the claims and the written description. *Athena*, 915 F.3d at 750. If a written description highlights the discovery of a natural phenomenon—e.g., by describing the natural phenomenon as the only "surprising" or "unexpected" aspect of the invention or that the invention is "based on the

discovery" of a natural law—the natural phenomenon likely constitutes the claimed advance. *See Ariosa*, 788 F.3d at 1376; *Athena*, 915 F.3d at 751; *Cleveland Clinic*, 859 F.3d at 1360 –61.

In *Ariosa*, we concluded that the claims were directed to a natural phenomenon based 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 a natural law" based 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 col. 1 ll. 54–61. Like in *Ariosa* and *Athena*, the patent's written description identifies the natural phenomenon as the only "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, 8. The claimed advance is, therefore, the natural phenomenon.

This conclusion is bolstered by the fact that the claimed method steps begin and end with a naturally occurring substance, as in *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, both naturally occurring substances.

*Id.* The inventors did not create or alter any of the genetic information encoded in the cff-DNA in the claimed method steps. *Id.*

Likewise, the claimed method here begins and ends with a naturally occurring substance. 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 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. The claimed method is therefore directed to a natural phenomenon.

*The Majority fails to identify the claimed advance*

The Majority's step one analysis ignores the claimed advance inquiry altogether. Contrary to the Majority's conclusion, the claims here are not directed to "a patent-eligible method that utilizes [the natural phenomenon]." Maj. Op. at 8–9. Although the Majority states that the claims "are directed to methods for preparing a fraction of cell-free DNA that is enriched in fetal DNA" (*id.* at 9), the Majority fails to address with specificity the patent's claimed advance.

Instead, the Majority only seems to suggest that the claimed advance is an improvement in "size discriminat[ion]" and "selective[] remov[al]" techniques. *See id.* at 9–10. 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 10–11. But whether the steps are concrete is not the appropriate analysis for determining the claimed advance.

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).

Here, the claimed advance is not an improvement in the underlying DNA-processing technology, as hinted by the Majority. The written description identifies the claimed method steps as well-known or performed using commercially available tools or kits. *See* '751 patent 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. For example, the table below highlights the commercially available tools and kits that are identified in the written description as used to perform each claimed method step.

**Performance of Claimed Method Steps**

| Claimed Method Step | Commercially Available Tool or Kit |
|---|---|
| Claim 1(a), "extracting DNA" | QIAgen Maxi kit ('751 patent col. 3 ll. 49–50) |
| Claim 1(b)(i), "size discrimination"<br>Claim 1(b)(ii), "selectively removing" | Invitrogen 1% agarose gel ('751 patent col. 3 ll. 66–67)<br>New England Biolabs 100 base pair ladder (*id.* at col. 4 ll. 4–5)<br>Lamda Hind III digest ('751 patent col. 4 ll. 5–6)<br>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 col. 4 ll. 14–38)<br>TaqMan System and TaqMan Minor Groove Binder (*id.* at col. 4 ll. 19–38) |

The selection of 300 and 500 base pairs resulted from using commercially available DNA size-markers. *See id.* at col. 4 ll. 3–9. 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 12–13. But *CellzDirect* is different from this case. In *CellzDirect*, the inventors created a new and useful cryopreservation technique comprising multiple freeze-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 *CellzDirect*, the claimed method steps here are not new nor are the claimed techniques used in a new or unconventional way. 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 13.

*The Majority's remaining reasoning fails*

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 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 reasoning is shortsighted. A process that merely changes the *composition* of a sample of naturally occurring substances, without altering the naturally occurring substances themselves, is not patent eligible. *See Genetic Techs.*, 818 F.3d at 1374 (using PCR to amplify genomic DNA in a sample before detecting it); *Ariosa*, 788 F.3d at 1373 (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. *Cf., Myriad*, 569 U.S. at 593 ("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 attempts to distinguish *Myriad*, reasoning that the claims at issue in *Myriad* were not method claims. Maj. Op. at 12 (citing *Myriad*, 569 U.S. at 595). But 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. Whether the asserted claims recite a composition of matter or a "method of preparation," the purpose of § 101 remains the same, to safeguard against claims that monopolize a law of nature, natural phenomenon, or abstract idea. *See Alice*, 573 U.S. at 216 ("We have described the concern that drives this exclusionary principal as one of pre-emption.").

Because the patent's claimed advance is the discovery of the natural phenomenon, the claims are directed to a natural phenomenon under the step one inquiry.

B. The Claims Fail to Recite an Inventive Concept

Step two of the *Alice* inquiry is a search for other elements that transform the ineligible claims into significantly more than a patent upon the natural law or phenomenon. *See Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 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 fail to 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. The written description indicates that the laboratory techniques of the claimed method are commercially available techniques. And the written description explains that step (b)'s producing a fraction by size discrimination "can be brought about by a variety of methods." '751 patent col. 2 ll. 49–51.

For step two purposes, that the size discrimination and selective removal method steps were never before applied to the newly discovered natural phenomenon does not render those steps new and useful. *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 notwithstanding that the inventors were the first to use PCR to detect the claimed natural phenomenon. *Id.* 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. They do not disclose an unconventional assay to the newly discovered natural phenomenon. Instead, they adapt 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, identifies "density gradient centrifugation" for the claimed size discrimination method).

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, under step two, the claims of the patent in this appeal that are directed to patent ineligible subject matter are not transformed and made eligible under *Alice* step two.

## 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 216–217. 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 innovation 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 with 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."). Like 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.

I do not doubt that process claims that involve naturally occurring phenomena from beginning to end could be directed to patent eligible subject matter, but this is not such a case.

## ECF-3(B)(2) REPRESENTATION

Pursuant to this Court's Administrative Order Regarding Electronic Case Filing, the undersigned represents under ECF-3(b)(2) that counsel for Defendant-Appellee Ariosa Diagnostics, Inc. has consented to her signature on this Petition and Certificate of Interest.

Dated: April 16, 2020

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## CERTIFICATE OF SERVICE

I hereby certify that, on this 16th day of April, 2020, I filed the foregoing with the Clerk of the United States Court of Appeals for the Federal Circuit via the CM/ECF system, which will send notice of such filing to all registered CM/ECF users.

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## CERTIFICATE OF COMPLIANCE

Pursuant to Fed. R. App. P. 32(g), the undersigned hereby certifies that this petition complies with the type-volume limitation of Fed. R. App. P. 35(b)(2).

1. Exclusive of the exempted portions of the petition, as provided in Fed. Cir. Rule 35(c)(2), the petition contains 3,860 words.

2. The petition has been prepared in proportionally spaced typeface using Microsoft Word 2016 in 14-point Times New Roman font. As permitted by Fed. R. App. P. 32(g), the undersigned has relied upon the word count feature of this word processing system in preparing this certificate.

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