Nos. 14-1139, 14-1142, and 14-1144

IN THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

ARIOSA DIAGNOSTICS, INC., NATERA, INC., and VERINATA HEALTH, INC.,
Plaintiffs-Appellees,
and
DNA DIAGNOSTICS CENTER, INC.,
Counterclaim Defendant-Appellee
and
THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,
Plaintiff,
v.
SEQUENOM, INC. and SEQUENOM CENTER FOR MOLECULAR MEDICINE, LLC
Defendants-Appellants
and
ISIS INNOVATION LIMITED,
Defendant.

Appeals from the United States District Court for the Northern District of California, Judge Susan Illston

CONSOLIDATED OPENING BRIEF OF APPELLANT SEQUENOM, INC.

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January 21, 2014

CERTIFICATE OF INTEREST

Pursuant to Federal Circuit Rule 47.4, undersigned counsel for Appellant Sequenom, Inc. certifies the following:

1. The full name of every party represented by me in this appeal is: Sequenom, Inc.

2. The names of the real parties in interest, if different from the parties named above, are: Not applicable.

3. The names of all parent corporations and any publicly held companies that own 10% or more of the stock of the party represented by me are: None.

4. The names of all law firms and the partners or associates that appeared for Appellant in the district court or are expected to appear in this court are:

> Kaye Scholer LLP: Michael J. Malecek, Peter E. Root, Stephen C. Holmes, Aton Arbisser, Gary Ross Allen, Hanna Cohen, Robert Estrin, and Lily Robinton.

Dated: January 21, 2014

/s/ Michael J. Malecek
Michael J. Malecek
Attorney for Appellant, Sequenom, Inc.

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STATEMENT OF RELATED CASES

There has been one previous appeal in these consolidated cases. In *Aria Diagnostics, Inc. v. Sequenom, Inc.*, Case No. 12-1531, 726 F.3d 1296 (Fed. Cir. 2013), decided on August 9, 2013, a panel of Chief Judge Rader and Judges Dyk and Reyna vacated and remanded on several grounds the District Court's order denying Sequenom's motion for a preliminary injunction, including reversing the District Court's claim construction and findings on equitable issues. The panel also remanded to the District Court for further consideration whether U.S. Patent No. 6,258,540 ("the '540 patent") satisfies 35 U.S.C. § 101, the issue again before this Court. *Id*. at 1304.

Federal Circuit Internal Operating Procedure # 3 applies to this appeal.

STATEMENT OF JURISDICTION

The District Court entered final judgments in two of the appealed cases and final judgment on the ’540 patent in the third case. This Court has jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

STATEMENT OF THE ISSUES

A. Whether the claims of the ‘540 patent recite patent-eligible subject matter under 35 U.S.C. §101 where (1) the patent does not claim a natural phenomenon, but instead claims only a limited method that makes use of and applies the natural phenomenon, and (2) the claimed method does not preempt all uses of the natural phenomenon.

B. Whether the District Court committed reversible error when, in considering the issue of preemption, it refused to consider alternative methods of using the natural phenomenon unless such methods were both (1) first disclosed before the challenged patent was filed and (2) proven to be “commercially viable.”

C. Whether the District Court committed reversible error when it separated each step of the patented method and determined if each individual step, standing alone, was “inventive” for purposes of Section 101.

STATEMENT OF THE CASES AND FACTS

A. The Inventors Made The Pioneering Invention To Detect Paternally-Inherited Cell-Free Fetal DNA In Maternal Blood Products That Had Previously Been Discarded As Waste.

For decades before 1996, medical professionals and scientists had analyzed fetal DNA for prenatal diagnosis by relying only on invasive methods, such as amniocentesis and chorionic villus sampling ("CVS"), which "presented risks to the fetus and the mother." *See Aria*, 726 F.3d at 1299 (summarizing the factual and scientific background of the '540 patent). Researchers had also sought to isolate fetal DNA through alternative methods that focused on extracting intact fetal cells which passed into maternal blood through the amniotic sac during pregnancy. *Id*. In this work, researchers routinely discarded the cell-free fractions of maternal blood, including the plasma and serum. *Id*.

In an original stroke of genius, in 1996, Dr. Dennis Lo and Dr. James Wainscoat discovered cell-free fetal DNA ("cffDNA") in maternal plasma and serum — that portion of maternal blood samples that other researchers had previously discarded as medical waste. *Id*.; Joint Appendix ("A") 0183, ¶¶ 20-21. Drs. Lo and Wainscoat described their landmark discovery of cffDNA in maternal plasma and serum in a Lancet article which has been cited over a thousand times.

Lo and Wainscoat used the knowledge gained from their discovery to invent a specific, limited method to detect and analyze fetal DNA, and, through this

method, created "a paradigm shift in non-invasive prenatal diagnosis." A0196, ¶ 52; A0188-0192, ¶¶ 33-41. Applying a combination of laboratory techniques to their discovery, Lo and Wainscoat invented a method for detecting paternally-inherited cffDNA to determine fetal characteristics, such as gender, RhD status, and chromosomal aneuploidies. *See Aria*, 726 F.3d at 1299; A0039-0040, 2:61-3:62.

The method invented by Lo and Wainscoat solved the particular problem that cell-free fetal DNA is largely indistinguishable in maternal blood from cell-free maternal DNA. A0038, 2:57-59. Their invention focused on detection of the small fraction of cffDNA in the mother's plasma or serum the fetus had inherited from the father — as little as 0.13 percent of the DNA in the sample —and then further focused on the even smaller fraction of paternally-inherited sequences that were not also possessed by the mother. *Id.*; A0352.

This pioneering invention, as commercialized by Sequenom in its MateriT21 test, has created an alternative for prenatal diagnosis of fetal DNA that avoids the risks to the fetus and the mother inherent in widely-used techniques like amniocentesis and CVS. *Aria*, 726 F.3d at 1299; A0158-0159, ¶¶ 10-11.

B. The '540 Patent Recites A Limited Method To Detect Paternally-Inherited Cell-Free Fetal DNA.

"[T]he '540 patent claims methods to detect fetal genetic characteristics by analyzing cffDNA obtained from a maternal blood sample." *Aria*, 726 F.3d at

1299. The method enables the detection of paternally-inherited sequences within cffDNA that differ from the mother's own DNA sequences. *Id.* at 1301.

The '540 patent involves a three-step combination:

(1) Fractionating maternal blood to produce plasma or serum samples; *see Aria*, 726 F.3d at 1299.

(2) Amplifying paternally-inherited fetal nucleic acid from the samples, *id.* at 1303 (discussing construction of "amplifying"); and

(3) Detecting paternally-inherited fetal nucleic acid in the samples. *Id.* at 1301-02 (discussing construction of "paternally-inherited").

See Addendum 5 (Claims 1, 21, 24, and 25). Dependent claims further limit this method to specified, bounded uses. *See, e.g.,* Claim 5 (limiting method to fetal nucleic acid sequence on Y-chromosome), Claim 8 (limiting method to fetal nucleic acid from paternally-inherited non-Y-chromosome), Claims 19 and 20 (limiting method to fractional concentrations), Claim 23 (limiting method to clotting in maternal samples).[1]

[1] *See also* claims 6 (limiting method to fetal nucleic acid sequence on the DSY14 locus of Y-chromosome), 7 (limiting method to fetal nucleic acid sequence on the SRY gene of Y-chromosome), 12 (limiting method to determining sex of the fetus), 13 (limiting method to determining concentration of the fetal nucleic acid sequence in the maternal serum or plasma), 15 (limiting method to detecting a fetal or maternal condition in which the level of fetal DNA in the serum or plasma is higher or lower than normal), and 18 (limiting method to detection of a fetal chromosomal aneuploidy). The District Court did not address these six additional

(continued...)

Before the invention of Lo and Wainscoat, no one had applied the techniques of fractionating a pregnant woman's blood to create a plasma or serum cell free sample, amplifying the DNA in that sample, and detecting the specific paternally-inherited nucleic acids present in that sample. Nor had anyone *applied these techniques in combination* to characterize fetal genomic makeup to provide a safe alternative to the conventional invasive methods for analyzing fetal DNA in pregnant women. A0142, 1:11-2:5; A0183, ¶¶ 20-21; A0191-0192, ¶¶ 38-41, A0197-0201, ¶¶ 57-72.

C. The '540 Patent's Method Transforms Naturally-Occurring cffDNA To Detect Fetal Characteristics From Paternally-Inherited cffDNA.

The patented three-step method transforms cffDNA from its naturally-occurring state.

The patent's "fractionating" step involves separating plasma and serum from whole blood collected from a pregnant woman. The laboratory technician centrifuges tubes of whole blood with an anticoagulant, separating out the liquid plasma portion. A0039-0040, 2:19-21, 26-27; 4:26-27, 38-51. Serum is the product left after the technician then removes the clotting factors from the plasma. A0194, ¶ 44. This plasma and serum are what was previously discarded as ***waste***

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dependent claims. The parties stipulated that, if the District Court's summary judgment ruling is not reversed, these claims also fall under the District Court's reasoning. Addendum 3, 4.

by researchers looking for fetal DNA in intact fetal cells. *Aria*, 726 F.3d at 1299. As the patent recites, the laboratory technician pipettes the supernatant plasma and serum into fresh tubes separate from the blood-cell-containing "buffy coat," and then subjects the plasma and serum samples to a "second centrifugation." A0040, 4:37-51.

In the "amplifying" step of the patent, DNA is extracted from the fractionated serum or plasma samples, and is amplified by PCR or another method. "PCR is a biochemical technique that enables measurement of relatively small quantities of nucleic acids by iteratively and exponentially 'amplifying' a sample to detectable levels." *Board of Trustees of the Leland Stanford Junior University v. Roche Molecular Systems*, 583 F.3d 832, 837 (Fed. Cir. 2009) (reversing invalidity finding on method using PCR to detect quantity of HIV cells in blood).

As used in the invention, amplification by PCR requires heating DNA isolated from the serum or plasma sample to high temperatures to "denature" the originally double-stranded DNA into two single-stranded DNA pieces by melting the hydrogen bonds between complementary nucleotides. After cooling, the laboratory technician adds nucleotide bases, and synthetic primers that anneal to the 3' ends of the two single-stranded fragments, introduces Taq polymerase enzymes, and induces numerous TaqMan amplification reactions. A0042, 7:4-30; A0192, ¶ 42; *see generally Hoffman-La Roche, Inc. v. Promega Corp.*, 323 F.3d

1354, 1358 (Fed. Cir. 2003) (describing PCR process). The primers anneal to portions of the separated single-stranded fragments, which serve as templates for synthesizing new DNA strands. DNA polymerase enzymes extend the primers to fill in the intermediating sequence in the template strands, synthesizing two identical double-stranded DNA fragments from the separated single strands of the original helix. A0192, ¶ 42; *Promega,* 323 F.3d at 1358.

This process of strand separation, primer annealment, and extension is repeated over numerous cycles, producing exponential amounts of double-stranded DNA segments. A thermocycler alters the reaction temperature frequently to promote DNA denaturing and synthesis. A0042, 7:26-30; *see also* Sequenom's Request for Judicial Notice ("RJN") at 12-13, and accompanying Declaration of Michael J. Malecek ("Malecek Dec."), ¶ 7 & Exh. F. Amplification of cffDNA as achieved by PCR does not occur in nature — cffDNA exists outside of the cell, by definition, and thus, does not naturally replicate, requiring the synthetic creation of new DNA copies using building blocks provided by laboratory scientists. *See* RJN at 9-10, Malecek Dec., ¶ 5 & Exh. D (DNA synthesis/replication occurs only during the S phase of the cell cycle, within the nucleus of a cell).

Naturally-occurring cffDNA is transformed by PCR amplification. First, PCR products are *physically different* from naturally-occurring cell-free fetal DNA. The synthetic primers used in PCR attach to complementary target

sequences and, when two primers are used in a head-to-head orientation, the target sequences and the DNA sequences between those targets are amplified. If "universal" or "linker-primed" PCR is used, this produces a longer segment than the natural cffDNA, but of a fixed length with a specific sequence. *See* RJN at 12-14, Malecek Dec., ¶ 7 & Exh. F. Other PCR processes generally produce shorter products than the naturally-occurring cffDNA template. *Id.*; A0192-0193, ¶ 42.

Second, PCR products are *chemically different* from naturally-occurring cffDNA. In vertebrate DNAs, a large fraction of CpG sites are methylated; fetal DNA is highly methylated. *See* RJN at 9-11, Malecek Dec., ¶¶ 5-6 & Exhs. D, E. Methylation occurs when enzymes within the cell take a methyl group and transfer the group to the 5 position of the base cytosine (C) when it is followed in the DNA sequence by the base guanine (G) ("a CpG site"). *See* RJN at 11, Malecek Dec., ¶ 5 & Exh. D. Compared to naturally-occurring cffDNA, copies of fetal DNA created in a laboratory through amplification lack methyl groups chemically bound to the CpG sites, differentiating them chemically. *See* RJN at 12, 14, Malecek Dec., ¶ 8 & Exh. G.

The "detecting" step of the claimed method requires additional laboratory manipulation. The lab technician adds the amplified DNA to an agarose gel containing ethidium bromide to stain and visualize the DNA. A0041, 5:23-24. Alternatively, DNA polymerase cleaves inserted probes (i.e., short

oligonucleotides) with fluorescent reporter dyes attached while synthesizing the complementary nucleotides strand. As the patent recites, a "real time sequence detector is able to measure the fluorescence intensity of the liberated reporter molecules cycle after cycle. . . . An amplification reaction in which the fluorescence intensity rises above the threshold during the course of thermal cycling is defined as a positive reaction." A0041, 6:36-59; A0043, 10:12-21.

D. The '540 Patent's Method Is Only One Among Several Alternative Methods Using cffDNA.

The claimed methods recited in the '540 patent are not the only methods for detecting fetal DNA (including cffDNA). Several alternative practical methods have been used to make prenatal diagnoses from cffDNA without duplicating the '540 patent's method. These alternatives do not include at least one of the '540 patent's essential limiting steps. Thus, there are peer-reviewed, scientifically validated methods that do not require fractionation, or do not require amplification, or do not detect paternally-inherited cffDNA. The existence of these alternative methods demonstrates that the '540 patent does not preempt all uses of cffDNA. The District Court, however, refused to consider these alternatives in finding, incorrectly, that the '540 patent preempts all uses of a natural phenomenon. Opinion at 19.

1. Methods Without Fractionation.

Researchers, such as Ariosa's expert Dr. Farideh Bischoff, champion a method that detects cffDNA from whole maternal blood without removing the cellular component — that is, without fractionating the maternal plasma or serum as the '540 patent requires. A0338-0340; A0229-0230, ¶ 27. Dr. Bischoff's team "devised a reliable method of fetal DNA detection using dried maternal blood specimens." A0338.

Dr. Bischoff's results from "whole blood samples" showed "Y-chromosome specific sequences were detected in all 19 (100%) pregnancies confirmed to have a male fetus." A0339. This "simple method . . . enabl[es] cell-free fetal DNA to be incorporated into non-invasive screening regimes." A0340.

2. Methods Without Amplification.

Other researchers detect aneuploidies in cffDNA using methods not involving amplification, much less amplification of paternally-inherited cffDNA as the '540 patent requires. A0342-0349. The van den Oever team accurately detected eleven trisomy-21 cases. A0345-0346. "[I]n this study, we have demonstrated successful fetal T21 detection using free DNA from maternal plasma by single molecule sequencing on the Helicos platform." A0348. Single molecule sequencing involves no DNA amplification. *Id*.

3. Methods Without Paternally-Inherited cffDNA.

Yet another method locates fetal markers in cffDNA without distinguishing between paternally-inherited and maternally-inherited DNA. A0359-0365. Poon and his colleagues detected cffDNA in maternal plasma from methylated alleles without identifying paternally-inherited cffDNA. A0360. They found that "it is possible to detect a maternally inherited fetal allele from maternal plasma." A0364. In contrast, the '540 patent's method is expressly limited to detecting paternally-inherited nucleic acids in plasma or serum.

E. The District Court Invalidated The '540 Patent For Claiming Patent-Ineligible Subject Matter Under Section 101.

In December 2011, Ariosa Diagnostics, Inc. filed a declaratory judgment action alleging it does not infringe the '540 patent, of which Sequenom is the exclusive licensee. A0058, docket no. 1. Sequenom counterclaimed for infringement. A0061, docket no. 33. In early 2012, Natera, Inc. and Verinata Health, Inc., two other competitors of Sequenom, each brought similar actions, and Sequenom counterclaimed. A0093, docket no. 1; A0096, docket no. 40; A0115, docket no. 1; A0116, docket no. 15. The District Court related the three actions for pretrial purposes. A0062, docket no. 41.[2]

[2] Verinata's action also alleges that Sequenom infringed certain of Verinata's patents. Those patents are not at issue in these appeals.

In July 2012, the District Court denied Sequenom's preliminary injunction motion, finding, in part, a substantial question whether the '540 patent's claims are eligible under Section 101. *See Aria*, 726 F.3d at 1304. This Court reversed:

> Because the district court did not have the benefit of [*Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013)] and also in light of this court's disagreement with the district court's claim construction, this court remands for the district court to examine subject matter eligibility in the first instance.

Id. at 1304.

After remand and claim construction, Ariosa sought summary judgment as to subject matter eligibility, and Sequenom cross-moved. On October 30, 2013, the District Court entered summary judgment for Ariosa. *See* Addendum 1 (reported at __ F. Supp.2d __, 2013 WL 586022 (N.D. Cal. 2013)).

In its Opinion, the District Court determined that the presence of cffDNA in the blood of a pregnant woman is a natural phenomenon. Opinion at 12. The District Court acknowledged that "the '540 patent does not claim as an invention the discovery of cffDNA in maternal plasma or serum." *Id*. Rather, "[t]he '540 patent claims methods of detecting paternally inherited cffDNA in maternal plasma or serum." *Id*.

The District Court divided the claims into individual steps and considered each technique in each step separately, as opposed to examining the claimed method as a whole. *Id*. at 13. The District Court did not determine whether the

combination of steps constituting the entire claimed process had been used previously, but instead found that, when the patent was filed, each step's laboratory technique, considered separately, was "well-understood, routine, and conventional activity." *Id.* at 13-15. Based on this conclusion, the District Court held that "the method steps contained in claims 1, 2, 4, 5, 8, 19-22, 24, and 25 of the '540 patent do not add enough to the natural phenomenon of paternally inherited DNA to make these claims patentable under §101." *Id*. at 13.

The District Court rejected Sequenom's argument that its method is a patent-eligible use or application of cffDNA. *Id.* at 15. The District Court concluded:

> It is only an innovative or inventive use of a natural phenomenon that is afforded patent protection . . . But, based on the undisputed facts before the Court, the only inventive part of the patent is that the conventional techniques of DNA detection known at the time of the invention are applied to paternally inherited cffDNA as opposed to other types of DNA. Thus, the only inventive concept contained in the patent is the discovery of cffDNA, which is not patentable.

Id. The District Court further found that, "looking at the claimed processes as a whole, the only inventive component of the processes in the '540 patent is to apply those well-understood, routine processes to paternally inherited cffDNA, a natural phenomenon." *Id*. at 18.

Finally, the District Court stated that "a court should consider whether the claim poses a risk of preempting a law of nature, natural phenomenon, or abstract idea." *Id*. It refused, however, to give any significance to Sequenom's evidence of

three alternative peer-reviewed, non-infringing methods of using cffDNA in maternal blood. *Id*. at 19. The District Court held that evidence of alternatives showing non-preemption is relevant *only* when the alternative methods were both (i) publicly disclosed before the challenged patent was filed and (ii) shown to be "commercially viable." *Id.*

The District Court found that "the articles cited by Sequenom were published after the issuance of the patent and well after the date of the invention." *Id*. The District Court also determined that no alternative method was commercially viable because "twelve years have passed since the issuance of the patent but Sequenom does not present the Court with any evidence of a commercially viable alternative method of detecting cffDNA." *Id*. Relying on these conclusions, the District Court rejected Sequenom's evidence of alternative non-preemptive methods, and concluded that, on the evidence it had considered, "it appears that the effect of issuing the '540 patent was to wholly preempt all known methods of detecting cffDNA at that time." *Id.*

The parties stipulated to final judgments on the '540 patent issues in all three cases based on the District Court's summary judgment opinion. *See* Addendum at 2-4. This Court consolidated the three appeals.

SUMMARY OF ARGUMENTS

The District Court misapplied Supreme Court and Federal Circuit law. This Court should reverse.

The '540 patent does not claim a natural phenomenon or a naturally occurring process. Nor does it preempt the use of fetal DNA, and specifically cffDNA. Rather, it claims a specific, non-preemptive, and limited diagnostic method using fetal DNA found in cell-free form in the serum or plasma in maternal blood. This method transforms naturally-occurring cffDNA by a three-step process of fractionation, amplification, and detection of paternally-inherited sequences.

Whether a patent applying a natural phenomenon preempts all other uses of the phenomenon is a primary principle motivating the judicial exceptions to Section 101. In considering the issue of preemption, the District Court erred by discounting entirely Sequenom's evidence of other, scientifically-validated alternative methods using cffDNA.

The undisputed evidence before the District Court is that there are several practical, peer-reviewed, non-infringing alternative methods to detect and use cffDNA which were invented since the '540 patent issued. Patent law encourages this innovation through burgeoning future uses of a natural phenomenon. Section 101's preemption doctrine allows and protects all of these applications, including

the first-disclosed application which, as evidenced by the existence of later alternative methods, could not have been preemptive. Had the District Court properly considered this evidence rather than imposing a new two-part standard of its own to dismiss the evidence, it could not have invalidated the patent under Section 101.

The District Court adopted an unprecedented and improper standard to determine the relevance of alternative methods offered to prove the claimed method does not preempt all uses of a natural phenomenon. It held that an alternative method would be relevant to show lack of preemption only if it *both* (i) was disclosed publicly before the '540 patent issued, *and* (ii) was shown by Sequenom to be commercially viable. Neither Supreme Court nor Federal Circuit authority supports the standard adopted by the District Court.

The requirement that alternative methods have been "previously disclosed" defies logic, especially for ground-breaking inventions. Inventors like Lo and Wainscoat would be unable to patent their method for using their discovery until others had already come up with and publicly disclosed their own alternative methods. Inventors would hold back on developing or applying to patent new methods, defeating the incentive to innovate and disclose that underlies all patent law.

The requirement that alternative methods be shown by the patent owner to be "commercially viable" has never been approved by any other court. It would irrationally exclude alternative methods that are patent eligible under Section 101, which requires only that such methods be useful, not commercially viable. The District Court's analysis also frustrates innovation by invalidating those patents that teach the best, and thus likely the most commercially successful, methods of applying natural phenomena.

The method of the '540 patent involves a three-step process of fractionation, amplification, and detection of paternally-inherited sequences. Other methods which omit the fractionation or amplification steps, or which detect nucleotides without regard to their maternal or paternal source, fall outside the '540 patent. The undisputed evidence is that there are several practical, peer-reviewed, non-infringing alternative methods to detect and use cffDNA. Had the District Court considered this evidence, the District Court could not have invalidated the patent under Section 101.

This Court should conclude that the claims of the '540 patent are non-preemptive and are drawn to patent-eligible subject matter. For this reason alone, this Court should reverse the District Court's judgments.

The District Court also misapprehended the Supreme Court's direction that Section 101 requires an "inventive concept." Contrary to the District Court's view,

the "inventive concept" requirement does not require that the individual elements of a claim, considered separately and apart from the natural phenomenon, must be novel or non-conventional to be patent-eligible under Section 101. Instead, Supreme Court precedent requires only that the combination of elements must, in practice, amount to more than a claim to the natural phenomenon itself.

The '540 patent meets this requirement. According to the invention, the maternal plasma or serum must be fractionated from the whole blood, the paternally-inherited cffDNA must be amplified, and thus transformed, by laboratory techniques to produce detectable quantities, and a means of detecting the nucleic acids—such as with fluorescent labels or other dyes—must be introduced to enable detection. The claims of the '540 patent are meaningfully limited, and thus contain the requisite inventive concept.

Further, the District Court disregarded the undisputed fact that no one had ever before combined fractionation, amplification, and detection protocols into a method of identifying paternally-inherited cffDNA in maternal serum or plasma for use in diagnosing fetal characteristics. Instead of considering the combined patented method as a whole in accordance with Supreme Court precedent, the District Court improperly dissected the claim elements and considered each step independently. The inventors of the '540 patent applied their discovery of cffDNA

in maternal plasma and serum to a new and useful end. Their claimed method is patent-eligible.

Finally, the District Court's decision misapplies *Association for Molecular Pathology v. Myriad Genetics*, 133 S. Ct. 2107 (2013). Previously, this Court directed the District Court to re-consider patent eligibility "in light of" *Myriad*. *Myriad* provided three points of certainty about what the Supreme Court accepts as patent-eligible.

First, a patent on a natural phenomenon or law of nature itself, such as the nucleotide sequence of the BRCA genes, fails Section 101. The '540 patent does not claim cffDNA in maternal blood.

Second, a patent that transforms a naturally-occurring phenomenon into matter not found in nature, such as cDNA, satisfies Section 101, even for composition claims available for any use whatsoever. Because laboratory-amplified nucleic acids differ chemically and physically from naturally-occurring cffDNA in maternal blood, the '540 patent falls outside the Section 101 exception. Moreover, unlike the *Myriad* composition patents, the '540 patent is limited to bounded method claims.

Third, a method combining known laboratory techniques into a new and useful method of using a discovery is also patent-eligible, as exemplified by the Supreme Court's view on Myriad's Claim 21. Like Claim 21, the '540 patent's

claims combine known laboratory techniques in a method and apply that method to a new discovery for a "new and useful end."

For any or all of these reasons, this Court should reverse and remand.

ARGUMENT

I. THIS COURT REVIEWS THE DISTRICT COURT'S DECISION DE NOVO, CONSTRUES SECTION 101 EXPANSIVELY, AND APPLIES JUDICIAL EXCEPTIONS NARROWLY.

A. This Court Reviews The Section 101 Issue De Novo.

This Court reviews a grant of summary judgment under the regional circuit's law. *See Accenture Global Services v. Guidewire Software, Inc.*, 728 F.3d 1336, 1340 (Fed. Cir. 2013). The Ninth Circuit reviews summary judgments *de novo*. *See Heinemann v. Satterberg*, 731 F.3d 914, 916 (9th Cir. 2013). This Court applies its "own law, however, with respect to issues of substantive patent law." *CLS Bank Int'l v. Alice Corp. Pty. Ltd.*, 717 F.3d 1269, 1276 (Fed. Cir. 2013) (en banc), *cert. granted*, 82 U.S.L.W. 3346 (U.S. Dec. 6, 2013) (No. 13-298).

"Patent eligibility under § 101 presents an issue of law that we review *de novo*." *Id. See Ultramercial, Inc. v. Hulu, LLC*, 722 F.3d 1335, 1338 (Fed. Cir. 2013) ("This court also reviews the ultimate determination regarding patent-eligible subject matter under 35 U.S.C. § 101 without deference."), *cert. filed*, 82 U.S.L.W. 3107 (U.S. Aug. 23, 2013) (No. 13-255).

B. Section 101 Must Be Construed Expansively And Its Exceptions Must Be Applied Narrowly.

"In cases of statutory construction, we begin with the language of the statute." *Diamond v. Diehr*, 450 U.S. 175, 182 (1981). "The statute controls the inquiry into patentable subject matter." *Ultramercial*, 722 F.3d at 1340. Section 101 of the Patent Act provides:

> 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, subject to the conditions and requirements of this title.

35 U.S.C. § 101.

The wide sweep of what is patent-eligible reflects Congressional intent. "In choosing such expansive terms . . . modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope." *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010). "As the Supreme Court has explained, Congress intended that the statutory categories would be broad and inclusive to best serve the patent system's constitutional objective of encouraging innovation." *CLS*, 717 F.3d at 1276. *See also id*. ("[T]he categories of patent-eligible subject matter recited in § 101 are broad . . . ."); *Ultramercial*, 722 F.3d at 1341 ("At a time when Congress considered § 101, it broadened the statute and certainly did not place any specific limits on it.").

The judicially-created exceptions to Section 101 — barring patents claiming natural phenomena, laws of nature, and abstract ideas — must be applied "narrowly." *Bilski*,130 S. Ct. at 3229. *See also CLS*, 717 F.3d at 1277 ("[D]anger also lies in applying the judicial exceptions too aggressively because 'all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.'" (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293 (2012)). As this Court has explained:

> To sum up, because eligibility requires assessing judicially recognized exceptions against a broad and deliberately expanded statutory grant, one of the principles that must guide our inquiry is these exceptions should apply narrowly. Indeed, the Supreme Court has cautioned that, to avoid improper restraints on statutory language, acknowledged exceptions thereto must be rare.

Ultramercial, 722 F.3d at 1342.

Section 101 provides a "threshold test" of eligibility, *Bilski*, 130 S. Ct. at 3225, not a test of substantive validity. *See CLS*, 717 F.3d at 1276 ("Congress's broad approach to subject-matter eligibility ensures that the patent office doors remain open to most inventions"). Thus, "to override the broad statutory categories of eligible subject matter," the "disqualifying characteristic" of an exception to Section 101 must exhibit itself "manifestly." *Research Corp. Techs., Inc. v. Microsoft Corp.*, 627 F.3d 859, 868 (Fed. Cir. 2010). "Taken too far, the exceptions could swallow patent law entirely." *CLS*, 717 F.3d at 1277.

C. Only Clear And Convincing Evidence Can Rebut The '540 Patent's Presumption Of Eligibility Under Section 101.

The general presumption of patent validity applies fully to challenges under Section 101. *See CLS*, 717 F.3d at 1284 ("it bears remembering that all issued patent claims receive a statutory presumption of validity," and "that presumption applies when § 101 is raised as a basis for invalidity in district court proceedings"). The '540 patent is presumed to satisfy the eligibility requirements of Section 101.

Because of this presumption of validity, "any attack on an issued patent based on a challenge to the eligibility of the subject matter must be proven by clear and convincing evidence." *Ultramercial*, 722 F.3d at 1342. As Chief Judge Rader stated in his *CLS* opinion:

> Because we believe the presumption of validity applies to all challenges to patentability, including those under Section 101 and the exceptions thereto, we find that any attack on an issued patent based on a challenge to the eligibility of the subject matter must be proven by clear and convincing evidence. . . . We believe, moreover, that application of this presumption and its attendant evidentiary burden is consistent with the Supreme Court's admonition to cabin the judicially created exceptions to Section 101 . . . .

717 F.3d at 1304-05.

Clear and convincing evidence is evidence producing "an abiding conviction that the truths of [] factual contentions are 'highly probable.'" *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984).

II. THE '540 PATENT DOES NOT CLAIM A NATURAL PHENOMENOM AND DOES NOT FALL WITHIN THE JUDICIALLY-CREATED NATURAL PHENOMENON EXCEPTION TO PATENT-ELIGIBILITY.

A. Controlling Precedent Establishes That A Method Applying A Natural Phenomenon Is Patent-Eligible Under Section 101.

Before the District Court, Ariosa did not attack the '540 patent for failing to satisfy the literal statutory requirements of Section 101. Ariosa's challenge, and the District Court's ruling, relied solely on the judicially-created "natural phenomenon exception" to Section 101 eligibility. Opinion at 5, 12.

As explained below, the '540 patent does not fall within the natural phenomenon exception. The '540 patent does not claim ownership of fetal DNA, the multiple forms of fetal DNA in maternal blood, cell-free fetal DNA in maternal blood, nor paternally-inherited DNA. Rather, it claims a specific, limited diagnostic method. This method does not claim ownership of a natural phenomenon, whether analyzed for "preemption," as discussed in Section B below, or "inventive concept," as discussed in Section C below

On the issue of preemption, Sequenom presented undisputed evidence describing three alternative practical, peer-reviewed, and non-preemptive ways of using cffDNA. The District Court's invalidation of the '540 patent based on this record was reversible error, resulting from its adoption of unprecedented and

improper requirements of commercial viability and predating the patent for considering proof of alternative, non-preemptive methods.

On the issue of inventive concept, Sequenom showed that the claimed method contains meaningful limitations. Further, to the extent more is required, the method reflects a significant human contribution in that Lo and Wainscoat combined and utilized man-made tools of biotechnology in a new way that revolutionized prenatal care. One simple measure of Lo and Wainscoat's contribution is that their 1997 Lancet publication has been cited over a thousand times. Future advancements in biotechnology are at significant risk if such an invention is found ineligible for patenting.

B. The Processes Claimed In The '540 Patent Do Not Preempt A Natural Phenomenon And Are Eligible Under Section 101.

1. Preemption Is A Primary Motivating Concern For Section 101 Eligibility Analysis.

The judicially-created exceptions to Section 101 rest on a core principle: patents cannot permissibly preclude all future uses of natural phenomena, natural laws, or abstract ideas. *See CLS*, 717 F.3d at 1277 ("The underlying concern is that patents covering such elemental concepts would reach too far and claim too much, on balance obstructing rather than catalyzing innovation."); *id*. at 1280 ("Preemption features prominently in the Supreme Court's recent § 101 decisions . . . .").

Therefore Congress cannot grant a legal monopoly over the exploitation of a natural phenomenon, law of nature, or abstract idea, all of which are "the handiwork of nature" and belong to everyone. *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 131 (1948). "Guarding against the wholesale preemption of fundamental principles should be our primary aim in applying the common law exceptions to § 101." *CLS*, 717 F.3d at 1281.

In *CLS*, this Court reviewed Supreme Court authority on Section 101 and concluded that the claims' preemptive effect on a fundamental concept is the primary determinant of Section 101 eligibility: "[T]he Supreme Court's foundational § 101 jurisprudence . . . turns primarily on the practical likelihood of a claim preempting a fundamental concept." 717 F.3d at 1277.

The *CLS* plurality opinion was categorical that preemption is the predominant Section 101 concern:

> First and foremost is an abiding concern that patents should not be allowed to preempt the fundamental tools of discovery. . . . Guarding against the wholesale preemption of fundamental principles should be our primary aim in applying the common law exceptions to § 101. . . . What matters is whether a claim threatens to subsume the full scope of a fundamental concept . . . .

Id. at 1280-81. Chief Judge Rader's concurring and dissenting opinion also reiterated that a patent-eligibility problem arises only "when a claim preempts all practical uses." *Id*. at 1300. *See also Accenture*, 728 F.3d at 1344 ("Having identified the abstract idea of the claim, we proceed with a preemption analysis to

determine whether . . . in practical terms, it does not so cover the full abstract idea itself.").

The District Court failed to respect the primacy and predominance of preemption in Section 101 analysis, concluding that preemption is only "a consideration when performing § 101 analysis." Opinion at 18 n.9. The District Court erred as a matter of law.

For over 150 years, the Supreme Court has reaffirmed that preemption principles lie at the heart of Section 101 law. *See Mayo,* 132 S. Ct. at 1301 ("The Court has repeatedly emphasized . . . a concern that patent law not inhibit further discovery by tying up the future use of laws of nature."). "What matters is whether a claim threatens to subsume the full scope of a fundamental concept, and when those concerns arise, we must look for meaningful limitations that prevent the claim as a whole from covering the concept's every practical application." *CLS*, 717 F.3d at 1281.

In *Ultramercial*, this Court described *O'Reilly v. Morse*, 56 U.S. 62 (1854), as "[a]n old example [but which] may be the most informative" on this point. 722 F.3d at 1344. *Morse* is the classic preemption case. *See Mayo*, 132 S. Ct. at 1301. Samuel Morse's first seven claims reciting methods applying his discovery of the telegraph were patent-eligible. However, Morse's eighth claim for "the use of the motive power of the electric or galvanic current" to communicate "intelligible

characters" "at any distances" was barred as patent-ineligible. *Morse*, 56 U.S. at 112-16. *See also Parker v. Flook*, 437 U.S. 584, 592 (1978) (*Morse* was a "landmark decision").

In contrast, in *The Telephone Cases*, 126 U.S. 1 (1888), the Supreme Court held that, because Alexander Graham Bell had claimed only methods "for transmitting vocal or other sounds telegraphically," his claims were all patent-eligible. *Id*. at 534-39. As the Supreme Court later explained, "Bell's claim, in other words, was not one for all telephone use of electricity." *Gottschalk v. Benson*, 409 U.S. 63, 69 (1972). "The concern underscoring *Morse*, which has become clearer through the Supreme Court's more recent precedents, is to deny patentability to an idea itself, rather than an application of that idea." *Ultramercial*, 722 F.3d at 1345.

The Supreme Court has variously stated the distinction it drew in the *Morse* and *Telephone* cases, but the essence is that a patent recites ineligible subject matter only when it claims for itself, or preempts all other uses of, an abstract idea, law of nature, or natural phenomenon. *See Bilski*, 130 S. Ct. at 3231 ("Allowing [the claims] would pre-empt use of this approach in all fields, and would effectively grant a monopoly over an abstract idea."); *Benson*, 409 U.S. at 71-72 ("The mathematical formula involved here has no substantial practical application except in connection with a digital computer, which means that if the judgment

below is affirmed, the patent would wholly pre-empt the mathematical formula and in practical effect would be a patent on the algorithm itself.").

Conversely, the concern about preemption of a natural law is not present when, as here, a patent *applies* a natural phenomenon in a limited, non-preemptive manner so that *other uses* may be made of it. *See Bilski,* 130 S. Ct. at 3230 ("[W]hile an abstract idea, law of nature, or mathematical formula could not be patented, an *application* of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection."); *Diehr,* 450 U.S. at 187 ("It is now commonplace that an application of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection."); *Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1293 (Fed. Cir. 2010) (Dyk, J., concurring and dissenting) (unlike isolated DNA sequence, "applications associated with the isolated nucleotide sequence . . . [may be] patentable subject matter").

As this Court recently explained, "It is not the breadth or narrowness of the abstract idea that is relevant, but whether the claim covers every practical application of that abstract idea." *Ultramercial,* 722 F.3d at 1346. If a patent implicates an identified abstract idea, law of nature, or natural phenomenon,

> [t]he §101 inquiry next proceeds to the requisite preemption analysis. With the pertinent abstract idea identified, the balance of the claim can be evaluated to determine whether it contains additional substantive limitations that narrow, confine, or otherwise tie down the

> claim so that, in practical terms, it does not cover the full abstract idea itself.

CLS, 717 F.3d at 1282. *See Accenture*, 728 F.3d at 1344-45 (stating same two-part preemption test).

Thus, a method applying or using a natural phenomenon in a manner that does not preclude alternative methods in the same field is non-preemptive, and, by definition, patent-eligible under Section 101. The '540 patent claims just such a method. The District Court's downgrading of preemption to merely "a consideration when performing a § 101 analysis" led it into reversible error.

The District Court also mistakenly characterized *Flook* and *Bilski* as cases invalidating a *non*-preemptive patent, and used this mischaracterization to devalue preemption as a Section 101 analytical tool. Opinion at 18 n.9. The District Court misread both cases.

In *Flook*, the patentee disclaimed use of his formula in some petrochemical-related functions, and argued his claim was therefore non-preemptive. *See* 437 U.S. at 589-90. The Supreme Court held that Flook's non-preemption argument "exalts form over substance." *Id*. at 590. A claim to the formula and nothing else, whether or not functionally self-limiting, is preemptive and fails Section 101. *See Accenture*, 728 F.3d at 1345 ("Accenture's attempts to limit the abstract concept to a computer implementation and to a specific industry thus do not provide

additional substantive limitations to avoid preempting the abstract idea of system claim 1.").

The District Court similarly mischaracterized *Bilski* as a non-preemption case. Opinion at 18 n.9. In *Bilski*, the patent claimed processes for hedging price risks in energy commodities markets. *See* 130 S. Ct. at 3223-34. The Supreme Court rejected the claims on preemption grounds: "Allowing petitioners to patent [the claims] would pre-empt use of this approach in all fields, and would effectively grant a monopoly over an abstract idea." *Bilski*, 130 S. Ct. at 3231.

The '540 patent does not claim exclusive use of cffDNA in maternal blood and the patent does not artificially self-limit their use, as the *Flook* and *Bilski* patentees sought to do with respect to the abstract idea or natural phenomenon at issue in those cases. Rather, the '540 patent claims one method of using cffDNA which is distinct from the several alternative methods available and which does not claim preemptive ownership over a natural phenomenon in any function or field.

2. The '540 Patent Does Not Claim A Natural Phenomenon And Does Not Preempt All Uses Of cffDNA.

The '540 patent neither claims a natural phenomenon nor claims a method that preempts a natural phenomenon. Instead, the '540 patent claims a method combining well-known laboratory techniques used for the first time to detect fetal characteristics from paternally-inherited fetal DNA from a particular sample type — cffDNA in maternal plasma or serum. The claimed method is but one among

several methods using and applying cffDNA from maternal blood. The District Court's decision that the '540 patent effectively claims all uses and applications of cffDNA in maternal blood, *see* Opinion at 19, misapplies the law and is contrary to the evidence.

In contrast to the method of the '540 patent, the alternative methods applying cffDNA either make use of whole blood rather than the fractionated plasma or serum, or do not amplify cffDNA, or search for fetal characteristics regardless of whether they are maternal or paternal in origin. *See* pages 9–11 *supra*. These differences set the '540 patent apart from, for example, the claims the Supreme Court invalidated in *Funk*, on which the District Court relied. Opinion at 6-7.

In *Funk*, the claim was for "a mixed culture of Rhizobia capable of inoculating the seeds of plants belonging to several cross-inoculation groups." 333 U.S. at 130. No specific combination of seeds was specified; the patent claimed *any* combination that worked. *Id*. The claim was to "no more than the discovery of some of the handiwork of nature and hence is not patentable." *Id*. at 131. As *Funk* explained, an invention can "come from the application of the law of nature to a new and useful end." *Id*. at 130. *See also Benson*, 409 U.S. at 67 ("If there is to be invention from such a discovery, it must come from the *application* of the

law of nature to a new and useful end.") (emphasis added). The '540 patent applies cffDNA to a new and useful end.

The '540 patent is analogous to the patent the Supreme Court validated in *Diehr*. The District Court inappropriately gave short shrift to *Diehr*. Opinion at 15-16.

Diehr recited a multi-step method for a molding process delivering rubber cured to the correct temperature and consistency. 450 U.S. at 177. The method determined the right time to open the mold by calculating the internal temperature through regular application of a mathematical formula, "the Arrhenius equation," an abstract idea. *Id.* at 177-79 & nn.2-5. Just as *Diehr* did not claim the Arrhenius equation but only one process applying the formula, *see id.* at 187, the '540 patent does not claim all uses of cffDNA in maternal blood but only one of several possible methods applying cffDNA. Combining steps in a new and useful method that is only one of several possible methods applying a fundamental concept, as in the '540 patent and the patent in *Diehr*, distinguishes those patents from the patent in *Flook*, on which the District Court substantially, and mistakenly, relied. Opinion at 8-9, 15-16, 18 n.9.

In *Flook*, the claim was for a formula to update alarm limits, an abstract idea, and nothing more. *See* 437 U.S. at 587-90. "The patent claims cover *any use* of respondent's formula for updating the value of an alarm limit on *any process*

variable involved in a process comprising the catalytic chemical conversion of hydrocarbons." 437 U.S. at 586 (emphasis added). *See Diehr*, 450 U.S. at 187 ("All that [the patent in *Flook*] provides is a formula for computing an updated alarm limit."); *Mayo*, 132 S. Ct. at 1299 ("And so the other steps [in the *Flook* patent] did not limit the claim to a particular application."). On the other hand, as with the '540 patent, *Diehr*'s claims were qualitatively different:

> In contrast [to *Flook*], the respondents here do not seek to patent a mathematical formula. Instead, they seek patent protection for a process for curing synthetic rubber. Their process admittedly employs a well-known mathematical equation, but they do not seek to pre-empt the use of that equation. Rather, they seek only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process. . . . Arrhenius' equation is not patentable in isolation, but when a process for curing rubber is devised which incorporates in it a more efficient solution of the equation, that process is at the very least not barred at the threshold by § 101.

Diehr, 450 U.S. at 187-88.

Here, like *Diehr* and unlike *Flook*, the '540 patent "does not seek to pre-empt the use" of cffDNA in maternal blood. *Id*. at 187. Indeed, there are at least three scientifically-proven, non-infringing alternative methods that use cffDNA. "Because the applicant claimed a specific application, rather than an abstract idea in isolation, the claims satisfied § 101." *CLS*, 717 F.3d at 1279.

The District Court also misread the Supreme Court's decision in *Mayo*. Opinion at 12-13, 16. The District Court glossed over the primacy *Mayo* gave to preemption analysis.

The methods claimed in *Mayo* optimized administration of thiopurine based on a natural correlation between a dose's therapeutic efficacy and the concentration of thiopurine metabolites in the patient's blood. *See Mayo*, 132 S. Ct. at 1294-95. The Supreme Court held the patent was no more than a claim over the relationship between the dose level and metabolite concentration, a law of nature. *Id*. at 1298. The claimed "invention" did not change the process: a doctor administering thiopurine would have acted in exactly the same manner whether or not the patent was in effect, but, after the patent, the doctor's application of this prior art would have been an infringement. *Id*. The Supreme Court invalidated the *Mayo* patent to prevent it from preempting all uses of the natural correlation. *Id*.

As this Court explained, "the [Supreme] Court [in *Mayo*] held that those steps [in the patent's claimed method] failed to render the claims patent eligible because, as a practical matter, they were necessary to every practical use of what it found to be a natural law and therefore were not truly limiting." *CLS*, 717 F.3d at 1283. There could be no alternative non-preemptive method using the natural law in *Mayo*. This contrasts sharply with the '540 patent, whose claim limitations are "truly limiting" — as demonstrated by the several scientifically-validated, non-infringing alternatives using cffDNA.

In sum, the Supreme Court's and this Court's precedents follow a consistent theme: where claims recite a natural phenomenon and no more, or when they recite

a method in terms so general that it covers all ways to use the natural phenomenon, then the claims are not patent-eligible. Where, as here, the patent claims a specific limited method and there are alternative methods available, then there is no preemption and no Section 101 eligibility concern. The District Court failed to follow this controlling Section 101 law.

3. The District Court Wrongly Discounted Entirely Sequenom's Evidence Of Three Non-Preemptive Alternative Methods Using cffDNA.

Sequenom presented the District Court with evidence of three peer-approved, practical, alternative methods using cffDNA in maternal blood, none of which infringes the '540 patent. *See* 9-11 *supra*. The authenticity and veracity of Sequenom's evidence was undisputed.

These three peer-reviewed articles demonstrate that each of the three primary limitations of the '540 patent are truly "meaningful limitations." According to this evidence, as an alternative to the '540 patent's method, cffDNA can be used (i) without fractionation, or (ii) without amplification, or (iii) without distinguishing paternally-inherited DNA. *See* 9-11 *supra*. No other court resolving a Section 101 dispute — whether finding invalidity or patent-eligibility — has ever been presented with such concrete, real-world evidence of multiple alternative ways to use the same natural phenomenon or natural law but without practicing the allegedly "monopolizing" method. Sequenom's evidence

demonstrates the patent's non-preemptive effect and the District Court's refusal even to consider this evidence, Opinion at 18-20, was reversible error.

As this Court has stated:

> [T]he analysis under §101, while ultimately a legal determination, is rife with underlying factual issues. . . . *Likewise, any inquiry into the scope of preemption — how much of the field is 'tied up' by the claim — by definition will involve historic facts: identifying the 'field,' the available alternatives, and preemptive impact of the claims in that field.*

Ultramercial, 722 F.3d at 1339 (emphasis added).

The District Court disregarded Sequenom's evidence of alternative methods. *See* Opinion at 18-20. The District Court ruled that evidence of an alternative method would be relevant *only* if Sequenom demonstrated that the alternative method (i) already had been disclosed when the '540 patent was filed *and* (ii) is commercially viable. *Id*. at 19. The District Court cited no legal authority for its ruling, which contradicts Section 101 jurisprudence and public policy. This ruling was clear error.

In holding evidence proving *non*-preemptive uses to be irrelevant, the District Court overrode this Court's mandate that, to invalidate a patent under Section 101, there must be a "practical likelihood of a claim preempting a fundamental concept." *CLS*, 717 F.3d at 1277. Sequenom's evidence of peer-reviewed alternative uses of cffDNA rebuts any suggestion of a "practical likelihood" that the '540 patent's method monopolizes the use of fetal DNA and in

particular cffDNA. *See Ultramercial*, 722 F.3d at 1353 (claims are patent-eligible because "[t]here are myriad ways to accomplish that abstract concept that do not infringe these claims.").

Had the District Court considered Sequenom's evidence of alternative methods — as it should have done — it could not have held that there was clear and convincing proof that the '540 patent is manifestly ineligible as "preemptive."[3]

4. There Is No Rule Or Logic That Only "Previously Disclosed" Alternative Methods Are Relevant For Preemption Analysis.

The District Court noted that, as evidence of alternative methods, Sequenom presented three peer-reviewed articles published after the '540 patent was filed. Opinion at 19. From this, the District Court erroneously concluded:

> Therefore, even assuming that the articles disclose alternative methods of detecting cffDNA, Sequenom has failed to show that any alternative methods existed *at the time of the invention or at the time*

[3] Having ruled that Sequenom's evidence of alternative methods was irrelevant under its new requirements, the District Court then reached its preemption conclusion by relying on two tiny snippets extracted from statements non-legal Sequenom staff made to investors about its ability to block its competitors' products. Opinion at 19. The District Court deemed these two comments prove that "Sequenom has itself acknowledged the preemptive effect of its patent." *Id*. That was an unreasonable inference. The District Court did not allow for the comments' context, nor their intended audience, nor the speakers' non-legal training, nor that the competitors the speakers were referring to were Ariosa, Natera, and Verinata, who all copied the specific method of the '540 patent. At a minimum, these two snippets are less than clear and convincing evidence of preemption, especially when proper weight is given to Sequenom's countervailing evidence of alternative methods using cffDNA.

> *of issuance of the patent.* Thus, it appears that the effect of issuing the '540 patent was to wholly preempt all known methods of detecting cffDNA at that time.

Id. (emphasis added). The District Court's "previously disclosed" requirement defies precedent and offends public policy.

No precedent requires that non-preemptive methods must exist at the time of invention or patent issuance. To the contrary, the law is explicit that the concern is with patents that "tie up" the use of a natural phenomenon and "inhibit *future* innovation premised on them." *Myriad*, 133 S. Ct. at 2116 (emphasis added). *See also Mayo*, 132 S. Ct. at 1302 ("basic underlying concern [is] that these patents tie up too much *future use* of laws of nature"), 1302 (claims "covering all processes that make use of the correlations after measuring metabolites, including *later discovered* processes that measure metabolite levels in *new ways*"); *Morse*, 56 U.S. at 113 (concern is that a "*future* inventor, in the onward march of science, *may* discover" alternative means of using the natural law); *Benson*, 409 U.S. at 68 ("claim is so abstract and sweeping as to cover both known and *unknown* uses" of abstract idea) (emphases added throughout).

The '540 patent's claims do not tie up all uses of cffDNA nor foreclose future innovation, as demonstrated by the specific limitations of the patented method and Sequenom's evidence of three alternative methods. That these alternatives were first publicly disclosed after the '540 patent's filing date does not

diminish their relevance. The District Court's reliance on this fact contravenes the numerous explicit Supreme Court directives set forth above.

The District Court's "previously disclosed" requirement offends the public policy of encouraging inventors to apply for claims expeditiously. *See Transco Prods. Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 558 (Fed. Cir. 1994) (rejecting "rule [which] would subvert the patent system's goal of promoting the useful arts through encouraging early disclosure"). Such a requirement also offends the public policy of encouraging others to develop alternative methods following disclosure of the patented method. *See WMS Gaming Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1355 (Fed. Cir. 1999).

As the Supreme Court observed in *Myriad*, it is expected that the original discoverers of a natural phenomenon or law of nature will invent the first (and perhaps best) method of applying their discovery. *See* 133 S. Ct. at 2120. However, the District Court's rule would require inventors, such as Lo and Wainscoat — who discovered cffDNA in 1996 and claimed a method applying it a few months later — to wait, perhaps indefinitely, to patent their method until other inventors have disclosed alternative methods using the discovery.

Further, the District Court's "previously disclosed" requirement turns the presumption of validity on its head. Under the District Court's rule, the first-to-invent is branded as a "preempter" whose method is doomed to be patent-

ineligible. Because Lo and Wainscoat came up with the first-filed method applying their ground-breaking discovery of cffDNA before any alternatives had been published, under the District Court's reasoning, their patent necessarily preempts all other methods that could apply their discovery. Someone has to file first, and the first inventors should not be required to hold back disclosure of their method until others disclose alternative methods. The net effect of the waiting game the District Court's rule creates would be to stymie the disclosure and exploitation of inventions — the reverse of the incentives the patent laws are intended to foster. *See CLS*, 717 F.3d at 1281-82 ("What is needed is a flexible, pragmatic approach that can adapt and account for unanticipated technological advances while remaining true to the core principles underlying the fundamental exceptions to § 101.").

Preemption analysis is directed to whether a patent's claims are so broad and abstract that they preclude all other methods until the patent expires. New methods using a natural phenomenon are not all invented or revealed at the same time. Years after a discovery is first made, advances in technology or a new insight can spark the invention of an alternative method using the phenomenon in another or better way. Moreover, limitations, like those in the claims of the '540 patent, increase the likelihood that others have developed, or will develop, alternative methods.

When a patent is challenged as preemptive under Section 101, evidence of alternative methods — including methods disclosed after the patent was filed — *is* relevant to determining whether the patent is truly preemptive when challenged. Evidence of new, later-in-time alternative methods provides proof that the patent does not preempt all uses of the natural phenomenon.

5. The District Court's "Commercially Viable" Requirement Lacks Legal Basis And Contradicts Public Policy.

The District Court also mandated that, to be relevant on the issue of preemption, alternative methods must be shown to be "commercially viable." Opinion at 19. The "commercially viable" requirement would impose a higher standard on alternative, non-preemptive methods than now exists for *patented* methods. Neither law nor logic can justify this mismatch.

To be eligible for patenting generally, a claimed invention need only be useful and "provid[e] some identifiable benefit." *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). There is no requirement that an invention be "commercially viable" to be patentable. *See CFMT, Inc. v. YieldUp Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003) ("Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect."); *Barmag Barmer Machinenfabrik AG v. Murata Machinery, Ltd.*, 731 F.2d 831, 839 (Fed. Circ. 1984) ("[C]ommercial marketability is not a requirement

of reduction to practice."). There is no logic in enforcing a standard for alternative methods offered to prove non-preemption that is more rigorous than the general law for patenting all other methods in all other contexts.

It is also irrational to base patent eligibility on whether the alternative method can maintain commercial traction. Under the District Court's reasoning, the Supreme Court should have invalidated Bell's telephone patents and Morse's telegraph claims because no commercially viable alternatives existed when their patents were filed or issued. No preemption-illuminating link is revealed by considering only those alternative methods which have fortuitously attracted the financial backing and managerial acumen necessary to sustain a commercially viable product.

Further, the District Court's standard has no factual mooring. The District Court gave no hint of what "commercial viability" means — does a failing, under-financed, or poorly-managed start-up count?; how profitable must a commercially viable competitor be?; how much of an otherwise successful diversified competitor's profits must come from the alternative method? The District Court's rule is as unworkable as it is misconceived.

The District Court's "commercially viable" standard would likely invalidate a first-filed patent teaching the *best* method of using a newly-discovered phenomenon. The market will winnow out inferior alternatives, eventually leaving

the market niche to the best application of the natural phenomenon. Yet, in these circumstances, rather than reward the inventor of the best method with a patent, the District Court's standard bars, or strips away, that patent as contrary to Section 101 because others are not commercially competitive.

This Court should reject the District Court's unprecedented and misconceived standard for determining what evidence is relevant for preemption analysis. The Court should reverse the District Court's rejection of Sequenom's compelling evidence of alternative methods. This Court's *de novo* review should give full weight to this evidence.

The undisputed evidence of at least these three alternative methods using cffDNA shows that the '540 patent does *not* preempt *all* uses of cffDNA in maternal blood. Each of the limitations in claims 1, 24, and 25 (and of the dependent claims) recites a combination of three essential steps using cffDNA, leaving the door open to other alternative methods applying the phenomenon. Those limitations are "meaningful." *Mayo*, 132 S. Ct. at 1302; *CLS*, 717 F.3d at 1281. This Court should conclude that there is no clear and convincing evidence that the '540 patent's method manifestly preempts all uses of cffDNA in maternal plasma or serum. Indeed, the relevant evidence is to the contrary. The Court should reverse for this reason alone.

C. The District Court Misconstrued The Meaning Of "Inventive Concept."

The District Court also committed error in holding that the '540 patent claimed patent-ineligible subject matter under Section 101 because the claims lacked an "inventive concept." Opinion at 14-15. The District Court reached this conclusion by misconstruing what the Supreme Court meant by an "inventive concept" inquiry in Section 101 eligibility analysis. Opinion at 15-17.

The District Court found no inventive concept because it decided that each element of the '540 patent's method, when separately considered, consisted only of "well-understood, routine and conventional activity by those in the field at the time of the invention." Opinion at 14. The Supreme Court has never equated "inventive concept" with the novelty or inventiveness of individual elements of a claimed method, but has instead explained the term as addressing whether the claims are sufficiently and meaningfully limited that the invention is not a claim on the natural phenomenon itself. *See Mayo*, 132 S. Ct. at 1294-97. The limitations recited in the '540 patent's method and the existence of several alternative methods using cffDNA demonstrate an inventive concept that crosses the Section 101 threshold.

Contrary to the District Court, "inventive concept" is a misnomer: under any reading of the Supreme Court's precedents, it does not require that the method, or any part of the method, be novel or inventive. *See Diehr*, 450 U.S. at 190 ("The

question therefore of whether a particular invention is novel is wholly apart from whether the invention falls into a category of statutory subject matter."). "We do not read the [Supreme] Court's occasional use of [inventive concept] in the § 101 context as imposing a requirement that such limitations must necessarily exhibit 'inventiveness'. . . ." *CLS*, 717 F.3d at 1282.

According to the *CLS* plurality opinion, "[a]n inventive concept in the § 101 context refers to a genuine human contribution to the claimed subject matter. . . . [A]n 'inventive concept' under § 101 — in contrast to whatever fundamental concept is also represented in the claim — must be a product of human ingenuity." *Id*. at 1283. The four-judge opinion by Judge Rader in *CLS* disagreed, finding no "ingenuity" requirement in Section 101. *Id*. at 1303 n.5. The '540 patent embodies an inventive concept whichever of these two views prevails because its method reflects a genuine human contribution that goes beyond the discovery of cffDNA by applying the discovery in a limited, useful, non-preemptive, and ingenious method of prenatal diagnosis.

In *Flook*, the Supreme Court "asked whether, to confer patent eligibility, the claim contained sufficient substance beyond the mathematical formula itself — that is, 'some other inventive concept in its application.'" *CLS*, 717 F.3d at 1278. (quoting *Flook*, 437 U.S. at 594). In *Mayo*, the Supreme Court cited to *Flook* and again referred to the need for an "inventive concept." *See* 132 S. Ct. at 1294.

In *Mayo*, the Supreme Court explained that "inventive concept" describes "other elements or a combination of elements" rendering the patent "significantly more than a patent upon the" prohibited subject matter alone. *Id*. at 1294. On this point, *Mayo* again relied on *Diehr*. The Supreme Court in *Diehr* had "found the overall process patent eligible because of the way the additional steps of the process integrated the equation into the process as a whole. . . . These other steps apparently added something to the formula that in terms of patent law's objectives had significance — they transformed the process into an inventive application of the formula." *Mayo*, 132 S. Ct. at 1298-99. In *Mayo*, as in *Flook*, the Supreme Court never suggested that the "other elements" must be novel or non-conventional or inventive. Rather, the method must not so closely embody the law of nature that the "inventive concept" recited in the patent was, in effect, the law of nature itself. *Id*. at 1294, 1297. If, as with the '540 patent, the method's limitations also reflect human ingenuity, *CLS*, 717 F.3d at 1283, Section 101 is amply satisfied.

Mayo "identified a two-step process." *Accenture*, 728 F.3d at 1341. Neither step focuses on whether the method's elemental techniques are novel or non-conventional. Instead, having first identified a patent-ineligible natural phenomenon, "the court must determine whether the claim poses 'any risk of preempting an abstract idea.'" *Id*. (quoting *CLS*, 717 F.3d at 1282 citing *Mayo*, 132 S. Ct. at 1302-03). The claim's limitations are "evaluated to determine

whether . . . [they] tie down the claim so that, in practical terms, it does not cover the full abstract idea itself." *Accenture*, 728 F.3d at 1341. *This* is the "inventive concept" determination, and, contrary to the District Court, it does not involve consideration of the novelty or conventionality of the method's elemental steps and techniques. In *Mayo*, the patent lacked any limitation over the relationship between the dose level and metabolite concentration. 132 S. Ct. at 1298. No doctor could administer thiopurine without using the relationship the patent claimed. *Id*. In *Mayo*, the patent consisted of the algorithm and nothing more, and thus lacked an inventive concept because it claimed a law of nature without meaningful limitations. *Id*.

Further, the District Court mistook *Mayo* and its reference to an "inventive concept" as requiring a bifurcating analysis: put the patent-ineligible matter to one side, and then scrutinize what remains for whether it "involves more than 'well-understood, routine, conventional activity' previously engaged in by those in the field." Opinion at 13-15. Once again, the District Court's analytical approach was off-base.

In *Diehr*, the examiner had rejected the patent because, in language reminiscent of the District Court here, the method's steps were "conventional and necessary to the process." 450 U.S. at 180-81. The Supreme Court disagreed. *Id*. at 193 n.15. "Those steps [in Diehr's patent] included steps that sound utterly old

and routine . . . . Indeed, even the Arrhenius equation was well-known in the art, but in combination was eligible." *CLS*, 717 F.3d at 1310. *Mayo* endorsed *Diehr*: "a new combination of steps in a process may be patentable even though all the constituents of the combination were well-known and in common use before the combination was made." *Mayo*, 132 S. Ct. at 1298 (quoting *Diehr*, 450 U.S. at 188). So too the '540 patent may rely on "steps that sound utterly old and routine" but in combination are patent-eligible.

The "conventional activity" in *Mayo* was the very method that Prometheus was trying to claim — administering the drug, measuring metabolite levels, and adjusting dosing based on the metabolite levels. 132 S. Ct. at 1297-98. Doctors were already doing just that before the patent, and could only continue this treatment by infringing the patent. *Id*. In contrast, before the '540 patent, *no one* was using the plasma or serum of pregnant mothers to amplify and detect paternally-inherited cffDNA. Indeed, what was "previously engaged in by those in the field" before the '540 patent was to throw away the maternal plasma and serum. *See Aria*, 726 F.3d at 1299. Unlike in *Mayo*, the '540 patent was a new combination and method.[4]

[4] As a Congressional Committee recently stated:

> But most fundamentally, were the Committee to take seriously the suggestion that an invention is unpatentable if it adds "nothing of

(continued...)

The District Court declared that "[i]t is only an innovative or inventive use of a natural phenomenon that is afforded patent protection." Opinion at 15. As the Supreme Court and this Court have made clear, that is not so. *See Ultramercial*, 722 F.3d at 1348 ("The Supreme Court's reference to 'inventiveness' in *Mayo* can be read as shorthand for its inquiry into whether implementing the abstract idea in the context of the claimed invention inherently requires the recited steps.").

As shown above, using cffDNA does not inherently require, unlike the specific method in the '540 patent, the limited (and ingeniously combined) human interventions of fractionation, amplification, and detection of paternally-inherited DNA from cffDNA in maternal blood. The availability of several alternative peer-reviewed methods using cffDNA proves that each of these steps is a meaningful limitation of the '540 patent. Under *Mayo*, these limitations establish an inventive concept for Section 101 purposes. This Court should reverse for this reason also.

> significance" to the natural laws that control its operation, it must also conclude that the Patent Office should be deauthorized, for nothing would remain patentable other than whatever business methods survive [Supreme Court review].

HOUSE REPORT OF THE COMMITTEE ON THE JUDICIARY ON H.R. 3309 (THE INNOVATION ACT), H.R. REP. NO. 113-279, at 39 n.87 (2013).

D. The District Court Erred By Dissecting The Combined Method Of The '540 Patent Into Its Individual Elemental Techniques.

The District Court compounded its erroneous interpretation of the "inventive concept" requirement by conflating the distinct requirements of patent-eligibility and novelty into a myopic analysis of whether each individual step in the '540 patent's three-step method was "well-understood," "conventional," and "routine." Opinion at 13-15. The District Court's dissection of the elemental techniques that make up the method, rather than considering the combination of techniques as a whole as the Supreme Court has mandated, was a further reversible error.

It is irrelevant whether fractionation, amplification, and detection of nucleic acid, individually and in the abstract, were well-understood or routine laboratory techniques when the '540 patent was filed. What *is* probative of patent-eligibility, and what the District Court erroneously denied, was the patent's *combination* of these steps for the first time in a groundbreaking method for the purpose of detecting paternally-inherited cffDNA in maternal plasma or serum and diagnosing fetal characteristics. This new combination for this new purpose was neither conventional nor routine, and it satisfies the requirements of Section 101. *See CLS*, 717 F.3d at 1303 ("[A] new combination of old steps is patentable.") (Rader, C.J., concurring and dissenting).

Indeed, the Patent Act defines "process" as a "method, and includes a new use of a known process." 35 U.S.C. § 100(b). The '540 patent recites method

claims applying individual processes in combination to a new use — detecting and analyzing paternally-inherited cffDNA. *See Diehr*, 450 U.S. at 193 n.15 ("Invention was recognized because [the inventors] combined ordinary elements in an extraordinary way — a novel union of old means was designed to achieve new ends.").

The District Court reviewed each step of the '540 patent's method in isolation to determine whether, individually, it was a broadly accepted laboratory technique when the '540 patent was filed. *See* Opinion at 13-15. Because the District Court found that the laboratory techniques, individually, were not newly conceived as part of the invention, the District Court condemned the entire patent. *Id*. at 15. The District Court's methodology contravened a key tenet of Section 101 law — it improperly dissected the method into its constituent parts, overriding the Supreme Court's direction that the method be considered only as a whole.

In *Diehr*, the Supreme Court held that conventional steps, when combined for a new purpose, can constitute a patent-eligible method. 450 U.S. at 180-81, 193 n.15. "The fact that one or more steps in respondents' process may not, in isolation, be novel or independently eligible for patent protection is irrelevant to the question of whether the claims *as a whole* recite subject matter *eligible* for patent protection under § 101." *Id*. at 193 n.15 (original emphasis).

The District Court should have looked at whether the techniques' *combination* for fractionating, amplifying, and detecting paternally-inherited cffDNA in maternal blood to diagnose fetal characteristics involved an inventive concept (as discussed above) when considered *as a whole*. As the Supreme Court held:

> It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis. This is particularly true in a process claim because a new combination of steps in a process may be patentable even though all the constituents of the combination were well known and in common use before the combination was made.

Diehr, 450 U.S. at 188. A properly focused, non-dissecting examination of the '540 patent's entire method shows it is patent-eligible.

The District Court maintained that it considered whether the combination of techniques was conventional when the patent was filed, and cited evidence it said supported this conclusion. Opinion at 18. This evidence is neither clear nor convincing. The cited evidence refers specifically to diagnosing *cancer* from DNA derived from plasma or serum, rather than using paternally-inherited cffDNA in maternal blood to detect fetal characteristics. *Id*. at 14; A0197, ¶ 58; A0199 ¶ 69. Among the many marked differences between the '540 patent and the prior art the District Court cited are those relating to who is being tested (cancer patients of all genders and ages vs. pregnant women) and to what is being detected (tumors vs. fetal characteristics). Thus, in this respect also, the District Court erred.

The '540 patent claims a specific and meaningfully limited use of paternally-inherited cffDNA in maternal plasma or serum by applying an original combination of steps. "In sum, as a practical application of the general concept . . ., the claimed invention is not 'so manifestly abstract as to override the statutory language of section 101.'" *Ultramercial*, 722 F.3d at 1354.

E. *Myriad* Supports The Eligibility Of The Invention Claimed In The '540 Patent.

When, in August 2013, this Court decided the *Aria* case, it vacated the District Court's finding of "a substantial question" as to whether the '540 patent satisfies Section 101. *See Aria*, 726 F.3d at 1304. The Court directed the District Court to re-consider its Section 101 ruling "in light of [*Myriad*]." *Id*. In *Myriad*, the Supreme Court provided an explicit analytical framework for determining whether claims involving a natural phenomenon are patent-eligible. In its subsequent summary judgment decision three months later, the District Court misapprehended and misapplied *Myriad*. This further error also requires reversal.

1. Claims To A Laboratory-Transformed Variant Of A Natural Phenomenon, Such As Amplified cffDNA, Are Patent-Eligible.

In *Myriad*, the Supreme Court considered whether the natural phenomenon exception to Section 101 applied to composition claims to isolated sequences of the BRCA-1 and BRCA-2 genes. *See* 133 S. Ct. at 2119. These composition claims were unlimited as to use. The claims "would, if valid, give [Myriad] the

exclusive right to isolate an individual's BRCA1 and BRCA2 genes . . . ." *Id*. at 2113. The Court found that "[s]eparating that gene from its surrounding genetic material is not an act of invention." *Id*. at 2117.

On the other hand, the Supreme Court held that Myriad's claim to a laboratory-based composition isolating complementary DNA "does not present the same obstacles to patentability as naturally occurring, isolated DNA segments." *Id*. at 2119 ("cDNA is not a 'product of nature'"). Creating cDNA was "an act of invention." *Id*. "[T]he lab technician unquestionably creates something new when cDNA is made." *Id*.

Thus, in *Myriad*, the Supreme Court drew the patent-ineligibility line tightly around the genes' DNA sequences themselves. Composition claims to non-naturally-occurring material created from those sequences by a conventional method, such as the routine laboratory work involved in making cDNA, were held to be patent-eligible. *Id*. The laboratory technique of amplifying cffDNA is analogous to making cDNA.

In nature, DNA is transcribed into RNA, and then into mRNA. *Id*. at 2111-12. cDNA is laboratory-made from the naturally-occurring mRNA: "cDNA is synthesized from mRNA using complementary base pairing in a manner analogous to RNA transcription." *Ass'n for Molecular Pathology v. United States Patent and Trademark Office*, 689 F.3d 1303, 1313 (Fed. Cir. 2012), *aff'd in part, rev'd in*

part, *Myriad*, 133 S. Ct. 2107. Similar to PCR amplification, the cDNA laboratory process uses an enzyme to make a strand that is a complementary copy of the mRNA, and another enzyme to make a second strand complementary to the first strand. This "results in a double-stranded DNA molecule with a sequence corresponding to the sequence of an mRNA produced by the body." *Id*.

Myriad holds that even a small step away from the natural phenomenon as the result of human intervention is sufficient for patent-eligibility. The patent-eligible cDNA molecules Myriad produced do not exist in nature, even though the sequence information in the cDNA is the same as it exists in nature. *Myriad*, 133 S. Ct. at 2111, 2116, 2119. "The nucleotide sequence of cDNA is dictated by nature, not by the lab technician." *Id*. at 2119. The only substantive difference is a single base nucleotide — a nucleotide base thymine ("T") in cDNA in place of a uracil ("U") in the original mRNA. *Id*. at 2111. Thus, *Myriad* holds that producing material that differs from that found in nature because a technician has applied a conventional laboratory technique to the naturally-occurring matter satisfies the patent-eligibility threshold of Section 101.

Unlike the unbounded composition claim in *Myriad*, a method claim includes limitations. By analogy, the limited method claims of the '540 patent create synthetic cffDNA by producing DNA strands that differ from the natural phenomenon that is, as with cDNA, a "*new application* [] of knowledge,"

"something new," and patent-eligible. *Id.* at 2119, 2120. "Transformation and reduction of an article 'to a different state or thing' is the clue to patentability of a process claim that does not include particular machines." *Benson*, 409 U.S. at 70.

Amplified cffDNA is physically and chemically distinct from naturally-occurring cffDNA. *See* pages 7-9 *supra*. In the first round of PCR, when the primers attach to the natural DNA at their complementary targets and amplify the DNA sequences between those targets, a physically longer (or shorter, if universal PCR is not used) segment is produced. Similarly, laboratory-produced amplified cffDNA has no methylated CpG sites, unlike almost all naturally-occurring cffDNA. *See id.*

When *Myriad* created cDNA, it applied a well-understood laboratory technique to the naturally-occurring BRCA gene to create patent-eligible cDNA from those sequences. *See Myriad*, 133 S. Ct. at 2112, 2119-20. Similarly, the '540 patent's method applies a combination of known laboratory techniques to naturally-occurring cffDNA to create patent-eligible amplified cffDNA sequences which then must be detected through additional laboratory manipulation.

2. Methods Applying Known Laboratory Techniques To A Newly-Discovered Natural Phenomenon, As In Myriad's Claim 21, Are Patent-Eligible.

The *Myriad* opinion provides another significant patent-eligibility guidepost. The Supreme Court indicated how it might have decided the patent-eligibility of Myriad's *method* claims had they also been challenged under Section 101:

> Similarly, this case does not involve patents on new *applications* of knowledge about the BRCA1 and BRCA2 genes. Judge Bryson aptly noted that, "[a]s the first party with knowledge of the [genes'] sequences, Myriad was in an excellent position to claim applications of that knowledge. Many of its unchallenged claims are limited to such applications."

Id. at 2120 (original emphasis) (quoting *Ass'n for Molecular Pathology*, 689 F.3d at 1349 (Bryson, J., concurring and dissenting)).

The "apt" portion of Judge Bryson's opinion referenced several "unchallenged claims." *See* 689 F.3d at 1349. Judge Bryson specifically identified claim 21 of Myriad's '441 patent as one such "unchallenged claim." *Id.* Myriad's claim 21 in its '441 patent recites a method for detecting a BRCA1 gene mutation:

> The method of claim 20 wherein a germline alteration is detected by hybridizing a BRCA1 gene probe which specifically hybridizes to an allele of one of said alterations to RNA isolated from said human sample and detecting the presence of a hybridization product, wherein the presence of said product indicates the presence of said allele in the sample.

See RJN at 3-5, Malecek Dec., ¶ 2 & Exh. A. Contrary to the District Court, Opinion at 15 n. 8, this Court has confirmed that "hybridizing" gene "probes" was a well-established technique long before Myriad's patent was filed. *See Enzo*

Biochem, Inc. v. Applera Corp., 599 F.3d 1325, 1328-29 (Fed. Cir. 2010) (discussing "hybridization" and "probe" techniques in a 1988 patent); *see also* RJN at 4-9 & Malecek Dec., ¶¶ 3-4 & Exhs. B, C (scientific treatises describing conventionality in 1989 of techniques recited in Claim 21).

Despite the Supreme Court's positive reference to Judge Bryant's "apt" statement, the District Court rejected any reference to Myriad's claim 21 because "the Supreme Court did not refer to claim 21." Opinion at 17 n.8. However, the Supreme Court went out of its way to discuss the likely Section 101 eligibility of method patents applying a natural phenomenon, quoting approvingly Judge Bryson's "apt" statement from his dissent in this Court. Because claim 21 was among the claims Judge Bryson cited in the passage the Supreme Court adopted, *see* 689 F.3d at 1349, it must have been among the potentially patent-eligible "applications" the Supreme Court had in mind. 133 S. Ct. at 2120. The District Court should not have dismissed the essential point the Supreme Court was making through Judge Bryson — that method claims like Myriad's unchallenged claim 21 are likely be patent-eligible under Section 101.

Comparing Myriad's claim 21 with claim 1 of the '540 patent is instructive. Both claims recite a combination of conventional techniques applied to a natural phenomenon. Myriad discovered that a variant of the BRCA gene is associated with breast cancer. Its claim 21 described a method for detecting that mutation

involving no more than hybridizing a probe to detect whether the variant is present. This method is text-book conventional and routine laboratory work, *see* RJN at 4-9 & Malecek Dec., ¶¶ 3-4 & Exhs. B, C, yet the Supreme Court has implied claim 21 claims patent-eligible subject matter. If, as the Supreme Court at least implied, Myriad's claim 21 is patent-eligible, then the combination of techniques described in the method recited in the '540 patent should likewise pass Section 101's threshold.

For this reason also, this Court should hold that the '540 patent is eligible under Section 101, and should reverse the District Court.

CONCLUSION

For the reasons set forth above, this Court should reverse. The Court should hold that the '540 patent describes a patent-eligible method satisfying Section 101.

Dated: January 21, 2014

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CERTIFICATE OF SERVICE

I, Michael J. Malecek, counsel for Appellant and a member of the Bar of this Court, certify that, on January 17, 2014, counsel of record for Appellees Ariosa Diagnostics, Inc., Natera, Inc., and Verinata Health, Inc. were each served a copy of the Opening Brief of Appellant Sequenom, Inc. by electronic means through CM/ECF. I further certify that all parties required to be served have been served.

Dated: January 21, 2014

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CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B). The brief contains 13,226 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6). The brief has been prepared in a proportionally spaced typeface using Microsoft Word 2007 in 14-point Times New Roman font.

Dated: January 21, 2014

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ADDENDUM

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