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ARIOSA DIAGNOSTICS V. SEQUENOM: METASTASIS OF *MAYO* AND *MYRIAD* AND THE EVISCERATION OF PATENT ELIGIBILITY FOR MOLECULAR DIAGNOSTICS

Philip Merksamer†

Before the advent of non-invasive prenatal testing, a doctor would insert a three-to-six-inch needle through the abdomen of a pregnant woman and into the amniotic sac surrounding the fetus to diagnose fetal disorders for certain high risk pregnancies.[1] This procedure, called amniocentesis, carried small but significant risks to the fetus and mother such as miscarriage, needle injury to the fetus, and transmission of an infection such as HIV or hepatitis C from an infected mother to fetus.[2] Fortunately for pregnant women living in the twenty-first century, Drs. Dennis Lo and James Wainscoat invented a non-invasive prenatal test that diagnoses fetal disorders with a simple blood draw and that carries none of the above-mentioned risks to mother and child.[3] Unfortunately for Drs. Lo and Wainscoat, the Court of Appeals for the Federal Circuit determined in *Ariosa Diagnostics v. Sequenom* that their invention is not eligible for patent protection.[4]

In *Ariosa*, the Federal Circuit applied recent Supreme Court patent eligibility decisions[5] in holding that the non-invasive prenatal test at issue is not patent-eligible subject matter under 35 U.S.C. § 101 of the U.S. Patent

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1. M. Cruz-Lemini et al., *How to Perform Amniocentesis*, 44 ULTRASOUND IN OBSTETRICS & GYNECOLOGY 727, 727–31 (2014); *see also Wallace Amniocentesis Needles*, https://www.smiths-medical.com/products/assisted-reproduction/amniocentesis-needles/wallace-amniocentesis-needles [https://perma.cc/W9E8-T75P].

2. *Amniocentesis Risks*, MAYO CLINIC (Oct. 30, 2015), http://www.mayoclinic.org/tests-procedures/amniocentesis/basics/risks/prc-20014529 [https://perma.cc/2XAQ-LWS4]; *see also* Faris Mujezinovic & Zarko Alfirevic, *Procedure-Related Complications of Amniocentesis and Chorionic Villous Sampling: A Systematic Review*, 110 OBSTETRICS & GYNECOLOGY 687, 687–94 (2007).

3. U.S. Patent No. 6,258,540 (filed Mar. 4, 1998) [hereinafter '540 Patent].

4. Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371 (Fed. Cir.), *reh'g denied*, 809 F.3d 1282 (Fed. Cir. 2015).

5. *See, e.g.*, Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289 (2012).

Act.[6] In his concurring opinion, Judge Linn lamented that he was denying patent eligibility only because he was "bound by the sweeping language of the test set out in [*Mayo*]."[7]

This Note explores and critiques how the Supreme Court in *Mayo Collaborative Services v. Prometheus Labs*[8] and *Association for Molecular Pathology v. Myriad*[9] and the Federal Circuit in *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation v. Ambry*[10] and *Ariosa* have broadened the scope of the law of nature and natural phenomena exceptions to patent-eligible subject matter to limit or foreclose patentability for molecular diagnostic innovations stemming from practical applications of new scientific discoveries. Part I explains the science underlying molecular diagnostics and nucleic acid chemistry to aid understanding of the fact patterns presented in the subsequent sections. Part II traces the origins of the law of nature and natural phenomena exceptions to patent-eligible subject matter and argues that *Mayo* and *Myriad* have not only broadened the scope of the exceptions but also crafted a framework where practical applications of new discoveries may not be patent eligible. Part III argues that the Federal Circuit has adopted an unnecessarily broad reading of *Mayo* and *Myriad*, which jeopardizes patent eligibility for molecular diagnostics. Part IV evaluates the policy merits of patent protection for molecular diagnostics and argues that diagnostic patents promote innovation. Finally, Part V concludes with suggestions to preserve patent eligibly for molecular diagnostics specifically and practical applications of scientific discoveries broadly.

I. THE SCIENCE OF MOLECULAR DIAGNOSTICS

The molecular biology underlying molecular diagnostics is relevant to the cases and issues discussed in the following Parts. Appendix I provides brief explanations of molecular biology terms used throughout this Note for quick reference.

A. MOLECULAR DIAGNOSTICS

Molecular diagnostics encompass the identification, characterization, and measurement of biological molecules—sometimes called biomarkers—

6. *Ariosa*, 788 F.3d at 1373.
7. *Id.* at 1380 (Linn, J., concurring).
8. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289 (2012).
9. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013).
10. *In re* BRCA1- & BRCA2-Based Hereditary Cancer Test Pat. Litig. v. Ambry Genetics Corp., 774 F.3d 755 (Fed. Cir. 2014).

that distinguish normal from abnormal processes and that provide indicators of disease.[11] Biomarkers may include any molecules present in the human body such as nucleic acids (e.g., DNA and RNA), proteins, and various small molecules or metabolites.[12] Molecular diagnostics may ascertain the presence of disease,[13] predict the likelihood of developing disease,[14] or predict the likelihood of therapeutic effectiveness for certain treatments.[15]

Diagnostic innovation depends broadly on two categories of advancements. One category involves the identification and characterization of the relationships between biomarkers and diseases.[16] A second category involves the improvement of analytical techniques to measure biomarkers less invasively and with greater accuracy, at greater scale, and at lower cost.[17] Inventors generally protect these types of inventions with process or method patent claims that describe measuring a biomarker and correlating it to a clinically relevant phenotype and with composition claims that describe detecting agents required to analyze biomarkers. The Supreme Court in *Mayo*[18] and *Myriad*[19] and the Federal

11. *See* N. Lynn Henry & Daniel F. Hayes, *Cancer Biomarkers*, 6 MOLECULAR ONCOLOGY 140, 140 (2012).

12. *See id.*

13. For example, assaying for the presence of antibodies against HIV provides a statistically conclusive diagnosis as to whether a patient is infected with the virus that causes AIDS. *See HIV Antibodies*, AIDS MAP, http://www.aidsmap.com/HIV-antibodies/page/1322961 [https://perma.cc/E6Z9-5UPY].

14. For example, diagnosing the presence of certain mutations in the BRCA1 and BRCA2 genes provides a certain statistical likelihood of developing breast or ovarian cancer. *See* U.S. Patent No. 5,747,282 (filed June 7, 1995) [hereinafter '282 Patent].

15. For example, the cancer therapeutic Herceptin is most effective against cancers that overexpress the HER2 gene. A diagnostic test to determine the amplification state of HER2 helps identify patients suitable for treatment with Herceptin. *See Herceptin*, http://www.herceptin.com [https://perma.cc/A8TX-LXTJ].

16. *See* MOUSUMI DEBNATH ET AL., MOLECULAR DIAGNOSTICS: PROMISES AND POSSIBILITIES 295–307 (18th ed. 2010).

17. *See, e.g.*, Linnea M Baudhuin, Leslie J. Donato & Timothy S. Uphoff, *How Novel Molecular Diagnostic Technologies and Biomarkers Are Revolutionizing Genetic Testing and Patient Care*, 12.1 EXPERT REV. MOLECULAR DIAGNOSTICS 25 (2012).

18. *See* Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289 (2012).

19. *See* Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013).

Circuit in *Ambry*[20] and *Ariosa*[21] have limited, jeopardized, or foreclosed both categories of claims.[22]

B. NUCLEIC ACID BIOLOGY

Nucleic acids, namely DNA and RNA, are important biomarkers, and nucleic-acid-based technologies are important tools for diagnosing disease.[23] DNA and RNA are biological polymers of nucleotides, and each nucleotide contains a specific nitrogen base.[24] The sequence, or linear order, of these nucleotides conveys genetic information.[25] The human genome consists of genomic DNA, which exists in chromosomes within cells.[26] Genes are segments of genomic DNA that provide instructions for making specific proteins.[27] Many human genes consist of exons and introns.[28] The exons of genes provide the actual instructions for making specific proteins.[29] When a cell endeavors to make a specific protein, the information encoded in the exons of genes is copied into mRNA.[30] mRNA contains the same protein-coding information as its corresponding gene, but its chemical composition is slightly different.[31] The protein-producing machinery of the cell 'reads' mRNA to produce a specific protein according to the instructions encoded therein.[32]

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20. *See In re* BRCA1- & BRCA2-Based Hereditary Cancer Test Pat. Litig. v. Ambry Genetics Corp., 774 F.3d 755 (Fed. Cir. 2014).

21. *See* Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371 (Fed. Cir.), *reh'g denied*, 809 F.3d 1282 (Fed. Cir. 2015).

22. *See infra* Parts II and III for further discussion.

23. *See* DEBNATH ET AL., *supra* note 16, at 6–7.

24. The nitrogen bases are adenine, guanine, cytosine, and thymine. RNA contains uracil instead of thymine. Uracil conveys the same genetic information as thymine. *See* BRUCE ALBERTS ET AL., MOLECULAR BIOLOGY OF THE CELL 192–97, 302–303 (4th ed. 2002).

25. *Id.* at 192–97.

26. *Id.* at 198.

27. *Id.* at 200.

28. *Id.* at 202.

29. *Id.* Understanding the role of introns is not important for understanding the following Parts other than the fact that genes and genomic DNA contain introns.

30. *Id.* at 302.

31. *Id.* at 302–04. The thymine base of DNA contains a methyl group that the uracil base of RNA lacks. The ribose sugar of DNA lacks a hydroxyl group that the ribose sugar of RNA contains. Neither of these differences changes the information content embodied in these molecules. To make a finer point, while thymine and uracil have different names, they contain identical genetic information for the purposes of coding protein sequences. *Id.*

32. *Id.* at 335–36.

While some patents refer to isolated DNA, the word "isolated" is somewhat of a misnomer.[33] The isolation of human DNA is not analogous to the isolation and purification of a drug from a tree growing in the Amazon.[34] Instead "isolated" human DNA refers to synthetic DNA that is often a copy of a naturally occurring nucleic acid or a segment thereof.[35] Synthetic DNA shares physical properties with its naturally occurring counterpart, but may possess novel functions or utilities.[36] To copy genomic DNA, scientists may extract it from cells, fragment it, and transfer the fragments into bacteria.[37] As the bacteria grow, they synthesize many copies of the DNA fragments. Scientists may also use polymerase chain reaction (PCR) to amplify DNA to create billions of synthetic copies.[38] PCR requires primers, which are short synthetic DNA molecules that anneal to specific regions of target DNA and initiate amplification.[39] Scientists design primers to have specific lengths and other physical characteristics such as melting temperature in accord with the needs for each PCR reaction.[40] To copy mRNA, scientists use a process called reverse transcription, which

33. *See, e.g.*, '282 Patent, *supra* note 14, at col. 2 l. 16.

34. *See* Eric Grote, Legal and Scientific Flaws in the Myriad Genetics Litigation 1, 17 (Sep. 12, 2014) (unpublished manuscript) (on file with the University of Maryland at Baltimore) (discussing the scientific inaccuracies of this hypothetical that the Supreme Court considered at oral argument in *Myriad*).

35. *See* '282 Patent, *supra* note 14, at col. 2 l. 16; *see also* Christopher Holman, *Mayo, Myriad, and The Future Of Innovation in Molecular Diagnostics and Personalized Medicine*, 15 N.C. J.L. & TECH 639, 649–50 (2014). These synthetic copies have different structural features than those found in naturally occurring DNA such as different methylation patterns. DNA methylation provides heritable information relating to gene expression and chromosome organization. *See* Grote, *supra* note 34, at 27.

36. *See* Ass'n for Molecular Pathology v. United States PTO, 653 F.3d 1329, 1365 (Fed. Cir. 2011) (Moore, J., concurring in part) ("The shorter isolated DNA sequences have a variety of applications and uses in isolation that are new and distinct as compared to the sequences as it occurs in nature.").

37. ALBERTS ET AL., *supra* note 24, at 491–513. DNA fragments are ligated into plasmids, which are DNA structures found naturally in certain bacteria. Scientists use synthetic versions of plasmids, which can be introduced into laboratory bacteria. This process facilitates copying and storing the information content found in naturally occurring DNA. *See id.*

38. *See id.* Copies of genes share the same protein-encoding information as their naturally occurring counterparts, but possess some chemical differences. Naturally occurring DNA is methylated whereas PCR-generated synthetic DNA is not. Naturally occurring human DNA and synthetic DNA are also structurally different because naturally occurring human DNA, but not synthetic DNA, exists in chromosomal structures. *See* Grote, *supra* note 34, at 18.

39. ALBERTS ET AL., *supra* note 24, at 491–513.

40. *See id.; see also* DEBNATH ET AL., *supra* note 16, at 133.

copies mRNA into cDNA.[41] Analogous to gene copies, cDNA shares the same protein-encoding information as mRNA, but possesses some chemical differences.[42] The above-mentioned techniques for copying nucleic acids are and have been conventional, routine, and well-understood activities at the time of filing for each of the patents at issue in the following Parts.[43]

II. THE SUPREME COURT HAS BROADENED THE MALLEABLE JUDICIAL EXCEPTIONS TO PATENT-ELIGIBLE SUBJECT MATTER

This Part critiques the Supreme Court's development of the "law of nature" and "natural phenomena" judicial exceptions to patent-eligible subject matter. Section II.A describes the statutory framework of patent-eligible subject matter. Section II.B traces the origins of the judicially created exceptions to the statutory framework and critiques how the Court in *Mayo* and *Myriad* has broadened the exceptions, which jeopardizes patentability for molecular diagnostic innovations specifically and practical applications of new discoveries generally.

A. THE CONSTITUTIONAL AND STATUTORY BASES FOR PATENT-ELIGIBLE SUBJECT MATTER

The United States Constitution authorizes Congress to grant inventors exclusive rights to their inventions for a limited time to encourage innovation.[44] Exclusive rights incentivize the public to invest in expensive and risky research by providing a limited period free from competition, which increases the chances of a return on investment.[45]

41. ALBERTS ET AL., *supra* note 24, at 491–513. Reverse transcription is a naturally occurring process that retroviruses such as HIV use to copy their genomes. *Id.*

42. *See id.* The chemical differences are that cDNA has thymine and deoxyribose while mRNA contains uracil and ribose.

43. *See id.*; *see also* David McDowell, *The Polymerase Chain Reaction Patents: Going, Going, . . . Still Going*, 99 J. ROYAL SOC'Y MED. 62 (2006) (discussing the invention of PCR in 1983); *see also Destroying Dogma: the Discovery of Reverse Transcriptase* ROCKEFELLER U. (Mar. 3, 2016), http://centennial.rucares.org/index.php?page=Destroying_Dogma [https://perma.cc/9E2L-BJYV] (discussing the discovery in 1970 of reverse transcriptase, the enzyme that creates cDNA from mRNA).

44. U.S. CONST. art. I, § 8, cl. 8 ("The Congress shall have power . . . [to] promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.").

45. *See* Kristina Lybecker, *Promoting Innovation: The Economics of Incentives*, IPWATCHDOG (July 21, 2014), http://www.ipwatchdog.com/2014/07/21/promoting-innovation-the-economics-of-incentives/id=50428 [https://perma.cc/25KQ-SWXU] (discussing how intellectual property provides economic incentives to promote innovation); *see also infra* Part IV (discussing how patents promote innovation in molecular diagnostics).

Congress created a statutory framework that provides a series of hurdles inventors must overcome to receive a patent.[46] The first hurdle described in § 101 of the Patent Act sets a minimum threshold for patent eligibility.[47] Any invention or discovery is eligible if it is new, useful, and drawn to one of the following four subject matter categories: process, machine, manufacture, or composition of matter.[48] Courts at one time interpreted § 101 expansively, citing the writings of Thomas Jefferson that "ingenuity should receive a liberal encouragement"[49] and congressional reports supporting Congress's intent for § 101 to "include anything under the sun that is made by man."[50] The remaining sections of the Patent Act require that inventions must be new, useful, non-obvious, and sufficiently described.[51] Together, these requirements intend to ensure that only meritorious inventions receive patent protection.[52]

B. JUDICIAL LIMITATIONS TO PATENT ELIGIBILITY

While Congress drafted the patent-eligible subject matter requirements expansively, the Supreme Court has limited patent-eligible subject matter with judicially created exceptions.[53] Since 1981, the Court has specifically held that laws of nature, natural phenomena, and abstract ideas[54] are not patentable under § 101.[55] For about thirty years since 1981, these judicial

46. *See* 35 U.S.C. §§ 101–03, 112 (2012).

47. *See* 35 U.S.C. § 101 (2012).

48. *Id.* ("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 . . . .").

49. Diamond v. Chakrabarty, 447 U.S. 303, 308 (1980) (quoting 5 WRITINGS OF THOMAS JEFFERSON 75–76 (Washington ed. 1871)).

50. *Id.* at 309 (quoting S. REP. NO. 1979, 82d Cong., 2d Sess., 5 (1952); H.R. REP. NO. 1923, 82d Cong., 2d Sess., 6 (1952)).

51. *See* §§ 101–03, 112. While an analysis of these requirements is beyond the scope of this Note, it is important to recognize that while this Note argues that the patent claims discussed in this Note should be patent-eligible under the subject-matter requirements of § 101, they may not necessarily be patentable under §§ 102, 103, 112 or the separate utility requirements of § 101.

52. *See id*; *see also* Michael Risch, *Everything is Patentable*, 75 TENN. L. REV. 591, 591–95 (2008) (proposing that the judicially created exceptions to patent eligible subject matter are not needed and rigorous application of §§ 101–03, 112 can ensure that only meritorious inventions receive patents).

53. *See* Bilski v. Kappos, 561 U.S. 593, 601–02 (2010) ("While these exceptions are not required by the statutory text, they are consistent with the notion that a patentable process must be 'new and useful.'").

54. The abstract idea exception will not be discussed further because courts do not typically use this exception to reject biotechnology patents.

55. Diamond v. Diehr, 450 U.S. 175, 185 (1981). Before 1981, the Court has used various combinations of terms to describe judicially created exceptions such as physical

exceptions did not impede the biotechnology industry but, on the contrary, coincided with an explosion of biotechnological innovation.[56] During this era, courts rarely invalidated biotechnology patents under § 101.[57] In the mid-2010s, however, after the Supreme Court's decisions in *Mayo*[58] and *Myriad*,[59] courts have invalidated, and the U.S. Patent Office has rejected, biotechnology patents under § 101 in record numbers.[60] *Mayo* and *Myriad* did not create any new judicial exceptions, yet something has clearly changed that impacts biotechnology. An exploration and critique of the origins of the law of nature and natural phenomena exceptions help to understand how the Court in *Mayo* and *Myriad* has broadened their scope to limit patent-eligible subject matter for biotechnology.

1. Origins of the Law of Nature and Natural Phenomena Exceptions

Justice Douglas first used the terms "law of nature" and "phenomena of nature" together in a Supreme Court decision in *Funk Bros. v. Kalo Inoculant Co.*, but he did not likely intend to create new categorical exceptions to patentable subject matter.[61] Instead, Justice Douglas elevated the patentability bar by invalidating a patent for a practical application of a new scientific discovery because the application of the discovery was not sufficiently inventive.[62]

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phenomena, mental processes, and abstract intellectual concepts. *See* Christopher Holman, *Patent Eligibility Post-Myriad: A Reinvigorated Judicial Wildcard of Uncertain Effect*, 82 GEO. WASH. L. REV. 1796 (2014) (analyzing the different terminology of the Court's judicial exceptions and discussing how the Court has failed to adopt clear definitions for the judicial exceptions).

56. *See History of Biotechnology*, BIOTECHNOLOGY INNOVATION ORG., http://www.bio.org/articles/history-biotechnology [https://perma.cc/VEU6-DB6Y].

57. *See* Rebecca S. Eisenberg, *Diagnostics Need Not Apply,* 21.2 B.U. J. SCI. & TECH. L. 256, 258–60 (2015) (finding that courts in this era used requirements other than subject matter eligibility, such as written description requirements, to invalidate overly broad claims on fundamental discoveries).

58. *See* Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289 (2012).

59. *See* Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013).

60. *See* Robert R. Sachs, *Update on Section 101 Rejections at the USPTO,* BILSKI BLOG (Oct. 19, 2015), http://www.bilskiblog.com/blog/2015/10/update-on-uspto-e-commerce-patent-applications.html [https://perma.cc/ZZ63-QY56]; Robert R. Sachs, *#Alicestorm For Halloween: Was It A Trick Or A Treat?*, BILSKI BLOG (Nov. 6, 2015), http://www.bilskiblog.com/blog/2015/11/alicestorm-for-halloween-its-scary-out-there-.html [https://perma.cc/GU2N-FTFR].

61. 333 U.S. 127, 130 (1948).

62. *See* Jeffrey A. Lefstin, *Inventive Application: A History,* 67 FLA. L. REV. 565, 629–30 (2015); *see also* Rebecca S. Eisenberg, *Wisdom of the Ages of Dead-Hand Control? Patentable Subject Matter for Diagnostic Methods After* In Re Bilski, 3 CASE W. RES. J.L. TECH. & INTERNET 1, 50 (2012).

Understanding Justice Douglas's opinion first requires understanding its historical context. In 1948, Congress had not yet created the non-obvious subject matter requirements present in the modern patent act.[63] In its void, Justice Douglas had previously created the "flash-of-genius" doctrine that required inventions to demonstrate a degree of ingenuity exceeding the skill of an ordinary practitioner.[64] In 1952, Congress rejected this exacting test by replacing it with a test of non-obviousness.[65] Congress further amended the definition of invention to include discoveries.[66]

In *Funk Bros.*, Bond had patented a composition of bacteria capable of inoculating a variety of plant seeds and conferring on them the ability to fix nitrogen.[67] This composition improved on the prior use of individual bacterial species to inoculate specific plant seeds.[68] Specific bacterial species were necessary because mixing bacterial species typically caused the bacteria to cross-inhibit their respective nitrogen-fixing properties.[69] Bond overcame this challenge by experimenting with different species and discovering combinations of species that did not cross-inhibit.[70]

In evaluating Bond's patent, Justice Douglas introduced the terms "laws of nature" and "phenomena of nature" as a rhetorical device to explain subject matter that has never been patentable. His often-cited passage reads:

> The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. They are manifestations of *laws of nature*, free to all men and reserved exclusively to none. He who discovers a hitherto unknown *phenomenon of nature* has no claim to a monopoly of it which the law recognizes. 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."[71]

63. Congress codified the non-obvious subject matter conditions for patentability in 35 U.S.C. § 103 in the 1952 Patent Act.

64. Cuno Engineering Corp. v. Automatic Devices Corp., 314 U.S. 84, 90–91 (1941).

65. *See* 35 U.S.C. § 103 ("Patentability shall not be negated by the manner in which the invention was made."); *see also* Graham v. John Deere Co., 383 U.S. 1, 15 (1966).

66. 35 U.S.C. § 100(a) (2012); It is possible but uncertain that Congress by enacting § 100 intended to overrule *Funk Bros. See* Lefstin, *supra* note 62, at 632–34 (discussing the legislative history of the 1952 Patent Act).

67. *See* Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948).

68. *Id.* at 129–30.

69. *Id.*

70. *See* Dennis Crouch, *Funk Brothers v. Kalo—Eligibility or Unobviousness*? PATENTLY-O (May 7, 2014), http://patentlyo.com/patent/2014/05/brothers-eligibility-unobviousness.html [https://perma.cc/5M7H-9M46].

71. *See Funk Bros.*, 333 U.S. at 130 (emphasis added).

Because "law of nature" and "phenomena of nature" were used to describe the same examples, Justice Douglas likely intended them to be synonyms.[72] While they were not explicitly defined, the examples and the cases cited suggest that Justice Douglas was not creating new exceptions. Instead, he was using new words to describe a long-established doctrine that a principle or a scientific truth, in the absence of a specific application, is not patentable.[73] Justice Douglas used this rhetorical device to demonstrate the difference between the qualities of bacteria, which have never been patentable, and Bond's act of combining bacteria that was patentable if it satisfied Justice Douglas's stringent requirements for invention.[74] To illustrate, his next often-cited passage reads:

> Discovery of the fact that certain strains of each species of these bacteria can be mixed without harmful effect to the properties of either is a discovery of their qualities of non-inhibition. It is no more than the discovery of some of the handiwork of nature and hence is not patentable. The aggregation of select strains of the several species into one product is an application of that newly-discovered natural principle. But however ingenious the discovery of that natural principle may have been, *the application of it is hardly more than an advance in the packaging of the inoculants*.[75]

Thus, Justice Douglas rejected Bond's patent, but not because it claimed ineligible subject matter. Instead, Justice Douglas separated Bond's new discovery of cross-inhibition with the application of packaging bacteria and found that packaging bacteria was not sufficiently inventive under the flash-of-genius test.[76] Mr. Bond had discovered a new property of nature and had practically applied it, but a practical application was insufficient grounds for

72. *See* Gottschalk v. Benson, 409 U.S. 63, 67 (1972). In *Gottschalk*, Justice Douglas describes the following exceptions: "Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." *Id.* The absence of "laws of nature" suggests that "phenomena of nature" can be used synonymously with "laws of nature."

73. Mackay Radio & Tel. Co. v. Radio Corp. of Am., 306 U.S. 86, 94 (1938); *see also* Rubber-Tip Pencil Co. v. Howard, 87 U.S. 498, 507 (1874) ("an idea of itself is not patentable"); Le Roy v Tatham, 55 U.S. 156, 175 (1852) ("a principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented").

74. *Funk Bros*, 333 U.S. at 131–32 ("But a product must be more than new and useful to be patented; it must also satisfy the requirements of invention or discovery." (citing Cuno Engineering Corp. v. Automatic Devices Corp., 314 U.S. 84, 90–91 (1941)).

75. *Id.* at 130–31 (emphasis added).

76. *Id.* at 131–32 (citing Cuno Engineering Corp. v. Automatic Devices Corp., 314 U.S. 84, 90–91 (1941)).

patentability for Justice Douglas.[77] If Bond had created an ingenious advance in packaging bacteria, then Justice Douglas would have likely affirmed Bond's patent. Importantly, Justice Douglas did not categorically prohibit the patentability of compositions of matter that contain bacteria.

In his prescient concurring opinion, Justice Frankfurter rejected Justice Douglas's use of the term "law of nature" to invalidate Bond's patent because Justice Frankfurter feared that future courts could use this "vague and malleable" term to deny patentability to a large swath of technology that Congress intended to be patent eligible.[78] Justice Frankfurter recognized that every invention incorporates "laws of nature" and the use of such a term does not aid a determination of patentability.[79]

Despite Justice Frankfurter's warnings, subsequent courts relied on Justice Douglas's heavily criticized opinion to determine patent-eligible subject matter requirements for biotechnology.[80] In 1980, the Court in *Diamond v. Chakrabarty* faced the issue of whether living organisms are patentable.[81] The Court held in the affirmative, and this holding expanded patentability for biotechnology.[82] However, in its analysis, the Court

77. *See* Lefstin, *supra* note 62, at 609, 629–30 (noting that this analysis was a departure from previous case decisions where practical applications of new discoveries were patentable); *see also* Eisenberg, *supra* note 62, at 51–52.

78. *Funk Bros.*, 333 U.S. at 134–35 (1948) (Frankfurter, J., concurring) ("It only confuses the issue, however, to introduce such terms as 'the work of nature' and the 'laws of nature.' For these are vague and malleable terms infected with too much ambiguity and equivocation. Everything that happens may be deemed 'the work of nature,' and any patentable composite exemplifies in its properties 'the laws of nature'. Arguments drawn from such terms for ascertaining patentability could fairly be employed to challenge almost every patent.").

79. *Id.* Justice Frankfurter invalidated Bond's patent because it failed to disclose the specific bacterial species that comprise the composition and because the patent claimed broadly the concept of mixing any species of Rhozidium. Bond's invalidated claims have analogies to Morse's invalidated claim 8 that claimed any use of electromagnetism to communicate at a distance, even uses that were not fully described in the patent's specification. *See* O'Reilly v. Morse, 56 U.S. 62, 112–13 (1853).

80. *See* Lefstin, *supra* note 62, at 625–26; *see also* John M. Golden, Flook *Says One Thing,* Diehr *Says Another: A Need for Housecleaning in the Law of Patentable Subject Matter*, 82 GEO. WASH. L. REV 1765, 1780–81 (2014) (citing several scholars that are critical of *Funk Bros.*).

81. 447 U.S. 303 (1980); *see also* Lefstein, *supra* note 62, at 625 n.425 (explaining that the *Chakrabarty* briefs argued only the issue of whether living organisms are patentable, not whether products of nature are patentable).

82. Douglas Robinson & Nina Medlock, Diamond v. Chakrabarty*: A Retrospective on 25 Years of Biotech Patents*, 17 INTELL. PROP. & TECH. L.J. 12, 13–15 (2005); *see also BIO Celebrates 30th Anniversary of* Diamond v. Chakrabarty *Decision,* BIOTECHNOLOGY INNOVATION ORG. (Jun. 16, 2010), http://www.bio.org/media/press-release/bio-celebrates-30th-anniversary-diamond-v-chakrabarty-decision [https://perma.cc/R4CY-LPXX] ("The

interpreted *Funk Bros.* as a prohibition against patenting unmodified bacteria and formally created a categorical prohibition to patenting compositions that are not "markedly different" from nature.[83] The *Chakrabarty* Court believed that while Bond's invention was simply a product of nature, Chakrabarty's invention was "markedly different" from nature and therefore a product of human ingenuity.[84] The Court's metaphysical analysis is ironic because Bond and Chakrabarty used similar microbiology principles to create their bacterial compositions.

Both Bond and Chakrabarty mixed bacteria, provided a selective condition, and selected bacteria that satisfied this condition. Chakrabarty mixed bacteria containing distinct plasmids that could metabolize distinct chemicals that comprise crude oil.[85] Bacteria naturally exchange plasmids in a process called conjugation, and mixing certain bacteria under certain well-understood conditions will naturally induce this plasmid exchange.[86] Chakrabarty then applied selection pressure to the mixture such that only bacteria that contained certain combinations of plasmids were capable of growth on the nutrients that Chakrabarty provided.[87] Thus, Chakrabarty could isolate a single bacterium that contained the desired combinations of plasmids.[88] Chakrabarty used the conventional, routine, and well-understood microbiology technique of selective pressure to create this new and useful composition of plasmids within a single bacterium.

Bond inoculated plants with different combinations of bacteria, measured the resulting amounts of fixed nitrogen, and selected the

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Supreme Court's decision in Diamond v. Chakrabarty thirty years ago today was instrumental in spurring the creation of a dynamic and flourishing biotech industry.").

83. *Compare Funk Bros.*, 333 U.S. at 130 (listing as examples *qualities* of bacteria and *qualities* of metals) *with Chakrabarty*, 447 U.S. at 303 (listing as examples the minerals and plants themselves instead of their qualities); *see* Lefstin, *supra* note 62, at 625–26. While *Ex parte Latimer*, 46 O.G., 1638 (1889), had denied a patent to a natural product, subsequent courts permitted patentability of isolated or purified natural products. *See* Merck & Co., Inc. v. Olin Mathieson Chem. Corp., 253 F.2d 156 (4th Cir. 1958); *see also* Parke-Davis & Co v. H.K. Mulford Co., 189 F. 95 (C.C.S.D.N.Y. 1911). *Diamond v. Chakrabarty*, 447 U.S. 303 (1980) created a formal natural product exception. *See* Holman, *supra* note 55, at 1821 ("*Chakrabarty*'s exhortation that naturally occurring minerals and plants are patent ineligible represents a judicial expansion of the literal language of Section 101.").

84. *See Chakrabarty*, 447 U.S. at 310.

85. U.S. Patent No. 4,259,444 col. 3 ll. 20–23 (filed June 7, 1972) [hereinafter '444 Patent].

86. *See* LUBERT STRYER, BIOCHEMISTRY, 827–28 (4th ed. 1995).

87. '444 Patent, *supra* note 85, at col. 9 ll. 1–20.

88. *Id.*

combinations that fixed the greatest amounts of nitrogen.[89] Both Bond and Chakrabarty mixed bacteria and provided a selective condition, which induced the bacteria to adapt in accord with how they adapt to new environments in nature. The primary difference between these facts (the "markedly different" element) is that Bond's invention ends with a composition of bacteria and Chakrabarty's with a composition of plasmids housed within a single bacterium. Neither composition should be considered a natural phenomenon, however, because neither composition exists without human ingenuity and human intervention.

Despite *Chakrabarty*'s expansion of the judicial exceptions to include compositions that are not "markedly different" from nature, subsequent courts and the U.S. Patent Office interpreted "markedly different" liberally, and biotechnology enjoyed a thirty-year period where subject matter eligibility was not a major impediment to patentability.[90]

2. Mayo *Expanded the "Law of Nature" Exception and Reintroduced Justice Douglas's Patentability Bar for Practical Applications of New Discoveries*

In 2012, the Supreme Court in *Mayo* addressed whether a method of optimizing the therapeutic efficiency of thiopurine drugs for the treatment of inflammatory bowel disease was patent-eligible subject matter.[91] At the time the patent was filed, doctors understood that the body produced certain toxic metabolites in response to thiopurine treatment.[92] Some doctors were thus reluctant to administer thiopurines due to complications associated with the resulting toxic metabolites.[93] In the patent at issue, the inventors discovered concentrations of metabolites in a significant number of patients that correlated with toxic side effects and therapeutic effectiveness.[94] Applying this discovery, the inventors disclosed a method to optimize thiopurine treatment by adjusting thiopurine dosage to maintain the resulting toxic metabolites within a certain concentration window.[95]

89. U.S. Patent No. 2,200,532 p. 5 ll. 9–24 (filed Aug. 24, 1938); *see also* Crouch, *supra* note 70, at 3.

90. *See* Robinson, *supra* note 82, at 13.

91. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289 (2012).

92. *See* U.S. Patent No. 6,355,623, at col. 1 ll. 61–65 (filed Apr. 8, 1999) [hereinafter '623 Patent].

93. *See id.*

94. *See id.* at col. 2 ll. 1–7.

95. *Mayo*, 132 S. Ct. at 1295–96 ("A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising: (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and (b) determining the level of 6-thioguanine in said subject having said

Thus, this patent improved an old method of treating patients with thiopurines where the improvement constituted a discovery of the relationship between metabolite concentrations and drug toxicity.[96] At issue before the Court was whether an improvement of an old method was patent eligible under § 101 where the only new and useful element of the improved method was a discovery.

The Court first determined that the relationship between concentrations of thiopurine metabolites and toxicity constituted a "law of nature."[97] The Court rested this decision on the fact that this relationship was a consequence of the body's metabolism of thiopurine drugs.[98] The Court reasoned that thiopurine metabolism was a natural process because it occurred in the human body.[99] Since the relationship was a consequence of a natural process, the Court concluded the relationship was a "law of nature."[100]

This analysis echoes Justice Frankfurter's warning that the term "law of nature" is so "vague and malleable" that a court could reduce anything and everything to a "law of nature."[101] Essentially every process ever patented builds from natural processes, and essentially all process patents that utilize or depend on a biological system could fall within the "law of nature" exception under the Court's analytical framework in *Mayo*.[102]

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immune-mediated gastrointestinal disorder, wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.").

96. *See* '623 Patent, *supra* note 92, at col. 8 ll. 40–46.

97. *Mayo*, 132 S. Ct. at 1290–91.

98. *Id.*

99. *Id.* at 1297.

100. *Id.*

101. *See* Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 135 (1948) (Frankfurter, J., concurring).

102. *Compare Mayo*, 132 S. Ct. at 1293 ("The Court has recognized, however, that too broad an interpretation of this exclusionary principle could eviscerate patent law. For all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.") *with id.* at 1302 ("The laws of nature at issue here are narrow laws that may have limited applications."); *see also* Christopher Holman, Mayo, Myriad, *And The Future of Innovation in Molecular Diagnostics and Personalized Medicine*, 15 N.C. J.L. & TECH. 639, 668 (2014) (showing the absurdity of the Court's conclusion with the following analogy: "an airplane, for example, interacts with the air in a particular manner that results in flight. The air and its properties are natural phenomena, but surely, that does not render the interaction of an airplane with the air a natural phenomenon.").

While a court could in theory classify any diagnostic process as a "law of nature," since the term is so "malleable,"[103] the relationship described in *Mayo* is not similar to the examples Justice Douglas used to describe a "law of nature" in *Funk Bros.*[104] No human intervention is required to provide the qualities of naturally occurring bacteria or metals. Likewise, the heat of the sun exists independently of human activity.[105] By contrast, the "law of nature" described in *Mayo* exists only as a result of human intervention because human activity is required to administer thiopurine drugs.[106] Furthermore, effective dosage and side-effects are human-created abstractions that do not exist in nature.[107] The specific metabolite concentrations that indicate a need to raise or lower the medication are not immutable like Newton's gravitational constant or the speed of light in a vacuum.[108] Instead, they represent a human decision based on a probabilistic analysis of clinical data.[109] While a "law of nature" should apply to all nature, the disclosed metabolite concentrations indicative of therapeutic effectiveness or side effects will not apply to all patients.[110] Therefore, these correlations cannot be considered a "law of nature."

The Court's cavalier use of the "law of nature" exception has thus broadened its scope beyond Justice Douglas's original description. Depending on how lower courts apply *Mayo*, the "law of nature" exception may encompass any relationship that arises from a natural process where a natural process is defined as any chemical transformation that occurs in the human body.[111] Because this description encompasses the entirety of

103. *See Funk Bros.*, 333 U.S. at 135.

104. *See id.* at 130 (listing as examples the qualities of bacteria and metals, the heat of the sun, and electricity).

105. *Id.*

106. *See* Eisenberg, *supra* note 57, at 266 ("These limits are not set by nature, but reflect human judgments about how to trade off the misery of immune-mediated gastrointestinal disorders against the misery of drug-side effects. This technological choice reflects human characterizations and preferences that are not inherent in nature.").

107. *See id.*

108. *See* Robert R. Sachs & Jennifer R. Bush, Prometheus *Unbound I: The Untethering of Laws of Nature and Patent Eligibility from Scientific Reality*, BILSKI BLOG (Jul. 3, 2013), http://www.bilskiblog.com/blog/2013/07/prometheus-unbound-the-untethering-of-laws-of-nature-and-patent-eligibility-from-scientific-reality.html [https://perma.cc/B7KS-REXJ]; Robert R. Sachs & Jennifer R. Bush, *Prometheus Unbound II: Does Prometheus' Claim Recite a Law of Nature?*, BILSKI BLOG (Jul. 11, 2013), http://www.bilskiblog.com/blog/2013/07/prometheus-unbound-does-prometheus-claim-recite-a-law-of-nature.html [https://perma.cc/S6EL-4AFR].

109. *See supra* note 108; *see also* '623 Patent, *supra* note 92, at col. 17 ll. 10–20.

110. *See id.*

111. *See* Eisenberg, *supra* note 57, at 266.

molecular diagnostic discoveries relating to biomarker correlations, this technological field may now fall within a judicial exception to subject matter eligibility.[112]

After determining that the patent at issue claimed a law of nature, the *Mayo* Court next examined whether the patent contained an "inventive concept," which the Court defined as an element or combination of elements "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself."[113] If so, the patent would satisfy subject-matter eligibility requirements despite claiming a law of nature.[114]

The essence of this analysis is not particularly new because courts for the past 150 years have examined whether a patent claims merely a patent-ineligible principle or a practical application, which is significantly more than a principle.[115] However, in formulating the requirements for an "inventive concept," the *Mayo* Court re-introduced Justice Douglas's exacting test that practical applications of new discoveries are not patentable unless they contain additional inventive elements. The *Mayo* Court separated the novel "law of nature" element from the patent claim and determined that the remaining elements, specifically administering thiopurine drugs and measuring the resulting metabolites, were "conventional, routine, and well-understood."[116] Since the remaining elements were conventional, the patent was not drawn to eligible subject

112. *See id.* at 268 ("This is the essential problem for diagnostic method claims under the Court's analysis: because the Court codes the heart of the diagnostic method—the determination of when it is appropriate to modify treatment for a particular patient—as belonging to the realm of natural laws, it does not recognize any *application* of those laws (whether 'inventive' or 'conventional') in the claim at all.").

113. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289, 1294 (2012); *see also* Alice Corp. Pty. Ltd., v. CLS Bank Int'l., 134 S. Ct. 2347, 2355 (2014) (citing *Mayo,* 132 S. Ct. at 1294).

114. *See supra* note 113.

115. *See* Lefstin, *supra* note 62, at 601; *see also* Le Roy v Tatham, 55 U.S. 156, 175 (1852) ("A new property discovered in matter, when practically applied, in the construction of a useful article of commerce or manufacture, is patentable . . .").

116. *See Mayo*, 132 S. Ct. at 1293. It is undisputed that administering thiopurine drugs and measuring metabolites were conventional at the time because doctors were already administering the drugs and measuring the resulting metabolites prior to this patent. The Court also expressed concern that a clever patent prosecutor could claim a law of nature as a process by appending a generic statement to apply the law. *Id.* at 1297. It is possible that the Court viewed the administering and measuring steps as generic steps.

matter.[117] This analysis echoed Justice Douglas's reasoning that, after separating away the discovery of bacterial non-inhibition, the packaging of bacteria was too conventional and not sufficiently inventive to merit patent protection.[118]

Scholars debate whether the *Mayo* Court's formulation of an "inventive concept" is consistent with nineteenth century case law.[119] Key to this debate concerns the interpretation of *Neilson v. Harford*, an English patent case from the nineteenth century that American courts have relied on for the development of American patent jurisprudence.[120] Neilson discovered that hot air improved the iron smelting process, and he applied this discovery by pre-heating air in a separate receptacle before introducing the air into the smelting furnace.[121] Professor Joshua Sarnoff contended that Neilson and subsequent nineteenth century patent cases support a patent eligibility doctrine that is consistent with *Mayo* and *Funk Bros.* in which (1) a newly discovered principle should be treated as if it were already well known, and (2) an application of the principle must exhibit sufficient creativity to be patent eligible.[122] Professor Jeffrey Lefstin argued, however, that Neilson stands for the doctrine that practical applications of new discoveries are patent eligible and that creative or unconventional application of the discovery is not necessary.[123] Through a careful examination of not only Neilson but also other nineteenth century patent cases, Lefstin demonstrated that Neilson's patent was affirmed not because Neilson's application was creative, but instead because his application was so trivial, conventional and well understood that he did not need to describe the

117. *See id.*; *see also* Kevin Collins, Prometheus *and Mental Steps*, 50 HOUS. L. REV. 391, 402 (2013) ("First, the Court identifies the laws of nature at issue and conceptually brackets them off from the remainder of the claimed subject matter.").

118. *Compare* Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 132 (1948) ("But once nature's secret of the non-inhibitive quality of certain strains of the species of Rhizobium was discovered, the state of the art made the production of a mixed inoculant a simple step.") *with Mayo*, 132 S. Ct. at 1298 ("[T]he claims inform a relevant audience about certain laws of nature; any additional steps consist of well understood, routine, conventional activity already engaged in by the scientific community . . . .").

119. *See, e.g.*, Lefstin, *supra* note 62.

120. *See, e.g.*, *Mayo*, 132 S. Ct. at 1300; *see also* O'Reilly v. Morse, 56 U.S. 62, 111–17 (1853).

121. Neilson v. Harford, 1 Web. P.C. 331 (1841).

122. Joshua D. Sarnoff, *Patent-Eligible Inventions After Bilski: History and Theory*, 63 HASTINGS L.J. 53, 67–74 (2011); *see also* Brief of Nine Law Professors as Amici Curiae in Support of Petitioners (No. 10-1150), Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289 (2012).

123. Lefstin, *supra* note 62, 569–70.

dimensions of the heating receptacle in any great detail.[124] Despite Neilson's conventional application of using a generic receptacle to heat air, his patent was sustained because his discovery of the principle that hot air is superior to cold air for smelting iron was novel.[125] Lefstin further demonstrated that throughout the nineteenth and early twentieth centuries, practical applications of new discoveries were patentable even when all the elements of the application were routine, conventional, and well understood.[126] Lefstin argued that Justice Douglas first introduced the doctrine of "inventive concept" in *Funk Bros.* in 1948 and that this doctrine radically departed from a century of English and American patent eligibility precedent.[127]

Justice Douglas's doctrine was further advanced in *Parker v. Flook*,[128] but was largely overridden in *Diamond v. Diehr*, decided in 1981, which forbade dissecting claim elements and held that "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."[129] The "inventive concept" doctrine also frustrated the plain text of § 100 of the 1952 Patent Act that explicitly defines discoveries as patent-eligible inventions and defines processes to include new uses of known processes.[130]

124. *Id.* at 586–87 (quoting *Neilson*, "The blowing apparatus was perfectly well known; the heating of air was perfectly well known; the twire was perfectly well known as applicable to blast furnaces; then what he really discovered is, that it would be better for you to apply air heated up to red heat, or nearly so, instead of cold air as you have hitherto done. That is the principle; that is the real discovery; but, in order to take out a patent, you must have an embodiment of the principle, and his embodiment of the principle is the heating of air in a separate vessel, intermediately between the blowing apparatus and the point where it enters the furnace.").

125. *Id.*

126. *See id.* at 588–623*; see also* Le Roy v Tatham, 55 U.S. 156, 175 (1852) ("A new property discovered in matter, when practically applied, in the construction of a useful article of commerce or manufacture, is patentable . . .").

127. Lefstin, *supra* note 62, at 645.

128. 437 U.S. 584 (1978).

129. Diamond v. Diehr, 450 U.S. 175, 188 (1981); *see also* Lefstin, *supra* note 62, at 571–72; Peter S. Menell, *Forty Years of Wondering in the Wilderness and No Closer to the Promised Land:* Bilski*'s Superficial Textualism and the Missed Opportunity to Return Patent Law to its Technology Mooring*, 63 STAN. L. REV. 1289, 1298 (2011).

130. *See* 35 U.S.C. § 100 (2012).

3. Myriad *Expanded the Natural Phenomena Exception for DNA-Based Technologies*

A year after *Mayo*, the Supreme Court in *Myriad* heard another case that impacted patent eligibility for molecular diagnostics.[131] The *Myriad* Court extended the principles of *Mayo* that practical applications of biological discoveries may no longer be patentable unless they contain sufficiently inventive steps in addition to the discovery.[132] Furthermore, the Court's metaphysical analysis of DNA technology broadened the scope of the natural phenomena exception,[133] which could jeopardize patent eligibility for many types of DNA-based diagnostic technology.[134]

The diagnostic company, Myriad Genetics, discovered the precise chromosomal location of the Breast Cancer 1 (BRCA1) gene, the sequence of BRCA1 mRNA, and a partial sequence of BRCA1 genomic DNA.[135] Myriad patented several methods and compositions stemming from its discovery that helped enable Myriad to develop tools for diagnosing breast and ovarian cancer.[136] At issue before the Court were composition claims of isolated DNA molecules coding for the BRCA1 protein.[137]

The Court focused primarily on two of the composition claims. Claim 1 described an isolated DNA that codes for the BRCA1 protein.[138] Claim

131. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013).

132. *Id.* at 2117 ("To be sure, it found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention.").

133. *See id*. The Court uses the term "product of nature," which is often treated synonymously as "natural phenomena" or "physical phenomena;" *see also* Diamond v. Chakrabarty, 447 U.S. 303, 308 (1980).

134. *See* Eisenberg, *supra* note 57, at 277–78 ("Of course, the more important outcome of the *Myriad* litigation for the patenting of diagnostics is not the patent-eligibility of some drug screening methods, but rather than patent-ineligibility of naturally-occurring biomarkers and methods of analyzing and comparing a patient's biomarker to a recited sequence. In broad terms, *Mayo* invalidates patents on diagnostic methods, while *Myriad* invalidates patents on diagnostic markers.").

135. *See* '282, *supra* note 14, at fig. 4, fig. 10. Myriad also discovered the chromosomal location of the BRCA2 gene. Certain mutations of the BRCA1 and BRCA2 genes are associated with breast and ovarian cancer. For further discussion of the BRCA1 discovery, see Mary-Claire King, *'The Race' to Clone BRCA1*, 343 SCIENCE 1462 (2014). For simplicity, only the BRCA1 gene and the contents of the '282 patent are discussed here because the *Myriad* Court determined the BRCA1 claims in the '282 patent were exemplary. *See Myriad*, 133 S. Ct. at 2113.

136. *See, e.g.*, '282 Patent, *supra* note 14.

137. *Myriad*, 133 S. Ct. at 2113; *see* Part I for an explanation of how DNA codes for protein.

138. '282 Patent, *supra* note 14, at col. 153 ll. 57–59.

2 described an isolated DNA of claim 1 where the DNA is defined by the BRCA1 cDNA sequence.[139]

The legal scope and meaning of claim 1 is uncertain because the district court did not hold a Markman hearing to formally construe the claim.[140] Claim construction typically occurs during a patent infringement suit, but did not formally occur here in part because this was a declaratory judgment action and not a patent infringement suit.[141] The district court presumed that claim 1 was directed to a naturally occurring DNA, which then necessarily meant that claim 1 was directed to BRCA1 genomic DNA.[142] The patent's specification, however, did not disclose the complete BRCA1 genomic DNA sequence, which should have raised doubts as to whether claim 1 should encompass naturally occurring BRCA1 genomic DNA.[143] Given the limitations of the specification, a more reasonable interpretation is that claim 1 encompasses any cDNA capable of coding for the BRCA1

139. *Id.* at col. 153 ll. 60-61. The Court also discussed Claims 5 and 6, which describe an isolated DNA having at least 15 nucleotides of the DNAs described in claims 1 and 2 respectively. These claims are arguably the broadest because they cover regions of the genome beyond what Myriad discovered. These claims also presented the greatest hurdle for competitors wishing to sequence clinically relevant segments of the BRCA1 and BRCA2 genes because the identification of cancer-causing mutations using classical Sanger sequencing requires only isolation of a region containing the mutation and not the entire protein-coding region. However, these claims could likely have been invalidated under §§ 102 and 112. DNAs of at least fifteen nucleotides of the BRCA1 DNA exist in other genes that were part of the prior art. Myriad did not disclose the complete genomic sequence of BRCA1 DNA and therefore did not have possession of every possible fifteen-nucleotide configuration of BRCA1 DNA. *See* Christopher Holman, Mayo, Myriad, *and The Future Of Innovation in Molecular Diagnostics and Personalized Medicine*, 15 N.C. J.L. & TECH 639, 659–60 (2014).

140. Claim construction is a question of law that typically requires opposing parties to submit briefs and a court to hold a hearing to ascertain the scope and meaning of the patent claims. Markman v. Westview Instruments, Inc., 517 U.S. 370 (1996). Claim construction requires a review of a patent's intrinsic evidence found in the patent's specification and prosecution history, and, when appropriate, extrinsic evidence. *See* Phillips v. AWH Corp., 415 F.3d 1303 (Fed. Cir. 2005).

141. *See* Holman, *supra* note 54, at 1811. Myriad's lawyers never appealed this construction, and so the Supreme Court construed the claims according to the district court. *See* Grote, *supra* note 34, at 23.

142. *See* Ass'n for Molecular Pathology v. United States Pat. & Trademark Office, 702 F. Supp. 2d 181, 217 (S.D.N.Y. 2010). When the Court describes "genes" it is implicitly referring to the segment of genomic DNA that defines the boundaries of the BRCA1 coding region.

143. *See* '282 Patent, *supra* note 14, at fig. 10, col. 5 l. 67–col. 6 l. 1; *see also* Ass'n for Molecular Pathology v. United States Pat. & Trademark Office, 653 F.3d 1329, 1376 (Fed Cir. 2011) (Bryson J., dissenting) (explaining that Myriad did not disclose the complete BRCA1 sequence).

protein.[144] Such an interpretation is consistent with claim 2, which depends on claim 1, and which describes one specific BRCA1 cDNA sequence.[145] Such an interpretation is also consistent with the text of claim 1 that defined an isolated DNA based on its ability to code for the BRCA1 protein.[146] Nevertheless, the Court interpreted claim 1 to include naturally occurring DNA.[147]

After determining that claim 1 described natural DNA, the Court applied a test for inventiveness similar to those Justice Douglas and the *Mayo* Court used. The Court discounted the discovery of the chromosomal location and sequence of the BRCA1 gene and determined that "isolating" BRCA1 DNA was not sufficiently inventive.[148] While not stated explicitly, this reasoning was consistent with the *Mayo* Court because at the time of Myriad's invention, once the chromosomal location and the sequence of a gene was discovered, making a synthetic copy from a gene library was conventional, routine, and well understood.[149] Furthermore, the Court focused its analysis on the genetic characteristics of the claim instead of its new uses. The Court expressed concern that Myriad did not create or alter any genetic information and that claim 1 shared the same genetic information as naturally occurring genomic DNA.[150] The Court, however, also recognized that "[a]s the first party with knowledge of the [BRCA1] sequences, Myriad was in an excellent position to claim applications of that

144. Claim 1 is necessary because many cDNAs similar to the cDNA described in claim 2 could be created to bypass claim 2. Because the genetic code is redundant, a person of ordinary skill in the art could create synonymous substitutions in the isolated DNA described in claim 2 to produce the BRCA1 protein sequence described in claim 1. For an explanation of codon degeneracy see STRYER, *supra* note 86, at 109–10.

145. This specific cDNA sequence was fully disclosed. *See* '282 Patent, *supra* note 14, at col. 67–80.

146. Isolated BRCA1 genomic DNA would not be able to drive expression of BRCA1 protein under standard laboratory conditions because the genomic DNA contains introns. *See* ALBERTS ET AL. *supra* note 24, at, at 491–513.

147. Because claim 5 depends on claim 1, the Court also determined that claim 5 encompassed any fifteen nucleotides of the BRCA1 genomic DNA. See note 139, *supra,* for an explanation why claim 5 interpreted in this manner is likely not patentable under §§ 102, 112.

148. *Myriad*, 133 S. Ct. at 2117 ("To be sure, it found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention."). While the Court used the term "isolating," Myriad did not directly isolate BRCA1 from a human, but instead made a synthetic copy from a DNA library. *See* Grote, *supra* note 34, at 17–19; *see also supra* Part I.

149. *See* Grote, *supra* note 34, at 17–19; *see also* '282 Patent, *supra* note 14, at col. 10 ll. 46-55.

150. *Myriad*, 133 S. Ct. at 2116.

knowledge."[151] An isolated DNA composition is one such useful application of the knowledge of the BRCA1 sequence because isolated DNAs can be directly sequenced using classical techniques to diagnose or prognose breast or ovarian cancer whereas naturally occurring BRCA1 genes cannot.[152]

Myriad also discovered the BRCA1 cDNA sequence and applied conventional, routine, and well-understood techniques to isolate it.[153] The Court, however, upheld patent eligibility for cDNA because the Court held that cDNA is not natural and therefore did not fall within a judicial exception.[154] cDNA, however, shares the same genetic information as naturally occurring mRNA.[155] In fact, both DNA compositions described in claim 1 and claim 2 share the same genetic information.[156] Thus, invalidating claim 1 while upholding claim 2 under the same analytical test was incongruous and created ambiguity as to what DNA technologies are patent-eligible under § 101.[157]

III. THE FEDERAL CIRCUIT HAS APPLIED AN EXPANSIVE READING OF *MAYO* AND *MYRIAD* AND ESTABLISHED A HEIGHTENTED THRESHOLD FOR PATENTING DNA-BASED DIAGNOSTIC TECHNOLOGIES

A year after *Myriad*, the Court heard another patent eligibility case.[158] During oral arguments, Justice Breyer, the author of the Court's opinion in *Mayo*, remarked that *Mayo* merely "'sketch[ed] an outer shell of the content' of the patent-eligibility test."[159] In support of the Justice's comment that

151. *Id.* at 2120 (citing Ass'n for Molecular Pathology v. United States PTO, 689 F.3d 1303, 1349 (Fed. Cir. 2012) (Bryson, J., dissenting)).

152. *See* Alberts, *supra* note 24, at 491–513 (discussing Sanger sequencing).

153. '282 Patent, *supra* note 14, at col. 11 ll. 29–51.

154. *Myriad*, 133 S. Ct. at 2119.

155. *See* Holman, *supra* note 102, at 656.

156. *See id.*

157. To be clear, cDNA contains more chemical differences than mRNA relative to the differences between isolated DNA and genomic DNA. However, these chemical differences do not alter any genetic information. Making distinctions between natural and synthetic DNAs based on the lack of a hydroxyl group or the presence of methyl group appears arbitrary and could create unsound policies regarding the patenting of DNA technologies or the patenting of other technologies related to natural products. For example, under *Myriad* a cDNA derived from a gene that contains introns would be patentable but a cDNA derived from a gene that does not contain introns would not be patentable. *See* Holman, *supra* note 102, at 657.

158. Alice Corp. Pty. Ltd. v. CLS Bank Int'l., 134 S. Ct. 2347 (holding that a business method implemented on a generic computer is not patent eligible under § 101).

159. *See* Lefstein & Menell, *Don't Throw Out Fetal Diagnostic Innovation with the Bathwater: Why* Ariosa v. Sequenom *Is an Ideal Vehicle for Constructing a Sound Patent*

Mayo did not articulate a precise or formulaic test for patent eligibility, Professors Lefstin and Peter Menell argued that *Mayo*'s requirement for an "inventive concept" does not necessarily mean a requirement for an unconventional application.[160] Non-preemptive or non-generic applications may also suffice.[161] Given the Court's prior rejection of the Federal Circuit's formalistic approaches to patent eligibility in 2010, it is possible that the Court sought to sketch a flexible patent eligibility framework for the lower courts to further develop.[162]

While the Court in *Myriad* strained the boundaries between natural and synthetic compositions, the Court provided a narrow holding that denied patent eligibility only to "genes and the information they encode."[163] Moreover, the Court emphasized that new applications of Myriad's discoveries may remain patent eligible.[164]

Thus, *Mayo* and *Myriad*, while problematic, may not necessarily foreclose patent eligibility for molecular diagnostics, depending on how the lower courts delineate the boundaries of the judicial exceptions to patent-eligible subject matter.[165] Since these decisions, the Federal Circuit has had opportunities to shape *Mayo* and *Myriad* to preserve patent-eligibility for molecular diagnostics.[166] Instead, the Federal Circuit has adopted a broad and exacting interpretation of *Mayo* and *Myriad*, which has foreclosed

Eligibility Framework, PATENTLY-O (Aug. 31, 2015) http://patentlyo.com/patent/2015/08/lefstin-sequenom-ariosa.html [https://perma.cc/7ZV4-FVVD].

160. *See* Brief of Professors Jeffrey A. Lefstin and Peter S. Menell as Amici Curiae in Support of Rehearing En Banc (Nos. 2014–1139, 2014–1144), Ariosa Diagnostics, Inc. v. Sequenom, Inc., 809 F.3d 1282 (Fed. Cir. 2015).

161. *Id.*; *see also* Jeffrey A. Lefstin, *The Three Faces of Prometheus: A Post-*Alice *Jurisprudence of Abstractions*, 16 N.C. J.L. & TECH. 647, 663–77. For a discussion of pre-emption, see Part IV, *infra*.

162. *See* Bilski v. Kappos, 561 U.S. 593, 601–02 (2010) (rejecting the Federal Circuit's formalistic machine-or-transformation test in favor of a less rigid framework where the machine-or-transformation test is merely a useful clue for assessing patent eligibility under § 101).

163. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2120 (2013).

164. *Id.*

165. This statement is practically relevant for *Myriad* because advances in DNA sequencing no longer require gene isolation as an intermediary step, which makes *Myriad's* narrow holding largely inconsequential to the biotechnology industry. *See* Grote, *supra* note 34, at 32–34.

166. *See In re* BRCA1- & BRCA2-Based Hereditary Cancer Test Pat. Litig. v. Ambry Genetics Corp., 774 F.3d 755 (Fed. Cir. 2014); Ariosa Diagnostics, Inc., v. Sequenom, Inc., 788 F.3d 1371 (Fed. Cir.), *reh'g denied*, 809 F.3d 1282 (Fed. Cir. 2015).

patent eligibility for some important diagnostic innovations.[167] In particular, two Federal Circuit decisions, *Ambry* and *Ariosa*, jeopardize patent eligibility for compositions and methods related to DNA-based diagnostic technology.

A. *AMBRY* EXPANDED THE NATURAL PHENOMENA EXCEPTION TO INCLUDE SYNTHETIC COMPOSITIONS THAT SHARE COMMON MOLECULAR SEQUENCES WITH NATURAL PRODUCTS

Following the Supreme Court's decision in *Myriad*, Ambry Genetics announced plans to sell BRCA testing services.[168] In response, Myriad sued Ambry, alleging infringement of several of Myriad's remaining valid patent claims.[169] Some of the claims at issue concerned a pair of DNA primers used for amplification of the BRCA genes, which is useful for sequencing and identifying cancer-related BRCA mutations.[170] DNA primers are synthetic and designed by scientists to amplify specific DNA sequences.[171] To amplify a discrete gene, at least a portion of the primers must contain a sequence of nucleotides in common with a sequence found in the gene of interest.[172] After the district court denied Myriad's preliminary injunction, Myriad appealed to the Federal Circuit, which affirmed the district court's denial of an injunction and invalided Myriad's primer claims under § 101.[173]

In invalidating the DNA primer claims, the Federal Circuit unnecessarily broadened the Supreme Court's narrow holding in *Myriad*

167. *See Ariosa*, 788 F.3d at 1377; *see also* Eneda Hoxha, Note, *Stemming the Tide: Stem Cell Innovation in the* Myriad-Mayo-Roslin *Era*, 30 BERKELEY TECH. L.J. 567 (2015) (discussing the challenges of patenting stem cell technologies under Federal Circuit jurisprudence).

168. *See Ambry Launches BRCA 1 & 2: Single Genes and NGS Panel Offerings*, *Ambry Genetics,* http://www.ambrygen.com/press-releases/ambry-genetics-launches-brca-1-2-single-genes-and-ngs-panel-offerings [https://perma.cc/5855-EAHW]. From this point onward, this Note uses the term "BRCA" as shorthand for both BRCA1 and BRCA2.

169. *See Ambry*, 774 F.3d at 758–59.

170. Myriad also alleged infringement of its method claims, which are not discussed in this Note. Claim 16 is a representative primer claim from the '282 patent: "A pair of single-stranded DNA primers for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction, the sequence of said primers being derived from human chromosome 17q, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA having all or part of the sequence of the BRCA1 gene." *See* '282 Patent, *supra* note 14, at col. 155 ll. 23–29. See ALBERTS ET AL., *supra* note 24, at 491–513 for a discussion of DNA sequencing.

171. *See* Part I, *infra*.

172. *See* ALBERTS ET AL., *supra* note 24, at 491–513.

173. *In re* BRCA1- & BRCA2-Based Hereditary Cancer Test Pat. Litig. v. Ambry Genetics Corp., 774 F.3d 755 (Fed. Cir. 2014). The Federal Circuit also invalidated Myriad's method claims, which are not discussed here. *Id.* at 765.

that isolated genes are not patentable. The *Ambry* court read *Myriad* to prohibit patenting any synthetically created composition of matter that is "structurally identical" to a composition found in nature.[174] The court did not define "structurally identical," but the court's holding that primers and human genomic DNA are "structurally identical" hints at an underlying definition.[175] The court likely meant "structurally identical" to mean "having identical primary structures" or "having identical sequences" because this is the only kind of structural identity that primers and human genomic DNA typically share.[176] For a biological polymer such as DNA, primary structure can refer to the sequence, or linear order, of nucleotides, while secondary or other higher order structures generally refer to the polymer's three-dimensional shape.[177] While primers and naturally occurring DNA may share the same sequence, their three-dimensional shapes differ.[178] The court likely did not appreciate these finer distinctions in nucleic acid structure when advancing this doctrine.

Moreover, the Federal Circuit unnecessarily read *Myriad* to be more restrictive than the Supreme Court's intention. The *Myriad* Court focused specifically on whether gene isolation was sufficient to permit the patenting of genes and the information they encode.[179] While perhaps unfounded, the

174. *Id.* at 760 ("As the Supreme Court made clear, neither naturally occurring compositions of matter, nor synthetically created compositions that are structurally identical to the naturally occurring compositions, are patent eligible."). For an explanation of why primers are not actually structurally identical, see Part I, *supra*. *See also* Grote, *supra* note 34, at 27.

175. *See Ambry*, 774 F.3d at 760.

176. While primers and naturally occurring DNA may share the same sequence, they may not necessarily be chemically identical due to methylation differences. *See* Grote, *supra* note 34, at 27. While the court did not search for an "inventive concept," which *Mayo* demands, DNA primers were routinely designed using conventional techniques at the time of Myriad's patent. *See* Part I, *supra*; *see also* ALBERTS ET AL., *supra* note 24, at 491–513.

177. The term "primary structure" is typically reserved for polymers of amino acids, called proteins, but the concept is applicable to any biological polymer. Scientists, however, typically use the term "sequence" instead of "primary structure" when referring to the linear order of nucleotides in DNA. Natural DNA exhibits several forms of higher-order structures that create unique three-dimensional shapes. Human genomic DNA is organized in chromosomal structures. *See* STRYER, *supra* note 86, at 35–36, 788–91; ALBERTS ET AL., *supra* note 24, at 196–97.

178. Human genomic DNA exists in a double-stranded double helix and further exists in complex chromatin structures. Primers, by contrast, may exhibit a variety of three-dimensional shapes based on their sequence including dimers and hairpins. *See* STRYER, *supra* note 86, at 788–91; ALBERTS ET AL., *supra* note 24, at 207–12; DEBNATH ET AL., *supra* note 16, at 133.

179. *See* Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2120 (2013) ("We merely hold that genes and the information they encode are not patent eligible

Myriad Court expressed concern that an isolated gene patent would preempt all uses of the information that the gene encodes.[180] Thus, the *Myriad* Court deliberately crafted a limited holding to bar isolated gene patents while asserting that new applications stemming from the discovery of the BRCA genes remain patent eligible.[181] BRCA-based DNA primers represent an example of a new application that stems from the discovery of BRCA genes. Under *Ambry*, however, new compositions stemming from a discovery of a natural product may no longer be patent eligible if a portion of the primary structure or sequence of the new composition is the same as that of a natural product.[182]

In addition to expanding the scope of the natural phenomena exception for DNA technologies, the *Ambry* court blurred the differences between functions and properties when it concluded that primers "do not perform a significantly new function."[183] Most natural products possess certain distinctive properties or qualities that inventors may leverage to create compositions with novel functions. Wood, for example, is a natural product consisting of cellulosic polymers that has the properties of strength and durability.[184] An inventor may create a chair consisting entirely of wood. The chair shares some of the same properties with the wood, such as strength and durability, but possess a novel function—it functions as a seat.[185]

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under § 101 simply because they have been isolated from the surrounding genetic material.").

180. *Id.* at 2118 ("Instead, the claims understandably focus on the genetic information encoded in the BRCA1 and BRCA2 genes."). The Court's concern is perhaps unfounded because reference human gene sequences have been freely available to the public since the completion of the human genome project in 2003, and modern advances in sequencing technology do not require possession of isolated DNAs encoding individual portions of genes. *See* Part IV, *infra*.

181. *Id.* at 2120 (citing Ass'n for Molecular Pathology v. United States PTO, 689 F.3d 1303, 1349 (Fed. Cir. 2012) (Bryson, J., dissenting) ("[A]s the first party with knowledge of the [BRCA1 and BRCA2] sequences, Myriad was in an excellent position to claim applications of that knowledge. Many of its unchallenged claims are limited to such applications.")).

182. *See In re* BRCA1- & BRCA2-Based Hereditary Cancer Test Pat. Litig. v. Ambry Genetics Corp., 774 F.3d 755, 761 (Fed. Cir. 2014).

183. *Id.* at 755, 760– 61.

184. *See, e.g.*, Chris Woodford, *Wood*, EXPLAIN THAT STUFF!, http://www.explainthatstuff.com/wood.html [https://perma.cc/5BBN-8JBZ].

185. A chair, of course, has a different three-dimensional shape than a block of a wood or a tree, but the primary structures or sequences of the cellulosic polymers are unchanged. Likewise, human genomic DNA and primers have different three-dimensional shapes but share common sequences. *See supra* notes 176, 177, and 178.

Likewise, DNA has the property of complementary base pairing.[186] Myriad leveraged this property to create a primer consisting entirely of synthetic DNA.[187] The primer shares some of the same properties as naturally occurring DNA, namely complementary base pairing, but possesses a new function—it catalyzes a polymerase chain reaction.[188] Using the language of *Chakrabarty*, the primer has a distinctive character and use.[189]

Ambry's holding that DNA compositions are not patentable unless they have different sequences from naturally occurring DNA further restricts patent-eligibility for DNA-based technologies essential to molecular diagnostics. *Ambry* creates a strict patentability threshold for DNA technologies, which is more stringent than what is required for other patented compositions that are derived from natural products.

B. *ARIOSA* EXPANDED THE LAW OF NATURE/NATURAL PHENOMENA EXCEPTION TO INCLUDE METHODS FOR DETECTING NATURAL PRODUCTS

In 1997, Drs. Lo and Wainscoat discovered trace amounts of fragmented fetal DNA circulating in maternal blood.[190] They applied this discovery of cell free fetal DNA (cffDNA) using well-understood DNA manipulation techniques to create a non-invasive prenatal test.[191] Thus, similar to the facts in *Mayo*, their invention improved an old method of fetal testing where the only new and useful element of the improved method was a scientific discovery.[192]

186. *See* ALBERTS ET AL., *supra* note 24, at 194–95.

187. '282 Patent, *supra* note 14.

188. *See supra* Part I. PCR is not a natural process. It does not occur in nature. In nature, DNA is replicated, but this replication does not use DNA primers. Instead, replication is primed by short RNAs. *See* STRYER, *supra* note 86, at 805–06.

189. *See* Diamond v. Chakrabarty, 447 U.S. 303, 308 (1980).

190. Lo et al., *Presence of Fetal DNA in Maternal Plasma and Serum*, 350 LANCET 485 (1997). Fetal DNA was known to exist in circulating fetal cells, but no one had yet found fetal DNA existing outside of fetal cells in circulating maternal blood.

191. *See* '540 Patent, *supra* note 3. At the time of filing, it was well understood to use PCR and other DNA manipulation techniques to amplify and detect fetal DNA from fetal cells, but not from maternal serum because no one knew that fetal DNA was present in maternal serum. The patent was subsequently licensed to Sequenom, a California-based company, for commercialization.

192. *See* Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289 (2012); *see also supra* Part II.B.

To illustrate the scope of the invention at issue, claim 25 of the '540 patent on the non-invasive prenatal test reads:

> A method for performing a prenatal diagnosis on a maternal blood sample, which method comprises obtaining a non-cellular fraction of the blood sample, amplifying a paternally inherited nucleic acid from the non-cellular fraction, and performing nucleic acid analysis on the amplified nucleic acid to detect paternally inherited fetal nucleic acid.[193]

Ariosa Diagnostics, Inc., Natera, Inc., and Diagnostics Center, Inc. each developed non-invasive prenatal tests based on the amplification and detection of cffDNA without a license to the '540 patent.[194] Beginning in December 2011, each company filed declaratory judgment actions against Sequenom, who had exclusively licensed the '540 patent, asserting that they were not infringing the '540 patent.[195] Sequenom countersued for patent infringement.[196] The district court granted summary judgment in favor of Ariosa et al. and invalidated the '540 patent under § 101.[197] The Federal Circuit affirmed the district court, holding that the claims of the '540 patent were not drawn to patent-eligible subject matter.[198]

In invalidating the '540 patent, the Federal Circuit applied *Mayo* and *Ambry*'s expansive reading of *Myriad* to determine that the patent claimed a natural phenomena.[199] The court asserted that the claims "are generally directed to detecting the presence of a naturally occurring thing or a natural phenomenon."[200] This reasoning further broadened *Mayo*'s "law of nature/natural phenomena" analysis because under *Ariosa*, an innovation that involves detecting a natural substance falls within the judicial exception. Professor Christopher Holman pointed out the problems with this reasoning with the following example: Under *Ariosa*, a method to detect human-made toxins in drinking water would be patent eligible, but a method to detect naturally occurring pathogens would fall within a judicial

193. '540 Patent, *supra* note 3, at col. 26 ll. 29–36.

194. Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1374 (Fed. Cir.), *reh'g denied*, 809 F.3d 1282 (Fed. Cir. 2015); *see also* Ashwin Agarwal, *Commercial Landscape of Noninvasive Prenatal Testing in the United States*, 33 PRENATAL DIAGNOSTICS 521, 522–23 (2013) (describing the non-invasive prenatal testing field).

195. *Ariosa*, 788 F.3d at 1374.

196. *Id.*

197. *Id.* at 1375.

198. *Id.* at 1380.

199. *See id.*

200. *Id.* at 1376.

exception and require additional scrutiny to determine patent eligibility.[201] Since essentially all molecular diagnostic methods involve the detection of naturally occurring substances, the *Ariosa* court firmly placed an entire technological field into a judicial exception. This analysis epitomizes Justice Frankfurter's warnings that a "law of nature/natural phenomena" analysis could lead judges to deny patents to technological areas that Congress intended to be patent eligible.[202]

In analyzing whether the patent claims encompassed a judicial exception, the *Ariosa* court stated twice that the method "begins and ends with a natural phenomenon," specifically cffDNA.[203] The court's emphasis of this statement suggests its importance to the determination of whether a method claims natural phenomena. While the method at issue—and essentially all other methods except for software and related digital processes—begins with a naturally occurring substance, the method does not end with a naturally occurring substance.[204] Instead, the method ends with an analysis or detection of synthetically created amplified cffDNA.[205] The court's framework, in both *Ambry* and *Ariosa*, would conclude that amplified cffDNA is a natural phenomenon because it contains the same sequence as naturally occurring cffDNA. But this framework ignores the fact that amplified cffDNA is a human-made composition with a new use not found in nature. Amplified cffDNA provides clinically useful information on fetal characteristics, whereas naturally occurring cffDNA, without any human manipulation, does not.[206] Only when naturally occurring cffDNA is transformed into a new substance—in this case through amplification—does it become useful for fetal testing.[207] Again

201. The Biotechnology Industry Organization (Bio) And Pharmaceutical Research And Manufacturers Of America (Phrma) As *Amici Curiae* Supporting Appellants And In Favor Of En Banc Reconsideration (Nos. 2014-1139, -1144), Ariosa Diagnostics, Inc. v. Sequenom, Inc., 809 F.3d 1282 (Fed. Cir. 2015).

202. *See* Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 134–35 (1948) (Frankfurter, J., concurring).

203. *Ariosa*, 788 F.3d at 1376, 1378.

204. For example, a method to create a new iron-based alloy begins with iron, a method to decontaminate polluted water begins with water, and a method to build a wooden chair begins with wood.

205. *See, e.g.*, '540 Patent, *supra* note 3, at col. 26 ll. 29–36.

206. *See id.*

207. *See id.*; *see also* Parke-Davis & Co v. H.K. Mulford Co., 189 F. 95, 103 (C.C.S.D.N.Y. 1911) (holding that purified adrenaline was patentable because for all practical purposes it was a new substance with commercial utility). Newer technologies using a technique called molecular combing can extract clinically useful data from cffDNA without amplification. *See Molecular Combing*, GENOMIC VISION http://www.genomicvision.com/technology/molecular-combing [https://perma.cc/3N3Q-2USY].

using the language of *Chakrabarty*, amplified cffDNA is "markedly different" than naturally occurring cffDNA because it has a distinctive character and use.[208]

After concluding that the '540 patent claimed a natural phenomenon, the *Ariosa* court next examined whether the patent claimed an "inventive concept" that would allow it to be patentable.[209] While *Ariosa* explained it was applying the *Mayo* framework, the court advanced a test that is even more exacting than *Mayo*'s. In *Mayo*, the additional elements of administering thiopurine drugs and measuring metabolites were already known and routinely performed at the time the patent was filed.[210] By contrast, no one was amplifying and detecting cffDNA at the time of the '540 patent because no one knew cffDNA existed.[211] Under the *Ariosa* "inventive concept" framework, the novelty of the discovery of cffDNA was completely discounted. After discounting this discovery, *Ariosa* determined that the amplification and detection elements of the claim were well-understood, routine, and conventional because in 1997, scientists generally understood how to amplify and detect DNA.[212] Implicit from this analysis is that the court analyzed the "inventiveness" of the additional elements as if scientists in 1997 knew that cffDNA already existed. The court thus separated the new discovery from the additional elements of amplifying and detecting DNA, which the Court in *Diehr* explicitly forbade.[213]

In concluding that the '540 patent lacked an "inventive concept," the court emphasized that "[t]he only subject matter new and useful as of the date of the application was the discovery of the presence of cffDNA in maternal [blood]."[214] This conclusion returns the patent eligibility analysis back to the Douglas framework, where practical applications of new

208. *See Diamond v. Chakrabarty*, 447 U.S. 303, 309–10 (1980) (citing Hartranft v. Wiegmann, 121 U.S. 609, 615 (1887)); *see also* Brief of Amicus Curiae Paul Gilbert Cole in Support of Appellants' Petition for Rehearing En Banc (Nos. 2014-1139, 2014-1144) Ariosa Diagnostics, Inc. v. Sequenom, Inc., 809 F.3d 1282 (Fed. Cir. 2015).

209. *Ariosa*, 788 F.3d at 1376.

210. *See* Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289, 1297–98 (2012).

211. *See* '540 Patent, *supra* note 3, at col. 1 ll. 50–55; *see also Ariosa*, 788 F.3d at 1381 (Linn, J., concurring).

212. *Ariosa*, 788 F.3d at 1377 ("The specification of the '540 patent confirms that the preparation and amplification of DNA sequences in plasma or serum were well-understood, routine, conventional activities performed by doctors in 1997.").

213. *See* Diamond v. Diehr, 450 U.S. 175, 188 (1981). While the majority opinion in *Ariosa* did not cite to *Diehr*, Judge Linn's concurrence mentioned the holding of *Diehr*, but argued that *Mayo* superseded *Diehr* when assessing the conventionality of the additional claim elements. *Ariosa*, 788 F.3d at 1380–81.

214. *Ariosa*, 788 F.3d at 1377.

discoveries are not patentable if the discovery itself is the only new and useful aspect of the invention.[215] But Congress rejected this framework, and *Ariosa* makes the statutory text of the Patent Act, stating that discoveries are inventions, a dead letter.[216]

IV. POLICY CONSIDERATIONS FAVOR PATENTABILITY FOR MOLECULAR DIAGNOSTICS

The primary policy objective of patent law is to promote innovation.[217] Patents promote innovation in at least three ways. First, they incentivize the public to invest in research by rewarding exclusive rights for useful inventions stemming from this research.[218] Second, the disclosure requirements of patent law enrich public knowledge of science and technology, which increases the flow of ideas and stimulates innovation.[219] Finally, because patents preempt or exclude public use of an invention, they incentivize ingenuity by encouraging the public to design around and improve upon existing patented technology.[220]

The issue of preemption, however, is a double-edged sword because overly broad patents may chill innovation if they preempt all uses of fundamental principles or naturally occurring materials.[221] This concern underlies the rationale for the judicially created exceptions to patentable subject matter.[222] In theory, these judicial exceptions make for sound policy. No one should have exclusive rights to the fundamental principles of gravitation or to the naturally occurring minerals of the earth.[223] In practice,

215. *See supra* Section II.B.

216. *See* 35 U.S.C. §§ 100–01 (2012).

217. *See* U.S. CONST. art. I, § 8, cl. 8 ("The Congress shall have power . . . [to] promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.").

218. *See* Lybecker, *supra* note 45.

219. *See* David Kline, *Do Patents Truly Promote Innovation?*, IPWATCHDOG (Apr. 15, 2014), http://www.ipwatchdog.com/2014/04/15/do-patents-truly-promote-innovation/id=48768 [https://perma.cc/2YPY-VDM5] (citing a 2006 study that found that "88 percent of U.S., European, and Japanese businesses rely upon the information disclosed in patents to keep up with technology advances and direct their own R&D efforts.").

220. *See id.* ("[P]atents also improve the allocation of resources by encouraging rapid experimentation and efficient ex post transfer of knowledge across firms.").

221. *See* Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289, 1305 (2012).

222. Alice Corp. Pty. Ltd. v. CLS Bank Int'l., 134 S. Ct. 2347, 2354 (2014) ("We have described the concern that drives this exclusionary principle as one of pre-emption.").

223. *See* Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980). At least for principles like gravitation, the judicial exceptions are likely unnecessary because a principle by

however, applying the judicial exceptions is challenging because courts rarely, if ever, hear such straightforward examples. Moreover, since the judicial exceptions have never been precisely defined, their malleable nature creates opportunities for judges to use the exceptions to foreclose patent eligibility to technological areas based on policy issues that are more suitable for Congress to address. For example, before Justice Breyer authored the *Mayo* decision, he wrote a dissenting opinion in *Lab Corp. of America Holdings v. Metabolite Labs., Inc.* that would have invalidated under § 101 a patent that claimed a diagnostic method that identified a vitamin deficiency by measuring a metabolite.[224] In his dissent, the Justice raised concerns that patents to such diagnostic methods may hinder the practice of medicine or increase the cost of health care.[225] In *Mayo*, Justice Breyer suggested that diagnostic patents, in contrast to pharmaceutical patents, undermine innovation because they preempt too much.[226]

Since the patentability of diagnostics has captured the Court's attention, perhaps in part due to public policy considerations, these policy considerations warrant a brief exploration.[227] As discussed below, policy considerations should weigh in favor of—not against—molecular diagnostic patents because such patents tend to promote rather than chill diagnostic innovation.

A. PATENTS PROMOTE DIAGNOSTIC INNOVATION

Diagnostic patents incentivize research and development of new diagnostic technologies. Similar to other biotechnological products,

definition is not a process, machine, manufacture, or composition of matter. *See* Holman, *supra* note 55, at 1821.

224. 548 U.S. 125 (2006) (Breyer, J., dissenting).

225. *Id.* at 138 ("[S]pecial public interest considerations reinforce my view that we should decide this case. To fail to do so threatens to leave the medical profession subject to the restrictions imposed by this individual patent and others of its kind. Those restrictions may inhibit doctors from using their best medical judgment; they may force doctors to spend unnecessary time and energy to enter into license agreements; they may divert resources from the medical task of health care to the legal task of searching patent files for similar simple correlations; they may raise the cost of healthcare while inhibiting its effective delivery.").

226. *See Mayo*, 132 S. Ct. at 1302.

227. *See* Eisenberg, *supra* note 57, at 281 ("[B]oth the Supreme Court and the Federal Circuit insist that patent policy decisions are the domain of Congress, and that they are merely applying longstanding principles of patent law to the cases before them. Yet a distinction between therapeutics and diagnostics seems to lurk beneath the surface of decisions that rest more explicitly on other distinctions.").

diagnostic tests require large investments in research and development.[228] The cost to develop diagnostic tests ranges from fifty to seventy-five million dollars.[229] The scientific research required to identify new biomarkers and clinically validate their efficacy to diagnose disease drives much of this cost.[230] An investor's willingness to commit capital to these research endeavors depends strongly on the ability to patent useful applications stemming from these research efforts.[231]

Historically, academic labs have discovered many of the biological correlations that form the basis of a new diagnostic test.[232] Some academics may be motivated solely from a deep curiosity about the molecular underpinnings of disease, while others may be motivated by the prospects of commercializing their discoveries.[233] Regardless of motive, without a patent, it is unlikely that any investor would fund a company to commercialize academic discoveries due to the costs associated with process engineering, scaling up, and assessing clinical efficacy and safety.[234]

Diagnostic patents encourage public disclosure of valuable scientific and clinical data. Myriad possesses a vast private database of disease relevant

228. Brief Of *Amicus Curiae* Twenty-Three Law Professors In Support Of Appellants' Petition For Rehearing *En Banc (*Nos. 2014-1139, 2014-1144) Ariosa Diagnostics, Inc. v. Sequenom, Inc., 809 F.3d 1282 (Fed. Cir. 2015).

229. *Id.*

230. *See* Christopher M. Holman, *The Critical Role of Patents in the Development, Commercialization, and Utilization of Innovative Genetic Diagnostic Tests*, CTR. FOR PROTECTION INTELL. PROP. 3 (July 2014), http://cpip.gmu.edu/wp-content/uploads/2014/04/Holman-Critical-Role-of-Patents-in-Genetic-Diagnostic-Tests.pdf [https://perma.cc/FJX8-TRSX].

231. *See id.* at 5.

232. *See, e.g.*, Lo, *supra* note 190, 485–87.

233. *See* DEP'T OF HEALTH & HUMAN SERVS., GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON PATIENT ACCESS TO GENETIC TESTS (2010), http://osp.od.nih.gov/sites/default/files/SACGHS_patents_report_2010.pdf [https://perma.cc/YSG6-6YFL] ("The Committee found that the prospect of patent protection of a genetic research discovery does not play a significant role in motivating scientists to conduct genetic research. Scientists typically are driven instead by factors such as the desire to advance understanding, the hope of improving patient care through new discoveries, and concerns for their own career advancement.").

234. *See* PRESIDENT'S COUNCIL OF ADVISORS ON SCIENCE AND TECHNOLOGY, PRIORITIES FOR PERSONALIZED MEDICINE 21 (2008), https://www.whitehouse.gov/files/documents/ostp/PCAST/pcast_report_v2.pdf [https://perma.cc/H98N-WLEZ] ("The ability to obtain strong intellectual property protection through patents has been, and will continue to be, essential for pharmaceutical and biotechnology companies to make the large, high-risk R&D investments required to develop novel medical products, including genomics-based molecular diagnostics.").

BRCA mutations stemming from its genetic research.[235] Myriad shared BRCA mutation data with the public until 2004.[236] Since 2004, Myriad has protected its BRCA mutation databases deliberately as trade secrets.[237] While it is impossible to know without insider knowledge what spurred this change, uncertainty as to whether BRCA-related diagnostic tests are patentable surely does not incentivize Myriad to share data.[238] Without the benefit of patent protection, trade secret protection for molecular diagnostics may become the only means to gain a competitive advantage.[239] Unlike patents, trade secrets potentially endure forever, which may harm public welfare by maintaining high health care costs for diagnostic methods.[240] Moreover, the public is deprived of the knowledge these databases provide, which impedes the sharing of ideas and stifles innovation.[241]

Finally, diagnostic patents encourage the public to improve existing technology. For example, while the '540 patent provided broad protection over the diagnostic use of cffDNA, it possessed at least one critical limitation.[242] The method required selective amplification of paternally inherited cffDNA.[243] Ten years after the discovery of cffDNA, in 2007, a research group from Stanford University invented and patented an improved non-invasive prenatal test that did not require selective amplification of paternally inherited cffDNA.[244] While it is impossible to know whether the Stanford group would have invented this improved prenatal test if the '540 patent did not exist, there would surely be less incentive to invest the capital necessary to commercially develop a new and

235. Robert Cook-Deegan et al., *The Next Controversy in Genetic Test: Clinical Data as Trade Secrets?*, 21 EUR. J. HUMAN GENETICS 585, 585–86 (2013).

236. *Id.* at 586.

237. *Id.*

238. *See* Andrew Pollack, *Despite Gene Patent Victory, Myriad Genetics Faces Challenges*, N.Y. TIMES (Aug. 24, 2011), http://www.nytimes.com/2011/08/25/business/despite-gene-patent-victory-myriad-genetics-faces-challenges.html [https://perma.cc/4H76-EXPA] (quoting Peter D. Meldrum, Myriad's chief executive, "If I had my druthers, I would not want to go into a new market in a heavy-handed fashion, trying to enforce patents.").

239. *See* Cook-Deegan, *supra* note 235, at 586.

240. *See id.* ("The practical effect of retaining such data as a trade secret is to extend Myriad's testing monopoly beyond the life of the patents on which it was founded").

241. *See id.*

242. *See* '540 Patent, *supra* note 3, at col. 23 ll. 64–65.

243. *See id.*

244. *See, e.g.*, U.S. Patent No. 7,888,017 (filed Feb. 2, 2007). Even newer technologies detect cffDNA without amplification. *See Molecular Combing*, GENOMIC VISION http://www.genomicvision.com/technology/molecular-combing [https://perma.cc/BJ97-PSY4].

improved prenatal test if the diagnostic industry could freely use the existing technology described in the '540 patent. [245]

B. PATENTS DO NOT CHILL DIAGNOSTIC INNOVATION

The Supreme Court in *Mayo* expressed concern that diagnostic patents claiming biological correlations may be fundamentally too broad, which may stifle innovation by foreclosing research opportunities related to the correlation.[246] However, there is little evidence that the patents at issue in *Mayo*, *Myriad*, *Ambry*, and *Ariosa* were so broad that they stifled diagnostic innovation. The patent in *Mayo* described optimization of a specific drug treatment and had little impact on other areas of personalized medicine.[247] The isolated BRCA DNA patents described in *Myriad* did not preempt sequencing the BRCA genes and identifying cancer-related mutations because advances in sequencing technology no longer require gene isolation as an intermediary step.[248] Likewise, the primers in *Ambry* are no longer required to sequence the BRCA genes because next-generation sequencing can use universal primers instead of gene-specific primers.[249] Finally, as described in Section IV.A, the '540 patent in *Ariosa* has not prevented the development of new patented improvements of non-invasive prenatal testing based on the detection of cffDNA.[250]

Some scholars have theorized that some diagnostic-related patents such as gene patents may create a "tragedy of the anticommons," where too many

245. The diagnostic company Verinata commercialized non-invasive prenatal tests based on the patented Stanford University technology. *See* Luke Timmerman, *Verinata's Big Day Arrives, With Prenatal Down Syndrome Test Debut*, XCONOMY (Feb. 29, 2012), http://www.xconomy.com/san-francisco/2012/02/29/verinatas-big-day-arrives-with-prenatal-down-syndrome-test-debut [https://perma.cc/N4MZ-6Z97]. In the absence of patent protection, the Stanford group may have still researched improvements of non-invasive prenatal tests, but it is highly doubtful that venture capitalists would have invested $58 million to commercialize this improved test. *See Verinata Health,* CRUNCHBASE, https://www.crunchbase.com/organization/verinata-health#/entity [https://perma.cc/AV74-64UD]. Illumina acquired Verinata in 2013 for $350 million in upfront payments. *See* Luke Timmerman, *Illumina Acquires Verinata Health, Prenatal Testmaker, for $350M*, XCONOMY (Jan. 7, 2013) http://www.xconomy.com/san-diego/2013/01/07/illumina-acquires-verinata-health-prenatal-testmaker-for-350m [https://perma.cc/B5FL-KDSL].

246. *See* Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289, 1303 (2012).

247. *See* Eisenberg, *supra* note 57, at 269 (explaining the narrowness of the claims at issue in *Mayo*, "The *Mayo* claim is a narrowing refinement of a particular application rather than a new scientific discovery that has not yet been reduced to a particular application.").

248. *See* Grote, *supra* note 34, at 32–33.

249. *See* Michael L. Metzker, *Sequencing Technologies—The Next Generation*, 11 NATURE REV.: GENETICS 31, 32–33 (2010).

250. *See, e.g.*, *supra* note 244.

patent holders of "upstream" research block the development of new biotechnology products due to prohibitive transactional costs associated with patent licensing.[251] However, empirical studies have not found evidence of serious anticommons problems in the biotechnology industry.[252] Moreover, these fears have been unfounded for the downstream development of non-invasive fetal tests because non-invasive prenatal testing is currently available in the marketplace.[253] Furthermore, two major noninvasive fetal test patent holders, Sequenom and Illumina, have formed a patent pool to share their patent resources, which should ensure that these companies continue to develop and market improvements to non-invasive fetal testing.[254]

Finally, there may be some concern that diagnostic patents that encompass scientific discoveries may impede the ability of academics to conduct basic research.[255] This concern, however, is largely unfounded because patent holders rarely sue universities for patent infringement.[256] If this practice were to change, Congress could enact safe harbor provisions to permit academic researchers to use patented technology for noncommercial research purposes.[257]

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251. Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698, 698–701 (1998).

252. Timothy Caulfield et al., *Evidence and Anecdotes: An Analysis of Human Gene Patenting Controversies*, 24 NATURE BIOTECHNOLOGY 1091, 1092 ("But despite the large number of patents and the numerous, heterogeneous actors—including large pharmaceutical firms, biotech startups, universities and governments—studies that have examined the incidence of anticommons problems find them relatively uncommon"); *see also* Rebecca Eisenberg, *Noncompliance, Nonenforcement, Nonproblem? Rethinking the Anticommons in Biomedical Research*, 45 HOUS. L. REV. 1059, 1062–63 (2008) (Symposium: Patent Law in Perspective Institute for Intellectual Property and Information Law) (suggesting a refinement of the anticommons theory that takes into account the burdens on a patent owner to detect and sue for infringement).

253. *See, e.g.*, *The Maternit21® Plus Prenatal Test*, SEQUENOM, https://laboratories.sequenom.com/patients/maternit21-plus [https://perma.cc/4PMQ-ACSU].

254. *See Illumina and Sequenom Pool Noninvasive Prenatal Testing Intellectual Property and End Outstanding Patent Disputes*, ILLUMINA, http://investor.illumina.com/mobile.view?c=121127&v=203&d=1&id=1994454 [https://perma.cc/2Z6F-72ZF].

255. *See, e.g.*, Tania Simoncelli & Sandra Park, *Making the Case Against Gene Patents*, 23 PERSPECTIVES ON SCIENCE 106, 121–23 (2014) (discussing negative effects of gene patents on research).

256. *See* Holman, *supra* note 230, at 4–5.

257. Congress has enacted safe harbor provisions for medical doctors under certain conditions. *See* 35 U.S.C. § 287(c) (2012).

V. CONCLUSION

Recent Supreme Court and Federal Circuit decisions collectively endanger patentability for molecular diagnostics. Sequenom has petitioned for a writ of certiorari,[258] and the Court should grant the writ because *Sequenom v. Ariosa Diagnostics* provides an excellent vehicle for the Court to clarify how to apply the judicial exceptions to molecular diagnostics specifically and to practical applications of new discoveries generally. If and when the Court revisits its § 101 jurisprudence, the Court should heed the wisdom of Judge Learned Hand whose concluding paragraph in *Parke-Davis* is as relevant today as it was over one hundred years ago:

> I cannot stop without calling attention to the extraordinary condition of the law which makes it possible for a man without any knowledge of even the rudiments of chemistry to pass upon such questions as these. The inordinate expense of time is the least of the resulting evils, for only a trained chemist is really capable of passing upon such facts. . . . How long we shall continue to blunder along without the aid of unpartisan and authoritative scientific assistance in the administration of justice, no one knows; but all fair persons not conventionalized by provincial legal habits of mind ought, I should think, unite to effect some such advance.[259]

Since courts are unlikely to employ unpartisan scientific advisors in the near future, the Supreme Court should follow the statutory text of §§ 100 and 101,[260] nineteenth century precedent,[261] the principles of *Diehr*,[262] and the wisdom of Justice Frankfurter[263] and Judge Hand[264] in determining patent eligibility for molecular diagnostics. Instead of dissecting out a patent's "laws of nature" and "natural phenomena" and searching for

258. Petition for Writ of Certiorari, Sequenom, Inc. v. Ariosa Diagnostics, Inc. (U.S. Mar. 21, 2016) (No. 15-1182), 2016 WL 1105544.

259. Parke-Davis & Co v. H.K. Mulford Co., 189 F. 95, 115 (C.C.S.D.N.Y. 1911); *see also* Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013) (Scalia, J., concurring).

260. *See* 35 U.S.C. §§ 100–01 (2012).

261. *See supra*, notes 124, 126.

262. *See* Diamond v. Diehr, 450 U.S. 175, 188 (1981) ("In determining the eligibility of respondents' claimed process for patent protection under § 101**,** their claims must be considered as a whole.").

263. *See* Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 134–35 (1948) (Frankfurter, J., concurring) ("It only confuses the issue, however, to introduce such terms as 'the work of nature' and the 'laws of nature.'").

264. *See Parke-Davis & Co*, 189 F. at 103 (discussing the patentability of purified adrenaline, "it became for every practical purpose a new thing commercially and therapeutically. That was a good ground for a patent.").

indicators of inventiveness in the patent's remains, the Court should consider a patent holistically and determine whether the patent claims merely a principle or a practical application of a principle. More specifically, the Court should articulate a framework in which (1) synthetic compositions that have properties, structures, or sequences in common with naturally occurring materials are patent eligible if they have new and useful functions, and (2) conventional, routine, and well-understood applications of new discoveries are patent eligible. If the Court fails to address these concerns, then Congress should consider amending the Patent Act to reflect these suggestions and to preserve patentability for molecular diagnostics.

APPENDIX

Definitions of Molecular Biology Terms

Term	Definition
Genomic DNA	Naturally occurring nucleic acids that contain an organism's genetic information.
Gene	A segment of genomic DNA that contains information for making protein.
Exon	A segment of a gSene that contains information for making protein.
Intron	A segment of a gene that does not contain information for making protein.
mRNA	A naturally occurring nucleic acid that contains information for making proteins according to the exons of genes.
Isolated DNA	A synthetic DNA, often a synthetically created copy of a segment of a naturally occurring DNA. Synthetic copies share the same genetic information as naturally occurring DNA but may have slightly different chemical compositions. Isolated DNA has similar properties as naturally occurring DNA but may have novel functions.
cDNA	A synthetically created copy of an mRNA. It shares the same genetic information as naturally occurring mRNA but has different chemical differences.
Plasmid	A DNA structure that exists in some bacteria. Scientists use plasmids to propagate and store isolated DNA and cDNA in bacteria.
PCR	A laboratory technique to amplify and make many copies of a DNA segment of interest.
Primer	Short segments of synthetic DNA that are necessary for initiating PCR. Primers may share some sequence elements in common naturally occurring DNA The primer's sequence determines which DNA segments are amplified during PCR.
Cell-free fetal DNA (cffDNA)	Naturally occurring fetal DNA fragments that circulate in maternal blood.
Biomarker	Any molecules present in the human body such as nucleic acids (e.g. DNA and RNA), proteins, and various small molecules (often referred to collectively as metabolites)