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ASSOCIATION FOR MOLECULAR PATHOLOGY V. MYRIAD GENETICS, INC.: THE PRODUCT OF NATURE DOCTRINE REVISITED

Tup Ingram[†]

In a highly anticipated decision that overturned two decades of U.S. Patent and Trademark Office (“USPTO”) practice,¹ called into question a century of lower court precedent,² and may have invalidated claims in up to forty thousand patents covering more than twenty percent of the human genome,³ the Supreme Court in *Association for Molecular Pathologists v. Myriad Genetics, Inc.* examined one certified question: “[a]re human genes patentable?”⁴ The Court answered: sometimes.⁵ In *Myriad*, the Supreme Court unanimously held that “genes and the information they encode are not

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1. The first DNA patent issued in the United States no later than 1984 for a recombinant DNA transfer vector (plasmid) containing the Chorionic Somatomammotropin gene. U.S. Patent No. 4,447,538 (filed Feb. 5, 1982) (issued May 8, 1984); *see also* Utility Examination Guidelines, 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001) (“[W]here the application [for a DNA patent] discloses a specific, substantial, and credible utility for the claimed isolated and purified gene, the isolated and purified gene composition may be patentable.”).

2. Isolated and purified natural substances, including biologically active molecules, have long been held patent-eligible. *See infra* Sections I.B, I.C.

3. *See* Eric J. Rogers, *Can You Patent Genes? Yes and No*, 93 J. PAT. & TRADEMARK OFF. SOC’Y 19, 19 (2011) (citing NAT’L ACAD. OF SCI., REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH: INTELLECTUAL PROPERTY RIGHTS, INNOVATION, AND PUBLIC HEALTH (2006); Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, SCI., Oct. 2005, at 239).

4. Order Granting Petition for Writ of Certiorari, *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 694, 694–95 (2012) (mem) (limiting review to this one question out of the three advanced). *See also* Petition for Writ of Certiorari, *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013) (No. 12-398), 2012 WL 4502947, at *i.

5. *Ass’n for Molecular Pathology v. Myriad Genetics, Inc. (Myriad IV)*, 133 S. Ct. 2107 (2013). The Court examined patents written on two types of DNA; isolated genomic DNA (“gDNA”) and isolated complementary DNA (“cDNA”). gDNA is synthesized from a template that consists of extracted portions of chromosomal DNA, while cDNA is synthesized from an RNA template. *See* Section III.C, *infra*, for a more complete discussion of these two types of DNA. The Court held that isolated gDNA is not patent-eligible and that some isolated cDNA is patent-eligible. *Myriad IV*, 133 S. Ct. at 2111.

patent eligible under 35 U.S.C. § 101 simply because they have been isolated from the surrounding genetic material.”⁶ The Court invalidated Myriad’s patents on isolated genomic human DNA (“gDNA”) because “a naturally occurring DNA segment is a product of nature,”⁷ but it upheld some of its claims directed toward complementary DNA (“cDNA”) molecules, determining that synthesizing these molecules “unquestionably creates something new.”⁸

Within an hour of the decision’s release, the American Civil Liberties Union (“ACLU”), which had filed the suit for declaratory judgment on behalf of twenty interested parties, declared: “VICTORY! Supreme Court Decides: Our Genes Belong to Us, Not Companies.”⁹ By the end of the day, three competing genetic testing companies announced that they would offer testing for mutations in the BRCA1 and BRCA2 genes, synthetic analogues with structures that had been covered by Myriad’s invalidated claims.¹⁰ Within a month, Myriad had sued two competitors for willful infringement of thirty-five claims found in ten patents on BRCA testing.¹¹ At the time of this writing, Myriad is currently embroiled in a multidistrict litigation (“MDL”) arising from five original actions, which could determine the validity of claims in fourteen of its DNA patents.¹² So far, the Court’s long-

6. *Myriad IV*, 133 S. Ct. at 2120.

7. *Id.* at 2111.

8. *Id.* at 2119. As discussed in Sections III.C and IV.C and Part V, *infra*, the bright line that the Court appears to have drawn between gDNA and cDNA is not very clear.

9. Sandra S. Park, *VICTORY! Supreme Court Decides: Our Genes Belong to Us, Not Companies*, ACLU BLOG OF RIGHTS (June 13, 2013, 11:35 AM), <https://www.aclu.org/blog/womens-rights-free-speech-technology-and-liberty/victory-supreme-court-decides-our-genes-belong>.

10. The three companies were Ambry Genetics, Gene-By-Gene, Inc., and GeneDx, Ltd. See Press Release, Ambry Genetics, Ambry Genetics Launches BRCA 1 & 2: Single Genes and NGS Panel Offering (June 13, 2013), *available at* <http://www.ambrygen.com/press-releases/ambry-genetics-launches-brca-1-2-single-genes-and-ngs-panel-offerings>; Press Release, Bio-Reference Labs, GeneDx to Launch Comprehensive Breast Cancer Genetic Test (June 13, 2013), <http://www.prnewswire.com/news-releases/genedx-to-launch-comprehensive-breast-cancer-genetic-test-211407911.html>; Press Release, Gene By Gene, Supreme Court Ruling Today Allows DNATraits to Offer Low Cost BRCA Breast and Ovarian Cancer Gene Testing in U.S., (June 13, 2013), <http://www.prnewswire.com/news-releases/supreme-court-ruling-today-allows-dnatraits-to-offer-low-cost-brca-breast-and-ovarian-cancer-gene-testing-in-us-211426171.html>.

11. *Univ. of Utah Research Found. v. Ambry Genetics Corp.*, No. 2:13-cv-00640-RJS (D. Utah filed July 9, 2013); *Univ. of Utah Research Found. v. Gene by Gene Ltd.*, No. 2:13-cv-00643-EJF (D. Utah filed July 10, 2013).

12. See *infra* Section IV.A.

awaited pronouncement regarding the patent eligibility of DNA seems to have generated more uncertainty and litigation than it resolved.¹³

The apparent uncertainty arising from the Court's latest foray into § 101 jurisprudence is not surprising, given the lack of a consensus even at the Federal Circuit regarding § 101's role in the adjudication of patent validity. The Federal Circuit's "opinions spend page after page revisiting [its] cases and those of the Supreme Court, and still [its judges] continue to disagree vigorously over what is or is not patentable subject matter."¹⁴ The Supreme Court has attempted to provide guidance regarding the resolution of these disagreements. Its *Benson*, *Flook*, and *Diehr* patent eligibility trilogy spanning 1972 to 1981 established broad guidelines regarding the patent eligibility of computer software.¹⁵ Its more recent *Bilski* and *Prometheus* decisions reiterated the patent ineligibility of abstract ideas and laws of nature.¹⁶ However, § 101 is still seen as a "vague and contentious . . . doctrine[]" that gives courts "rather thin material to work with" when fashioning holdings.¹⁷ Judges are placed in the role of "oenologists trying to describe a new wine. They have an abundance of adjectives—earthy, fruity, grassy, nutty, tart, woody, to name just a few—but picking and choosing . . . which ones apply . . . depends less on the assumed content of the words than on the taste of the tongue pronouncing them."¹⁸ This lack of clarity was recently reaffirmed in the Federal Circuit's fractured *en banc* decision in *CLS Bank International v. Alice Corp. Pty.*, which resulted in a terse per curiam ruling accompanied by five separate opinions. The outcome led Chief Judge Rader to note that, "[a]lthough a majority of the judges on the court agree that the

13. See generally Bill Malone, *Effects of Gene Patent Ruling Uncertain*, CLINICAL LABORATORY NEWS, July 2013, at 14, available at <http://www.aacc.org/publications/cln/2013/july/Pages/Gene-Patent.aspx>; Emma Barraclough, *What Myriad Means for Biotech*, WORLD INTELL. PROP. ORG. MAG., Aug. 2013, at 21, available at http://www.wipo.int/wipo_magazine/en/2013/04/article_0007.html; Am. Soc'y for Cell Biology, *The Supreme Court's Myriad Decision: Little or No Impact on Basic Research?*, ASCB POST (June 19, 2013, 12:09), <http://www.ascb.org/ascbpost/index.php/ascbpost-home/item/77-the-supreme-court-s-myriad-decision-little-or-no-impact-on-basic-research>.

14. *MySpace, Inc. v. GraphOn Corp.*, 672 F.3d 1250, 1259 (Fed. Cir. 2012) (listing a litany of Federal Circuit cases reaching inconsistent decisions).

15. See *Gottschalk v. Benson*, 409 U.S. 63 (1972); *Parker v. Flook*, 437 U.S. 584 (1978); *Diamond v. Diehr*, 450 U.S. 175 (1981).

16. See *Bilski v. Kappos*, 130 S. Ct. 3218 (2010); *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012).

17. Dennis Crouch & Robert P. Merges, *Operating Efficiently Post-Bilski by Ordering Patent Doctrine Decision-Making*, 25 BERKELEY TECH L.J. 1673, 1683, 1691 (2010).

18. *MySpace*, 672 F.3d at 1259.

method claims do not recite patent-eligible subject matter, no majority of those judges agrees as to the legal rationale for that conclusion.”¹⁹

This Note proceeds in five Parts. Part I discusses how courts have interpreted § 101 in relation to the patent eligibility of naturally occurring molecules. Part II describes the chemical properties of chromosomal and isolated DNA in light of the judicial carve outs discussed in Part I. Part III describes the procedural history of the *Myriad* case. Part IV discusses the state of *Myriad* one year after it was decided, in light of ongoing litigation and the USPTO’s reaction to the Court’s holding. Part V briefly examines a number of possibilities regarding *Myriad*’s legacy in § 101 jurisprudence.

I. PATENT ELIGIBILITY OF BIOLOGICALLY ACTIVE CHEMICALS

Section 101 of the Patent Act of 1952 defines what qualifies for patent protection: “any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof.”²⁰ Section 101’s inclusive nature “embodie[s] [Thomas] Jefferson’s philosophy that ‘ingenuity should receive a liberal encouragement.’”²¹ Despite § 101’s broad language and inclusive intent, the Supreme Court has rejected the suggestion “that § 101 has no limits or that it embraces every discovery.”²² “[L]aws of nature, natural phenomena, and abstract ideas”²³ are judicially created exceptions to patentable subject matter.²⁴ When one of these exceptions applies to a composition of matter, the composition is patent-ineligible subject matter because it is a “product of nature.”²⁵ Applying this

19. *CLS Bank Int’l v. Alice Corp. Pty.*, 717 F.3d 1269, 1292 n.1 (Fed. Cir. 2013) (Rader, C.J., concurring in part and dissenting in part), *cert. granted*, 134 S. Ct. 734 (2013).

20. 35 U.S.C. § 101 (2012). Note that this statutory language closely parallels that of the original Patent Act of 1793, which “defined statutory subject matter as ‘any new and useful art, machine, manufacture, or composition of matter, or any new or useful improvement [thereof].’” *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980) (quoting the Patent Act of Feb. 21, 1793, § 1, 1 Stat. 319); *see also* 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, 1294–97 (2011) (discussing the essential equivalence of the 1793 and 1952 laws’ formulations of patent-eligible subject matter). The 1952 Patent act “intended to perpetuate the existing contours of patentable subject matter as . . . recognized in patent jurisprudence.” *Id.* at 1302.

21. *Chakrabarty*, 447 U.S. at 308.

22. *Id.* at 309; *see also MySpace*, 672 F.3d at 1260, 1261 (referring to § 101 as a “coarse filter” through which a “swamp of verbiage” leads to a “murky morass”).

23. *Diamond v. Diehr*, 450 U.S. 175, 185 (1981).

24. *See id.*

25. *See infra* Section I.A.

doctrine to Myriad's patents on isolated DNA, the *Myriad* Court invalidated Myriad's composition claims to gDNA, holding that "a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated."²⁶

A. THE PRODUCT OF NATURE EXCEPTION TO PATENT ELIGIBILITY

The product of nature doctrine generally states that naturally occurring products are not patent eligible. However, the "underlying difficulty . . . deals with defining what precisely constitutes a product of nature. The line [between products of nature and inventions of 'human ingenuity'] is extremely difficult to draw."²⁷ Courts are torn between two conflicting intuitions. Patent eligibility is constrained because "[p]henomena of nature, . . . mental processes, and abstract intellectual concepts . . . are the basic tools of scientific and technological work."²⁸ However, "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."²⁹

The product of nature doctrine was first expressed in *Ex parte Latimer*.³⁰ Latimer applied for a patent on "the fiber . . . consisting of the cellular tissues

26. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc. (Myriad IV)*, 133 S. Ct. 2107, 2111 (2013).

27. Richard Seth Gipstein, *The Isolation and Purification Exception to the General Unpatentability of Products of Nature*, COLUMBIA SCI. & TECH. LAW REVIEW (Jan. 15, 2003), <http://www.stlr.org/html/volume4/gipstein.pdf>, at 8.

28. *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972).

29. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293 (2012). This tension has led some to observe that the product of nature doctrine has been applied in an "inconsistent and unclear" manner by courts, which have "cobbled [it] together from dicta." See Samantak Ghosh, Note, *Gene Patents: Balancing the Myriad Issues Concerning the Patenting of Natural Products*, 27 BERKELEY TECH. L.J. 241, 246 ("[T]he application of the judicial doctrine has been inconsistent and unclear."); Dan Burk, *The "Runcible" Product of Nature Doctrine*, SCOTUSBLOG (Feb. 4, 2013, 3:50 PM), <http://www.scotusblog.com/2013/02/the-runcible-product-of-nature-doctrine> ("That three judges with vast experience in patent law could find no distinct provenance for the 'product of nature' doctrine separate from the other patentability criteria of Title 35 should come as no surprise, given that the doctrine has been cobbled together from dicta in older cases decided before the current patent statute was codified in 1952."); see also Can Cui, *Patent Eligibility of Molecules: "Product of Nature" Doctrine After Myriad*, 2 N.Y.U. J. INTELL. PROP. & ENT. L. LEDGER 73 (2011) (summarizing the product of nature doctrine as applied to molecules and chemical elements).

30. *Ex parte Latimer*, 1889 Dec. Comm'r Pat. 123. For excellent discussions of the origins of the product of nature doctrine and explanations of why *Latimer* and not *American Wood-Paper Co. v. Fibre Disintegrating Co.*, 90 U.S. 566 (1874), or *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293 (1884), was the first case in this line, see, e.g., Christopher Beauchamp, *Patenting Nature: A Problem of History*, 16 STANFORD TECH. L. REV. 257, 271–74

of the *Pinus australis* [tree].”³¹ In language that the Court echoes in *Myriad*, the Commissioner recognized that Latimer had developed a “process which enables him to procure the fiber in its natural free state.”³² The Commissioner found that Latimer’s fiber, so procured, “differ[s] [from other cellulose fibers] in characteristics as to length, strength, and fineness”³³ However, the Commissioner held that “these differences are not at all due to the processes by which they are removed from the [plant] . . . but to the process of nature in developing and growing them.”³⁴ Ultimately, Latimer’s fiber could not be patented because “the pure fiber . . . is essentially the same thing and possesses the same construction” as when it was found in “the natural matrix of the leaf or stalk or wood in which nature form[ed] and develop[ed] it.”³⁵

The Commissioner concluded that although Latimer’s “alleged invention is unquestionably very valuable,”³⁶ it nonetheless was “a natural product and can no more be the subject of a patent in its natural state when freed from its surroundings than wheat which has been cut by a reaper.”³⁷ Having seen value in Latimer’s discovery, the Commissioner recited some further steps that the putative inventor might have taken in order to obtain a patent: “If applicant’s process had another final step by which the fiber . . . were

(2013); John M. Conley & Roberte Makowski, *Back to the Future: Rethinking the Product of Nature Doctrine as a Barrier to Biotechnology Patents (Part I)*, 85 J. PAT. & TRADEMARK OFF. SOC’Y 301, 319–330 (2003); Leslie A. Demers, *Product of Nature Doctrine: Myriad’s Effect Beyond Nucleic Acids 3–4* (May 1, 2013) (unpublished manuscript), available at <http://ssrn.com/abstract=2279754>. Note that the patent examiner’s initial rejection of the patent application at issue in *Latimer* referenced both *American Wood-Paper* and *Cochrane*. See *Latimer*, 1889 Dec. Comm’r Pat. at 124.

31. *Latimer*, 1889 Dec. Comm’r Pat. at 123.

32. *Id.* at 126. See, e.g., *Ass’n for Molecular Pathology v. Myriad Genetics, Inc. (Myriad IV)*, 133 S. Ct. 2107, 2111 (2013) (“[A] naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated.”); *id.* at 2113 (“Myriad’s patents would . . . if valid, give it the exclusive right to isolate . . . genes . . . by breaking the covalent bonds that connect the DNA to the rest of the . . . genome.”); *id.* at 2114 (“The central dispute among the [Federal Circuit] panel members was whether the act of *isolating* DNA . . . is an inventive act.”); *id.* at 2117 (“Nor are Myriad’s claims saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a nonnaturally occurring molecule.”) *But see id.* at 2118 (“Myriad’s claims [do not] rely in any way on the chemical changes that result from the isolation of a particular section of DNA [but rather] focus on . . . genetic information.”), 2119 (“[T]here are no method claims before this Court. . . . [T]he processes used by Myriad to isolate DNA were well understood by geneticists.”).

33. *Latimer*, 1889 Dec. Comm’r Pat. at 125.

34. *Id.*

35. *Id.*

36. *Id.* at 127.

37. *Id.*

changed, . . . [it would probably be patentable] . . . because the natural fiber . . . would . . . become something new and different from what it is in its natural state.”³⁸ Although *Latimer* held that the “alleged invention” was patent ineligible, this portion of the opinion suggests that even a minor transformation of a natural product might have rendered it patentable.³⁹ As discussed in Section I.B., isolating and purifying natural products is an example of a transformation that courts frequently deemed adequate to impart patent eligibility on otherwise ineligible natural products.

B. THE “PURIFIED AND ISOLATED” EXCEPTION TO THE PRODUCT OF NATURE DOCTRINE

For over a century, purified and isolated natural substances were deemed patent eligible “if the act of isolation render[s] [the substance] greatly more useful than the product in its natural state.”⁴⁰ In 1910, the Seventh Circuit upheld a patent covering “substantially pure” aspirin, acetylsalicylic acid in *Kuehmsted v. Farbenfabriken of Elberfeld Co.*⁴¹ Comparing the patented substance to another, previously disclosed yet less pure substance, the court held that, even “assuming that the compounds, chemically, are not different—that the two bodies are analytically the same,”⁴² substantially pure aspirin was patent eligible because “two substances, having the same chemical formula, may differ widely, as to impurities, upon qualitative analysis.”⁴³ Purified and isolated aspirin was patent eligible because it was “therapeutically different” from the impure form.⁴⁴

This line of reasoning informed Judge Learned Hand’s influential opinion in *Parke-Davis & Co. v. H.K. Mulford Co.*⁴⁵ Judge Hand upheld the patentability of purified adrenaline because it was “a new thing commercially and

38. *Id.*

39. *Id.*

40. Beauchamp, *supra* note 30, at 276. The earliest cases concerned what now would fall under § 102’s novelty requirement. *Id.* at 277–80 (discussing early cases in which the idea of novelty figured prominently).

41. *Kuehmsted v. Farbenfabriken of Elberfeld Co.*, 179 F. 701, 702, 704 (7th Cir. 1910). Aspirin is a derivative of salicylic acid, which itself was known to Hippocrates and is found naturally in willow bark. See *What is Aspirin? 100 Years of Aspirin*, ASPIRIN FOUND., <http://www.aspirin-foundation.com/what/100.html> (last visited Apr. 9, 2014).

42. *Kuehmsted*, 179 F. at 704.

43. *Id.* at 703–04.

44. *Id.* at 704.

45. *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95 (S.D.N.Y. 1911), *aff’d in part, rev’d in part* 196 F. 496 (2d Cir. 1912) (“Upon all the main fundamental questions we fully concur in Judge Hand’s reasoning and conclusions.”).

therapeutically” when compared with the naturally occurring salt form.⁴⁶ The purified chemical possessed new properties, which constituted a “distinction not in degree, but in kind” from adrenaline as found in nature.⁴⁷ Judge Hand then stated that, “even if [adrenaline] were merely an extracted product without change, there is no rule that such products are not patentable.”⁴⁸ The Court of Customs and Patent Appeals echoed this reasoning in *In re Merz*: “Th[e] general rule [that natural products cannot be patented] is a well-settled one, but like all other rules it has an exception. The exception is that if the process produces an article of such purity that it differs not only in degree but in kind it may be patentable.”⁴⁹

In *Funk Brothers Seed Co. v. Kalo Inoculant Co.*,⁵⁰ the Supreme Court addressed the patent eligibility of a composition of matter and held that a mixture of naturally occurring bacterial strains was patent ineligible because the mixture merely exhibited a law of nature. By combining three strains of mutually inhibitory bacteria in specific ratios, the patentee had produced a hitherto unknown combination that had useful properties in commercial agriculture. However, the Court held that the patentee had not “create[d] a state of inhibition or of noninhibition in the bacteria. Their qualities are the work of nature . . . [and thus] of course [were] not patentable.”⁵¹ The Court recognized the commercial benefits but held that the “aggregation of species fell short of invention within the meaning of the patent statutes,” since “[t]he qualities of these bacteria, like the heat of the sun, . . . are manifestations of laws of nature, free to all men and reserved exclusively to none.”⁵²

The *Funk Brothers* inoculant was determined to be patent ineligible as a law of nature, rather than as a natural product, and the Court only addressed a mixture of natural bacteria, rather than a purified natural product. Accordingly, in the first § 101 case after the 1952 Patent Act, the Fourth

46. *Id.* at 103, 115.

47. *Id.* at 103.

48. *Id.*

49. *In re Merz*, 97 F.2d 599, 600–01 (C.C.P.A. 1938) (invalidating a patent on naturally occurring ultramarine because the claimed product was “the same old ultramarine with the same old use”). Jurisprudence on the product of nature doctrine has been inconsistent and plagued with the recurrent conflation of subject matter eligibility, novelty, and nonobviousness issues. *See, e.g., In re Williams*, 171 F.2d 319 (C.C.P.A. 1948) (upholding a patent on the naturally occurring laevorotatory form of a lactone); *In re King*, 107 F.2d 618, 619–20 (C.C.P.A. 1939) (upholding a patent on Vitamin C); *Ex parte Berkman & Berkman*, 90 U.S.P.Q. 398, 400 (Pat. Off. Bd. of Appeals 1951) (invalidating patents on chlorophyll-containing extracts).

50. 333 U.S. 127 (1948).

51. *Id.* at 130.

52. *Id.* at 127, 130.

Circuit was not strictly bound by the *Funk Brothers* holding when it upheld a patent on purified Vitamin B12.⁵³ In *Merck & Co. v. Olin Mathieson Chemical Corp.*, the court held that “[t]here is nothing in the language of the [Patent] Act which precludes the issuance of a patent upon a ‘product of nature’ when it is a ‘new and useful composition of matter.’”⁵⁴ The court held that the purified product, which was “identical in chemical structure and function” to the natural product, nevertheless was “not the same as the old [composition of nature], but [was a] new and useful composition . . . entitled to the protection of the patent.”⁵⁵

The Court of Customs and Patent Appeals echoed this line of thought in *In re Bergstrom*,⁵⁶ where it reversed the Patent Office’s refusal to patent Prostaglandin E2 (“PGE₂”) and Prostaglandin E3 (“PGE₃”).⁵⁷ The Patent Office had reasoned that “inasmuch as the ‘claimed compounds are naturally occurring’ . . . they therefore ‘are not ‘new’ within the connotation of the patent statute.”⁵⁸ The court reversed the Patent Office’s application rejection, clarifying that “what appellants claim—pure PGE₂ and PGE₃—is not ‘naturally occurring.’”⁵⁹

Prior to the biotechnology revolution of the late twentieth century, a large body of law had established an inconsistently applied exception to the patent ineligibility of products of nature. But until *Myriad*, no appellate court had ever invalidated a claim covering a molecule, including a DNA molecule, under the product of nature doctrine.⁶⁰

53. *Merck & Co. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156 (4th Cir. 1958).

54. *Id.* at 161. The *Merck* court held the purified natural product to be patent eligible because, prior to the patent, B12 had been “unidentified and unknown” and because the natural product was “not known to contain the desired activity in even the slightest degree.” *Id.* at 163. Vitamin B12 treated pernicious anemia. The *Merck* court recognized the product’s “great therapeutic and commercial worth” as a factor to be considered in determining its patent eligibility. *See id.* at 164. For an interesting discussion of the influence of *Parke-Davis* on *Merck* and on twentieth-century adjudication of the product of nature doctrine, see Beauchamp, *supra* note 30, at 303–06.

55. *Merck*, 253 F.2d at 160, 161.

56. 427 F.2d 1394, 1397 (C.C.P.A. 1970).

57. Prostaglandin E2 and E3, naturally occurring hormones, are produced in the body and mediate a number of physiological effects. Clinically, PGE₂ induces labor, and PGE₃ inhibits tumor cell proliferation. *See, e.g.*, W.F. O’Brien, *The Role of Prostaglandins in Labor and Delivery*, 22 CLINICS IN PERINATOLOGY 973, 973 (1995).

58. Application of Bergstrom, 427 F.2d 1384, 1397 (C.C.P.A. July 16, 1970) (quoting *Ex parte Snell*, 86 U.S.P.Q. 496 (1950)).

59. *Id.* at 1401 (“[The claimed] compounds, as far as the record establishes, do not exist in nature in pure form, and appellants have neither merely discovered, nor claimed sufficiently broadly to encompass, what has previously existed in fact in nature’s storehouse, albeit unknown, or what has previously been known to exist.”).

60. *See Cui, supra* note 29.

C. THE PRODUCT OF NATURE DOCTRINE AS APPLIED TO
BIOTECHNOLOGY

The biotechnology industry uses living cells to synthesize useful molecules. It manipulates naturally occurring intracellular biochemical processes to create new molecules or to modify naturally occurring molecules.⁶¹ As such, these processes and products are especially likely to implicate the product of nature doctrine when biotechnology companies seek patent protection for their inventions and discoveries. Biotechnology is one of the world's most research-intensive industries; its companies invest up to fifty percent of their revenues in research. Biotechnology companies rely heavily on strong intellectual property protection because of these high research and development costs, as well as the low expense of product imitation.⁶² Since the Supreme Court's *Diamond v. Chakrabarty* decision in 1980,⁶³ the biotechnology industry generally has received patent protection from the USPTO and courts.

In *Chakrabarty*, the Supreme Court took up § 101 patent eligibility of “compositions of matter” for the first time under the 1952 Patent Act.⁶⁴ The patentee had genetically modified a bacterium by inserting synthetic DNA into its cytoplasm.⁶⁵ The Court held this bacterium to be an invention and therefore patent eligible: “[Chakrabarty’s] micro-organism plainly qualifies as patentable subject matter. His claim is not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity ‘having a distinctive name, character [and] use.’”⁶⁶ It later stated in dictum that “[h]ere, by contrast [to *Funk Brothers*], the patentee has produced a new bacterium with *markedly different* characteristics from any found in nature. . . . His discovery is not nature’s handiwork, but his own; accordingly it is patentable subject matter

61. *Biotechnology*, 6 THE COLUMBIA ENCYC. (2000).

62. Esteban Burrone, *Patents at the Core: The Biotech Business*, WORLD INTELL. PROP. ORG., http://www.wipo.int/sme/en/documents/patents_biotech_fulltext.html (last visited Apr. 3, 2014). This research expenditure compares to five percent of revenue in the chemical industry and thirteen percent in the pharmaceutical industry. *Id.*

63. *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

64. The *Chakrabarty* Court held only that living organisms were “compositions of matter” and thus comprised patent-eligible subject matter. *Id.* at 309–10.

65. The inserted DNA plasmid coded for enzymes that degrade crude oil. The transformed bacterium was useful in accelerating the natural processes by which bodies of water digest oil spills. *Id.* at 305.

66. 447 U.S. at 309–10 (quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887), a nineteenth-century tax case that used the quoted language to illuminate whether polished seashells were considered “manufactured” under the then-extant tax codes).

under § 101.”⁶⁷ The question before the *Chakrabarty* Court was whether living organisms were patent eligible, not the degree to which Chakrabarty’s bacterium differed from the naturally occurring bacterium into which the inventor had injected a plasmid.⁶⁸ The *Chakrabarty* Court did not rely on its “markedly different” characterization to establish the patent eligibility of the claimed invention, nor did it elucidate how to distinguish a “marked” difference from a mere difference.⁶⁹

Chakrabarty was the first Supreme Court § 101 case of the biotech age. It was interpreted as broadly supportive of DNA patents.⁷⁰ The USPTO’s policy of issuing gene patents since the early 1980s “rang in a period of liberal patentability based on the ‘isolation and purification’ doctrine.”⁷¹ Since then, the USPTO has issued up to “40,000 DNA-related patents, covering about 20 percent of the genes in the human genome.”⁷² It has also issued patents on isolated and purified proteins and on cell lines.⁷³

67. *Id.* at 308–10 (emphasis added).

68. *Id.* at 307. (“The question before us in this case is a narrow one of statutory interpretation requiring us to construe 35 U.S.C. § 101. . . . Specifically, we must determine whether respondent’s micro-organism constitutes a ‘manufacture’ or ‘composition of matter’ within the meaning of the statute.”).

69. Similarly, the *Myriad* Court, although apparently seeking to require a marked difference from a naturally occurring product, gives no guidance on how to make such a determination. *See infra* Section III.C, Part V. The USPTO, in contrast, does seek to provide its examiners with criteria for recognizing “significant[] differen[ces]” between such compositions. *See infra* Section IV.C.

70. “*Chakrabarty* represents . . . the patenting not only of living things but of genes as well. . . . *Chakrabarty* ushered in the genomics age.” KAREN F. GREIF & JON F. MERZ, CURRENT CONTROVERSIES IN THE BIOLOGIC SCIENCES: CASE STUDIES OF POLICY CHALLENGES FROM NEW TECHNOLOGIES 53 (2007).

71. Demers, *supra* note 30, at 8. The number of biotechnology patent applications in the United States rapidly increased after *Chakrabarty*: 18,695 applications were filed in 1996, compared to 47,473 applications in 2002. *See Gene Patents and Global Competition Issues: Protection of Biotechnology Under Patent Law*, GENETIC ENG’G & BIOTECH. NEWS (Jan. 1, 2006), <http://www.genengnews.com/keywordsandtools/print/1/11595>; *see also* Utility Examination Guidelines, 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001). The USPTO regulation states:

An isolated and purified DNA molecule . . . is eligible for a patent because (1) an excised gene is eligible for a patent as a composition of matter or as an article of manufacture because that DNA molecule does not occur in that isolated form in nature, or (2) synthetic DNA preparations are eligible for patents because their purified state is different from the naturally occurring compound.

Id.

72. Rogers, *supra* note 3.

73. *See generally* Vincent J. Filliben III, *Patent Law and Regenerative Medicine: A Consideration of the Current Law and Public Policy Concerns Regarding Upstream Patents*, 9 WAKE FOREST INTELL. PROP. L.J. 239 (2009).

Appellate jurisprudence regarding the USPTO's patent eligibility practices is sparse.⁷⁴ In general, the Federal Circuit has endorsed the USPTO's policy of broad patent eligibility of DNA molecules during the last two decades. In *Amgen, Inc. v. Chugai Pharmaceutical Co.*,⁷⁵ the Federal Circuit upheld a claim directed to a "purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin."⁷⁶ The district court had distinguished between the patentable "purified and isolated DNA sequence" and "the [naturally occurring] DNA sequence encoding human erythropoietin (EPO)," which it considered "a non-patentable natural phenomenon 'free to all men and reserved exclusively to none.'"⁷⁷ The Federal Circuit affirmed this interpretation: "[t]he subject matter of [the] claim [is] the novel purified and isolated sequence which codes for EPO."⁷⁸ In *Schering Corp. v. Amgen Inc.*,⁷⁹ the Federal Circuit upheld the district court's claim construction of a patent written on recombinant DNA molecules, "which code on expression for a polypeptide of the [gamma Interferon] type."⁸⁰ The trial court had held that "the claim language . . . refers to [either] a naturally occurring or non-naturally occurring DNA sequence."⁸¹

For the last two decades, the USPTO had issued patents for purified and isolated DNA molecules whose sequences corresponded to naturally occurring DNA and which were identified as coding for specific naturally occurring proteins. As discussed below, the USPTO's policy and the Federal Circuit's legal interpretation were consistent with the many significant chemical differences between naturally occurring chromosomal DNA, the biological repository of genomic information, and synthetic isolated DNA, the molecules biochemists use to perform the types of genetic testing that some of Myriad's contested patents covered.

74. Neither of the two immediately following Federal Circuit cases directly addressed § 101 patent eligibility. Prior to *Myriad*, the Federal Circuit had not been called on to answer the question of DNA patents' § 101 eligibility, since the cases it saw were decided on other grounds.

75. 927 F.2d 1200 (Fed. Cir. 1991). This opinion was written by Judge Lourie, who twice voted to uphold the patent eligibility of Myriad's gDNA and cDNA claims.

76. *Id.* at 1202, 1204, 1206. Note also that § 101 eligibility was not at issue on appeal in *Chugai*.

77. *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, No. 87-2617-Y, 1989 WL 169006 (D. Mass. Dec. 11, 1989) *aff'd in part, vacated in part*, 927 F.2d 1200 (Fed. Cir. 1991) (quoting *Diamond v. Chakrabarty*, 447 U.S. 303 (1980)).

78. *Chugai*, 927 F.2d at 1206. Note that the *Chugai* court's determination turned on the question of novelty, not § 101 patent eligibility.

79. 222 F.3d 1347, 1348 (Fed. Cir. 2000). Note that, like *Chugai*, *Schering* did not present the Federal Circuit with a question of § 101 patent eligibility.

80. U.S. Patent No. 4,530,901 (filed Feb. 4, 1980).

81. *Schering Corp. v. Amgen Inc.*, 18 F. Supp. 2d 372, 400 (D. Del. 1998).

II. CHEMICAL PROPERTIES OF DNA MOLECULES

The patent eligibility of a purified and isolated molecule depends on a comparison of the molecule's structure and uses to those of the molecule as it occurs in nature. The *Myriad* Court seems to have indicated that the isolated and purified molecule must be "markedly different" from its naturally occurring homologue to be patent eligible under § 101.⁸² This Part explores some of the fundamental differences between chromosomal DNA and isolated DNA molecules, which inform how DNA exists in a natural state and what happens to that same DNA after it is manipulated in a laboratory.⁸³

A. CHROMOSOMAL DNA

Genomic DNA contains all of an organism's genetic information.⁸⁴ The human genome consists of large DNA molecules called chromosomes. Each human cell has forty-six chromosomes, which are made partially of DNA but also contain large amounts of proteins and RNA.⁸⁵ Chromosomal DNA contains genes, discrete regions that encode RNA molecules. Genes, in turn, typically consist of numerous coding sequences (exons), noncoding sequences (introns), and regulatory sequences that control gene expression. Most chromosomal DNA does not code for any specifically known protein,

82. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc. (Myriad IV)*, 133 S. Ct. 2107, 2117 (2013) (citing *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980)).

83. See *Chromosomal DNA and Its Packaging in the Chromatin Fiber*, in B. ALBERTS ET AL., *MOLECULAR BIOLOGY OF THE CELL* (4th ed. 2002). The DNA in the nucleus of a eukaryotic cell exists primarily in the form of chromosomes, which are complex structures that consist mainly of DNA, RNA, and proteins. Chromosomal DNA is the DNA within one of these complex structures. Although there are other types of naturally occurring biologically active DNA, this Part contrasts only chromosomal DNA with isolated and purified DNA because the *Myriad* Court's certified question was limited to "human genes" and because the patents in suit were written on isolated DNA.

84. Each court that ruled in the *Myriad* case provided an excellent summary of the structure of DNA and of the basic processes by which DNA is transcribed to an RNA molecule, which in turn is modified and then translated into a protein through natural biochemical mechanisms. See *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office (Myriad I)*, 702 F. Supp. 2d 181, 192–99 (S.D.N.Y. 2010); *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office (Myriad III)*, 689 F.3d 1303, 1310–13 (Fed. Cir. 2012); *Myriad IV*, 133 S. Ct. at 2111–12.

85. In fact, human chromosomes are only approximately twenty percent DNA by weight. See Norman P. Salzman, Dorothy E. Moore & John Mendelsohn, *Isolation and Characterization of Human Metaphase Chromosomes*, 56 *PROC. NAT'L ACAD. SCI. USA* 1449, 1453 (1966). RNA and proteins compose fifteen percent and sixty-six percent, respectively, of human chromosomes. See *id.*

although much of this noncoding DNA affects the structure of chromosomal DNA and regulates gene expression.⁸⁶

Chromosomal DNA's functional structure consists of more than the linear sequence of its familiar guanine, adenine, thymine, and cytosine base pairs (frequently abbreviated as "G," "A," "T," and "C," respectively), which is termed its primary structure. It also includes higher levels of structure such as the pairing of bases from adjacent strands (chromosomal DNA's secondary structure), DNA's well-known double helix (its tertiary structure), and chromosomal DNA's association with cellular proteins and RNA, as well as its modification by methyl, acetyl, and phosphate groups (its quaternary structure).⁸⁷

This quaternary structure results in chromosomal DNA's being folded and twisted in specific and functionally important ways. Segments of chromosomal DNA wrap around a core of eight histone proteins, forming a functional chromosomal unit of DNA called a nucleosome.⁸⁸ This structure is significant because the uncoiled DNA molecule is too large to fit inside a cell's nucleus. The histone proteins, through their interactions with DNA and the smaller chemical substituents (such as the methyl, acetyl, or phosphate groups listed above), increase or decrease the rate at which genes are expressed, aid in the replication of chromosomal DNA required for cell division, and play a role in the repair of damaged or defective DNA.⁸⁹

B. ISOLATED DNA

DNA isolation involves many complex chemical processes. A biochemist begins by extracting chromosomal DNA from a blood or tissue sample, cutting the large molecules into numerous short fragments with enzymes, and then chemically modifying these fragments to make recombinant DNA vectors.⁹⁰ These vectors are inserted into bacterial or yeast cells, which are placed in a culture where they reproduce asexually. The cultured cells'

86. See Frederick Roth et al., *Finding DNA Regulatory Motifs Within Unaligned Noncoding Sequences Clustered by Whole-Genome mRNA Quantitation*, 16 NATURE BIOTECHNOLOGY 939, 939 (1998).

87. See Leslie Pray, *Discovery of DNA Structure and Function: Watson and Crick*, 1 NATURE EDUC. 100 (2008), available at <http://www.nature.com/scitable/topicpage/discovery-of-dna-structure-and-function-watson-397>; Leonide Sipski & Thomas Wagner, *Probing DNA Quaternary Ordering with Circular Dichroism Spectroscopy: Studies of Equine Sperm Chromosomal Fiber*, 16 BIOPOLYMERS 573, 581–82 (1977).

88. See Srinivas Chakravarthy et al., *Structure and Dynamic Properties of Nucleosome Core Particles*, 579 FED'N OF EUR. BIOCHEMICAL SOCIETIES LETTERS 895, 895–97 (2005).

89. See *id.*

90. HARVEY LODISH ET AL., MOLECULAR CELL BIOLOGY 176 (6th ed. 2008).

multiplication causes the inserted DNA vectors to replicate inside the host cells.⁹¹ Many generations of reproduction create a collection of cells, each containing fragments of recombinant DNA corresponding to the DNA sequences initially extracted from the target cells' chromosomal DNA.⁹² This collection of bacteria or yeast is termed a "DNA library" because it contains numerous synthetic DNA molecules whose sequences correspond to portions of the target cells' chromosomal DNA.⁹³

After creating a DNA library, a biochemist can synthesize a large amount of a particular DNA sequence by identifying a specific cell that contains the desired DNA fragment and then causing that cell to replicate.⁹⁴ This process results in a culture of identical cells containing large amounts of identical recombinant DNA fragments.⁹⁵ These isolated fragments are typically much shorter than the chromosomes from which they initially were extracted. They also contain only a small portion of the DNA and of the genetic information that the chromosome contained, and they are not associated with the same RNA, proteins, and chemical substituents as chromosomal DNA.⁹⁶

C. FUNCTIONAL DIFFERENCES BETWEEN CHROMOSOMAL AND ISOLATED DNA MOLECULES

Because of these structural differences between isolated DNA fragments and chromosomal DNA, isolated DNA does not possess many of the properties of chromosomal DNA discussed above.⁹⁷ Once extracted from the cellular milieu and removed from the intracellular machinery, which enable these properties, isolated DNA is much smaller than the chromosomes from which it was derived.⁹⁸ It is not self-replicating, and it does not possess the higher-level structure of chromosomes.⁹⁹ It is not

91. *Id.* at 178.

92. *Id.* at 179.

93. *Id.* For a more detailed description of the process of creating gDNA and cDNA libraries, see generally Steven R. Head et al., *Library Construction for Next-Generation Sequencing: Overviews and Challenges*, 56 BIOTECHNIQUES 61, 62–65 (2014); Michael O'Connor, Mark Peifer & Welcome Bender, *Construction of Large DNA Segments in Escherichia Coli*, 244 SCI. 1307, 1307–12 (1989).

94. LODISH ET AL., *supra* note 90, at 181.

95. *Id.* at 182.

96. *Id.*

97. *See supra* Section II.A.

98. *See Chromosomal DNA and Its Packaging in the Chromatin Fiber*, in BRUCE ALBERTS ET AL., *MOLECULAR BIOLOGY OF THE CELL* (4th ed. 2002), available at <http://www.ncbi.nlm.nih.gov/books/NBK26834/>.

99. *See generally* Stephen Cederbaum et al., *Recombinant DNA in Medicine*, 141 W. J. MED. 210, 210–22 (1984).

associated with histone proteins or with other chemical substituents, which regulate its translation into RNA.¹⁰⁰ Most isolated DNA molecules do not possess the “promoter” regions that facilitate the initiation of RNA translation. Even if they were reinserted into a human nucleus, most isolated DNA molecules would neither be expressed as proteins nor passed on to succeeding generations of the host cells.¹⁰¹ In the cell nucleus, these molecules would lack almost all of the biologically important properties of the chromosomal DNA from which they were isolated.

However, the biochemists who isolate DNA do not do so in order to replicate these biologically important properties. They do so precisely because the isolation of chromosomal DNA creates new molecules that, having been shortened and stripped from the histones and other structural elements of chromosomes, have new properties that are useful in the laboratory.¹⁰² Perhaps most importantly, isolated DNA, unlike chromosomal DNA, can be used as a template for the extracellular synthesis of identical molecules of isolated DNA.¹⁰³ Just as isolated DNA is extremely unlikely to be expressed or replicated inside a cell’s nucleus, chromosomal DNA cannot be replicated in the laboratory.

Isolated DNA, not chromosomal DNA, is what biochemists use to perform all of the diagnostic and synthetic processes now associated with the biotechnology industry. Isolated DNA can be used to synthesize DNA hybridization probes, which in turn can be used to detect a specific DNA sequence in a sample, a necessary step for genetic testing and forensic DNA

100. See S.A. Miller, D.D. Dykes & H.F. Polesky, *A Simple Salting Out Procedure for Extracting DNA from Human Nucleated Cells*, 16 NUCLEIC ACIDS RES., 1215, 1215 (1988).

101. See Geoffrey Cooper, *Recombinant DNA*, in THE CELL: A MOLECULAR APPROACH (2d ed. 2000), available at <http://www.ncbi.nlm.nih.gov/books/NBK9950/>.

102. Michael O’Conner, Mark Peifer, and W. Bender, *Construction of Large DNA Segments in Escherichia coli*, 244 SCIENCE 1307, 1307 (1989).

103. It is possible to amplify isolated DNA outside of the cell, creating multiple identical copies of the isolated DNA using a process called a polymerase chain reaction. Although this process is similar to the natural process whereby chromosomal DNA is replicated in anticipation of cell division, it is the only process that enables replication of isolate human DNA. Human chromosomes are simply too long to synthesize outside the body using current technology, disregarding the fact that such synthesis would not duplicate the higher level structure imposed by the histone proteins, methylation, acetylation, etc. See Coco Ballantyne, *Longest Piece of Synthetic DNA Yet*, SCI. AM. (Jan 24, 2008), <http://www.scientificamerican.com/article/longest-piece-of-dna-yet/?print=true> (describing the synthesis of a 582,000 base pair bacterial genome and comparing it to the shortest human chromosome, chromosome 21, which contains forty-eight million nucleotides).

identification.¹⁰⁴ It can be directly used in the synthesis of DNA vectors, which can be inserted into bacteria or yeast in order to cause the host cell to express the foreign DNA.¹⁰⁵ Isolated DNA can be used as a direct template to create recombinant DNA, which is a prerequisite for the laboratory synthesis of numerous useful and commercially important biochemicals.¹⁰⁶ Because of the many structural differences between chromosomal and isolated DNA, chromosomal DNA cannot be used for any of the immediately preceding purposes.

The *Myriad* Court considered the patent eligibility of two types of synthetic isolated DNA: gDNA and cDNA. The coding regions of these two categories of molecules are chemically indistinguishable but are derived from different naturally occurring templates.¹⁰⁷ gDNA, which the Court ultimately held patent ineligible, comes from DNA libraries composed of fragments of chromosomal DNA.¹⁰⁸

cDNA, ultimately held patent eligible, is synthesized from a different starting material. cDNA synthesis, rather than employing digested DNA as the initial template for the polymerase chain reaction, starts with messenger RNA (“mRNA”) molecules.¹⁰⁹ cDNA synthesis begins with the extraction of mRNA from the body. The biochemist then synthesizes a complementary strand of DNA (hence the “c” in “cDNA”) from the mRNA, before employing the same steps as described above for the synthesis of gDNA.

104. See Marilena Aquino de Moro, *Probe Design, Production, and Applications*, in *MEDICAL BIOMETHODS HANDBOOK* 13–23 (John Walker & Ralph Rapley eds., 2005).

105. This was the process by which Chakrabarty used synthetic DNA to genetically modify his bacterium. *Diamond v. Chakrabarty*, 447 U.S. 303, 305 (1980).

106. These biochemicals include recombinant human hormones, recombinant blood clotting factors, and recombinant antiviral vaccines. Examples of each of these categories of molecules have been issued patents. See, e.g., U.S. Patent No. 4,658,021 (filed Sept. 25, 1984) (patenting human growth hormone); U.S. Patent No. 4,632,981 (filed Feb. 1, 1985) (patenting human antithrombin III); U.S. Patent No. 8,506,968 (filed Dec. 28, 2009) (patenting SARS vaccine).

107. See *Ass’n for Molecular Pathology v. Myriad Genetics, Inc. (Myriad IV)*, 133 S. Ct. 2107, 2119 (2013).

108. See *id.* at 2112.

109. See *id.* mRNA forms through the body’s natural biochemical processes, using chromosomal DNA as its template. *Messenger RNA*, GENETICS HOME REFERENCE, <http://ghr.nlm.gov/glossary=messengerrna> (last visited June 3, 2014). The mRNA molecules leave the cell nucleus, where they in turn are used as templates for protein synthesis. *Id.*

III. THE *MYRIAD* CASE: IS ISOLATED DNA PATENT ELIGIBLE?

Myriad was an atypical patent infringement case. It was the first patent case filed by the ACLU in its ninety-year history.¹¹⁰ It was the first diagnostic gene patent infringement case adjudicated by a U.S. court.¹¹¹ It was not filed by a patent holder who sought to prevent infringement, but rather by a public interest group seeking declaratory judgment on behalf of “an assortment of [twenty] medical organizations, researchers, genetic counselors, and patients.”¹¹² Out of *Myriad*’s twenty-seven patents and over five hundred claims involving the BRCA1/2 genes and methods of genetic testing,¹¹³ the plaintiffs contested only fifteen claims in seven patents.¹¹⁴ The plaintiffs characterized these patents as claiming natural human genes, natural human genes with mutations, methods of looking for mutations in natural human genes, and thoughts or abstract ideas.¹¹⁵ The plaintiffs asserted that the challenged claims encompassed “products of nature” and thus were invalid under the Patent Clause and 35 U.S.C. § 101.¹¹⁶ They also sought to invalidate the patents on the grounds that they violated the First and Fourteenth Amendments of the Constitution.¹¹⁷

The Supreme Court ultimately held that isolated gDNA is not patent eligible under § 101 because “separating [a] gene from its surrounding genetic

110. See Brendan L. Smith, *Wrangling Genes*, ABA J. (July 1, 2009, 10:10 PM), http://www.abajournal.com/magazine/article/wrangling_genes.

111. See Robert Cook-Deegan & Christopher Heaney, *Patents in Genomics and Human Genetics*, 11 ANN. REV. GENOMICS & HUMAN GENETICS 383, 397 (2010).

112. Ass’n for Molecular Pathology v. U.S. Patent & Trademark Office (*Myriad II*), 653 F.3d 1329, 1333 (Fed. Cir. 2011).

113. See Press Release, Myriad Genetics, Supreme Court Upholds Myriad’s cDNA Patent Claims (June 13, 2013), available at http://files.shareholder.com/downloads/MYGN/2967288803x0x670662/dd23be22-ca26-4919-b7e1-64630b9e47c9/MYGN_News_2013_6_13_General.pdf.

114. Plaintiffs contested the following claims: U.S. Patent No. 5,747,282 (filed Jun. 7, 1995); U.S. Patent No. 5,693,473 (filed Jun. 7, 1995); U.S. Patent No. 5,709,999 (filed Jun. 7, 1995); U.S. Patent No. 5,710,001 (filed Jun. 7, 1995); U.S. Patent No. 5,753,441 (filed Jan. 5, 1996); U.S. Patent No. 5,837,492 (filed Apr. 26, 1996); and U.S. Patent No. 6,033,857 (filed Mar. 20, 1998).

115. Complaint at 20–24, Ass’n for Molecular Pathology v. U.S. Patent & Trademark Office, 702 F. Supp. 2d 181 (S.D.N.Y. 2009) (No. 09 Civ. 4515).

116. *Id.* at 1, 3, 29.

117. *Id.* at 29 (“All of the challenged claims represent patents on abstract ideas or basic human knowledge and as such are unconstitutional under the First and Fourteenth Amendments to the United States Constitution.”).

material is not an act of invention.”¹¹⁸ In contrast, the Court found that isolated cDNA does constitute patent-eligible subject matter because “cDNA is not a ‘product of nature.’”¹¹⁹ The following summarizes the findings and rationales of the four decisions that were handed down by the three courts that took up this matter, focusing on their interpretations of the product of nature doctrine and the purified and isolated exception.

A. MYRIAD IN THE DISTRICT COURT: DNA AS INFORMATION

Since *Chakrabarty*, neither the Supreme Court nor the Federal Circuit has distinguished DNA from other chemicals. In assessing the patent eligibility of molecules other than DNA, the Federal Circuit has focused on the molecular structure and properties of the claimed molecules.¹²⁰ The USPTO has routinely issued patents on DNA sequences since 1990, reasoning:

Like other chemical compounds, DNA molecules are eligible for patents when isolated from their natural state and purified or when synthesized in a laboratory from chemical starting materials. A patent on a gene covers the isolated and purified gene but does not cover the gene as it occurs in nature.¹²¹

But in a 146-page opinion, Judge Sweet of the Southern District of New York held that Myriad’s patents on isolated human DNA were invalid because they read on products of nature; further, its diagnostic and analytical techniques consisted of abstract ideas and thus were written on patent-ineligible subject matter as well.¹²²

Judge Sweet used the construct of DNA as information as the “legal hook”¹²³ to distinguish a generation of Federal Circuit precedent. Citing

118. *Ass’n for Molecular Pathology v. Myriad Genetics, Inc. (Myriad IV)*, 133 S. Ct. 2107, 2117 (2013).

119. *Id.* at 2119.

120. The Federal Circuit’s analysis of Myriad’s composition claims likewise emphasized molecular structure and properties. *See infra* Section IV.B.2.

121. Utility Examination Guidelines, 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001).

122. *Ass’n for Molecular Pathology v. U.S. Patent & Trademark Office (Myriad I)*, 702 F. Supp. 2d 181, 184–85 (S.D.N.Y. 2010).

123. *See* Conley & Makowski, *supra* note 30, at 307–08 (arguing for a reinvigoration of the product of nature doctrine). Judge Sweet’s opinion built on the logic of Conley and Makowski’s article. *See Myriad I*, 702 F. Supp. 2d at 185 (“DNA represents the physical embodiment of biological information, distinct in its essential characteristics from any other chemical found in nature. It is concluded that DNA’s existence in an ‘isolated’ form alters neither this fundamental quality of DNA as it exists in the body nor the information it encodes.”); *see also id.* at 198 (“Because it is derived from mRNA, a cDNA molecule represents an exact copy of one of the protein coding sequences encoded by the original

“DNA’s unique qualities as a physical embodiment of information,” the district court disagreed with the USPTO’s position on the patent eligibility of isolated DNA and invalidated Myriad’s patents on both gDNA and cDNA.¹²⁴ The court held that “[g]enes and the information represented by human gene sequences are products of nature universally present in each individual.”¹²⁵ Citing the above-mentioned dictum from *Chakerabarty*,¹²⁶ the court stated that neither Myriad’s isolated gDNA nor its cDNA was “markedly different” from a product of nature.¹²⁷ The court held, therefore, that none of the composition claims were valid under § 101.¹²⁸

The district court also invalidated Myriad’s process patents regarding testing for mutations in the BRCA1 and BRCA2 genes.¹²⁹ It held that Myriad’s claimed comparisons of DNA sequences were “abstract mental processes,” which therefore “also constitute[d] unpatentable subject matter under §101.”¹³⁰ It invalidated Myriad’s claimed process for determining the efficacy of potential cancer chemotherapeutic agents through cell cultures utilizing recombinant DNA technology, holding that the last process sought “to patent a basic scientific principle” and was therefore ineligible for patent protection.¹³¹ Myriad appealed the matter to the Court of Appeals for the Federal Circuit.

B. MYRIAD AT THE FEDERAL CIRCUIT: DNA IS LIKE EVERY OTHER MOLECULE

Myriad’s patents were evaluated twice by the Federal Circuit, as the Supreme Court vacated the Federal Circuit’s first judgment and remanded the case for further proceedings in light of *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*¹³² Both times, the same three-judge Federal Circuit panel ruled in the same way, reversing the district court’s ruling in part and

genomic DNA. . . . cDNA contains the identical protein coding informational content as the DNA in the body, even though differences exist in its physical form.”).

124. *Myriad I*, 702 F. Supp. 2d at 229, 181.

125. *Id.* at 229.

126. *See supra* note 67 and accompanying text.

127. *Myriad I*, 702 F. Supp. 2d at 194.

128. *Id.* at 229–30, 232.

129. *Id.* at 185.

130. *Id.*

131. *Id.* at 238.

132. 132 S. Ct. 1289 (2012). In *Prometheus*, the Court invalidated biotechnology patent claims which “involve[d] [only the application of] well-understood, routine, conventional activity.” *Id.* at 1294.

affirming it in part.¹³³ The court upheld patents on both types of isolated DNA (gDNA and cDNA), as well as Myriad's process claims for screening potential cancer therapeutics.¹³⁴ It affirmed the lower court's invalidation of Myriad's method claims for "comparing" or "analyzing" BRCA sequences as abstract mental processes but upheld Myriad's claims teaching methods for screening cancer therapeutics.¹³⁵

The Federal Circuit relied on *Chakrabarty*¹³⁶ and *Funk Brothers*¹³⁷ as the relevant framework for determining the patent eligibility of isolated DNA molecules under § 101 in light of the product of nature doctrine. The Federal Circuit held that "[t]he distinction, therefore, between a product of nature and a human-made invention for purposes of § 101 turns on a change in the claimed composition's identity compared with what exists in nature."¹³⁸ Writing for the court, Judge Lourie, a Ph.D. organic chemist, stated that the act of cleaving isolated gDNA from a naturally occurring DNA molecule creates an "independent molecular species" since "a covalent bond is the defining boundary between one molecule and another."¹³⁹ Thus, isolated gDNA is chemically distinct from naturally occurring DNA. It is not a product of nature and therefore is patent eligible. The Federal Circuit explicitly rejected the DNA-as-information formulation adopted by the district court and urged by the plaintiffs, but it recognized that this formulation could facilitate challenges to the validity of gDNA patents or method patents tied to the genome on other grounds, including nonobviousness.¹⁴⁰ Myriad's claimed inventions were held to be patent

133. Both times, each judge ruled in the same way on each of the four broad questions: patent eligibility of (1) isolated gDNA, (2) cDNA, (3) Myriad's BRCA comparison and analysis methods, and (4) Myriad's chemotherapeutic agent efficacy analysis method). See *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office (Myriad III)*, 689 F.3d 1303 (Fed. Cir. 2012); *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office (Myriad II)*, 653 F.3d 1329 (Fed. Cir. 2011).

134. *Myriad III*, 689 F.3d at 1332, 1337; *Myriad II*, 653 F.3d at 1350, 1357.

135. *Myriad III*, 689 F.3d at 1335; see also *Myriad II*, 653 F.3d at 1357.

136. *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

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

138. *Myriad II*, 653 F.3d at 1351.

139. *Id.* at 1352.

140. The Federal Circuit stated:

Adopting this approach, the district court disparaged the patent eligibility of isolated DNA molecules because their genetic function is to transmit information. We disagree, as it is the distinctive nature of DNA molecules as isolated compositions of matter that determines their patent eligibility rather than their physiological use or benefit. Uses of chemical substances may be relevant to the non-obviousness of these substances or to method claims embodying those uses. . . . The claimed isolated DNA molecules

eligible because “Myriad’s claimed isolated DNAs exist in a distinctive chemical form—as distinctive chemical molecules—from DNAs in the human body.”¹⁴¹

C. *MYRIAD* IN THE SUPREME COURT: SPLITTING THE BABY

The Supreme Court granted certiorari on one issue: “Are human genes patentable?”¹⁴² Thus, it reexamined only the patent eligibility of isolated DNA. Unlike the two lower courts, the Supreme Court distinguished between two types of isolated DNA, gDNA and cDNA. It unanimously held (1) that isolated gDNA “is a product of nature and not patent eligible merely because it has been isolated” from the “surrounding genetic material,”¹⁴³ and (2) that cDNA is a “new and useful . . . composition of matter” and thus is patentable under § 101.¹⁴⁴ In rejecting the patent eligibility of isolated gDNA molecules, the Supreme Court endorsed the district court’s DNA-as-information paradigm: “Myriad’s claims are simply not expressed in terms of chemical composition. . . . Instead, [they] focus on the genetic information encoded in the . . . genetic *sequence*, not with the specific chemical composition of a particular molecule.”¹⁴⁵

The Court cited *Prometheus* regarding the unpatentability of “[l]aws of nature, natural phenomena, and abstract ideas” and determined that the isolated gDNA molecules Myriad claimed were unpatentable products “of nature,” rather than patent-eligible products “of invention.”¹⁴⁶ It held that “Myriad did not create or alter . . . the BRCA1 and BRCA2 genes. . . . Instead, Myriad’s principal contribution was uncovering the [genes’] precise location[s] and genetic sequence[s].”¹⁴⁷ The Court ruled that Myriad’s patents did not define a “new and useful . . . composition of matter”¹⁴⁸ “with markedly different characteristics from any found in

are distinct from their natural existence as portions of larger entities, and their informational content is irrelevant to that fact. . . . [G]enes are in fact materials having a chemical nature and, as such, are best described in patents by their structures rather than their functions.

Id. at 1353.

141. *Id.* at 1351.

142. Order Granting Petition for Writ of Certiorari, *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 694, 695 (2012) (mem).

143. *Ass’n for Molecular Pathology v. Myriad Genetics, Inc. (Myriad IV)*, 133 S. Ct. 2107, 2111, 2120 (2013).

144. *Id.* at 2116, 2119.

145. *Id.* at 2118.

146. *Id.* at 2116–17.

147. *Id.* at 2116.

148. *Id.* (citing 35 U.S.C. § 101 (2012)).

nature.”¹⁴⁹ Rather, it found that Myriad’s patent descriptions primarily had detailed the iterative process of discovery by which Myriad narrowed the possible locations for the gene sequences that it sought.¹⁵⁰

The Court rejected the Federal Circuit’s analysis of gDNA’s patent eligibility, which had focused on the breaking of covalent bonds as the step whereby a new chemical moiety—and thus a “new . . . composition of matter”—had been created.¹⁵¹ It held instead that “Myriad’s claims [are not] saved by the fact that isolating DNA from the human genome severs chemical bonds.”¹⁵² The Court found gDNA too similar to naturally occurring chromosomal DNA to be patent eligible, since it consists of the same nucleotide sequence and carries the same genetic information.¹⁵³ The Court distinguished Myriad’s isolated gDNA molecules, which “existed in nature before Myriad found them,”¹⁵⁴ from the patentable bacteria in *Chakrabarty*, which possessed “markedly different characteristics from any found in nature.”¹⁵⁵ It likened Myriad’s possibly “[g]roundbreaking, innovative, or even brilliant discovery”¹⁵⁶ to the patent-ineligible discovery described in *Funk Brothers*, which “was not patent eligible because the patent holder did not alter the bacteria in any way.”¹⁵⁷

The Court’s analysis of cDNA was brief and consistent with the Federal Circuit’s ruling: cDNA “is distinct from the DNA from which it was derived. As a result, cDNA is not a ‘product of nature’ and is patent eligible under §101.”¹⁵⁸ The natural process that synthesizes mRNA using a

149. *Id.* at 2117 (citing *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980)).

150. *Id.* at 2117–18.

151. 35 U.S.C. § 101 (2012).

152. *Myriad IV*, 133 S. Ct. at 2118.

153. *Id.* at 2116–18.

154. *Id.* at 2116.

155. *Id.* at 2117 (citing *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980)).

156. *Id.* at 2117.

157. *Id.* (citing *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 132 (1948)).

158. *Id.* at 2119. Note that Claim 6 of the ’282 patent claims any isolated cDNA “having at least 15 nucleotides of the DNA” of the isolated cDNA specified in SEQ ID NO:1, where this abbreviation refers to a sequence of 5914 nucleotides that comprises a “composite full length BRCA1 cDNA.” *Id.*; see also U.S. Patent No. 5,747,282 (filed June 7, 1995). The Court here appears to exclude from patentability isolated cDNAs that arise from a single exon, possibly because these cDNAs would possess identical sequences to unpatentable isolated gDNA. See *Myriad IV*, 133 S. Ct. at 2119. However, in the case of BRCA1, one exon (exon 11) contains more than three thousand nucleotides. Thus, the ’282 patent claims millions of cDNA molecules (up to over 3000 base pairs long), which apparently satisfy the Court’s “very short series of DNA” criterion. See Deng Chu-Xia, *BRCA1: Cell Cycle Checkpoint, Genetic Instability, DNA Damage Response and Cancer Evolution*, 34 NUCLEIC ACIDS RES. 1416, 1417 (2006) (mentioning exons longer than one thousand base pairs); David Favy et al., *Real-Time PCR Quantification of Full-Length and Exon 11*

chromosomal DNA template generally involves the removal of some areas of the mRNA that are homologous to portions of the original DNA. Therefore, the laboratory process that creates “a cDNA sequence from mRNA results in an exons-only molecule that is not naturally occurring.”¹⁵⁹ The Court determined that cDNA differs from chromosomal DNA in its nucleotide sequence and, therefore, in its informational content. It held these differences adequately inventive for patent eligibility: “cDNA is not a ‘product of nature’ and is patent eligible under § 101.”¹⁶⁰

Despite the apparent clarity of the Court’s ruling, a number of ambiguities arise when the decision is examined closely. First among these is the inconsistent manner in which the Court characterizes gDNA. The opinion begins by holding “that a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated.”¹⁶¹ But after distinguishing the inventiveness of Chakrabarty’s patent-eligible bacteria from Myriad’s claimed invention,¹⁶² the Court states that “Myriad’s claims [are not] saved by the fact that isolating DNA from the human genome severs chemical bonds and *thereby creates a nonnaturally occurring molecule.*”¹⁶³

The Court explains this apparent contradiction by reference to the DNA-as-information paradigm first brought into the § 101 analysis by Judge Sweet: “Myriad’s claims are simply not expressed in terms of chemical composition. . . . Instead, the claims understandably focus on the genetic information encoded in the BRCA1 and BRCA2 genes.”¹⁶⁴ The opinion then seemingly ignores the fact that Myriad’s patent claims are written on more

Spliced BRCA1 Transcripts in Human Breast Cancer Cell Lines, 274 BIOCHEMICAL & BIOPHYSICAL RES. COMM. 73, 75 (2000) (mentioning BRCA1 exons longer than one thousand base pairs).

159. *Myriad IV*, 133 S. Ct. at 2119.

160. *Id.* Note that the Court ignores the fact that, when analyzed with the same degree of scientific scrutiny with which it considers gDNA’s similarities to chromosomal DNA, cDNA is just as chemically homologous to and informationally identical with naturally occurring mRNA.

161. *Id.* at 2111. This characterization of gDNA seems to beg the question of patentability and to contradict the Court’s characterization of isolated gDNA as “nonnaturally occurring.”

162. *Id.* at 2117 (“In this case, by contrast, Myriad . . . found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention.”).

163. *Id.* at 2118 (emphasis added).

164. *Id.* at 2118. As seen in Section IV.B.2, *supra*, the language used by Myriad to claim DNA molecules conforms with standard patent claiming language since the early 1990s.

than one quadrillion specific and unique molecules, not on the information content of the BRCA genes.¹⁶⁵

If the patents depended upon the creation of a unique molecule, then a would-be infringer could arguably avoid at least Myriad's patent claims on entire genes . . . by isolating a DNA sequence that included both the BRCA1 or BRCA2 gene and one additional nucleotide pair. . . . But Myriad obviously would resist that outcome because its claim is concerned primarily with the information contained in the genetic *sequence*.¹⁶⁶

Myriad located, sequenced, and cloned the BRCA genes to be able to sell tests that inform people of their risks of contracting certain forms of cancer.¹⁶⁷ However, Myriad's DNA patents were written on the specific molecules through which that information is transmitted, not on the sequences of As, Ts, Gs, and Cs through which scientists communicate that information.¹⁶⁸

Whereas the *Myriad* Court's scientific analysis appears to be inconsistent, its legal analysis of patent eligibility seems superficial, citing no case whose outcome was determined by judicial interpretation of the product of nature doctrine. The opinion substantively refers to only three prior patent cases: *Prometheus*, *Chakrabarty*, and *Funk Brothers*.¹⁶⁹ The Court cites *Prometheus* in a prefatory manner to establish the "important implicit exception"¹⁷⁰ to § 101's inclusive language regarding patent-eligible subject matter, which renders "[l]aws of nature, natural phenomena, and abstract ideas . . . not

165. Brief of Eric S. Lander as Amicus Curiae in Support of Neither Party at 9, *Myriad IV*, 133 S. Ct. 2107 (2013) (No. 12-398) ("In total, the claims cover more than *one quadrillion* distinct fragments from chromosome 17.').

166. *Myriad IV*, 133 S. Ct. at 2118. The Court's holding in *Myriad* is strongly informed by its conception that Myriad's patents attempt to exclude others from using information or laws of nature. As discussed in Part II, none of Myriad's genetic tests requires the use of "entire genes," and the Court's description of the information transfers during intranuclear molecular processes incompletely reflects the current state of molecular biology. *See supra* Part II.

167. *BRCA Analysis: The Value of Hereditary Cancer Testing*, MYRIAD GENETICS, <https://myriad.com/products/bracanalysis/> (last visited May 25, 2014).

168. The '282 patent contains twenty claims. The first seven are written on specific isolated DNA molecules; the remaining thirteen are written on various molecules, transformed cells, methods, and testing kits. Not one of the twenty claims includes the word "information."

169. *See Myriad IV*, 133 S. Ct. at 2116–19 (Part II of the opinion, relying almost exclusively upon *Mayo Collaborative Servs. v. Prometheus Labs.*, 132 S. Ct. 1289 (2012), *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), and *Funk Bros. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948)).

170. *Myriad IV*, 133 S. Ct. at 2116 (citing *Prometheus*, 132 S. Ct. at 1293).

patentable.”¹⁷¹ After briefly discussing this exception, the Court emphasizes the patent system’s fundamental goal of “promot[ing] the Progress of Science and useful Arts.”¹⁷² It states that “[w]e must apply this well-established standard to determine whether Myriad’s patents claim any ‘new and useful . . . composition of matter’ or instead claim naturally occurring phenomena.”¹⁷³ The Court seems to refer to *Prometheus* in order to lay a foundation for the policy considerations underlying issues of patent-eligible subject matter, rather than to cite particular precedent that specifically informs its decision in *Myriad*.¹⁷⁴

The Court relied on *Funk Brothers* and *Chakrabarty* to delineate its requirement for inventiveness in patent-eligible products.¹⁷⁵ It distinguished Myriad’s DNA molecules from Chakrabarty’s genetically engineered bacteria, which in dictum the *Chakrabarty* Court described as “new, with markedly different characteristics from any found in nature.”¹⁷⁶ It found Myriad’s position more like that of the putative inventor in *Funk Brothers*, whose

171. *Id.* For a fuller discussion of the product of nature doctrine, see *supra* Part I.

172. U.S. CONST., art. I, § 8, cl. 8. The *Myriad* Court stated: “As we have recognized before, patent protection strikes a delicate balance between creating ‘incentives that lead to creation, invention, and discovery’ and ‘imped[ing] the flow of information that might permit, indeed spur, invention.’” *Myriad IV*, 133 S. Ct. at 2116 (quoting *Prometheus*, 132 S. Ct. at 1305).

173. *Myriad IV*, 133 S. Ct. at 2116 (internal citations omitted) (citing 35 U.S.C. § 101 (2012)).

174. The Court was aware of the policy ramifications of its decision, which the Justices addressed during oral argument:

JUSTICE KENNEDY: And—and that avoids giving special industries special subsidies. . . . If we were to accept the Government’s position that the DNA is not patentable but the cDNA is, would that give the industry sufficient protection for innovation and research? And if not, why not?

Transcript of Oral Argument at 58, *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013) (No. 12-398).

JUSTICE SOTOMAYOR: Is there some value to us striking down isolated DNA and upholding the cDNA? If we were to do what the Government is proposing in this case, what’s the consequences?

Id. at 61.

175. “Myriad recognizes that our decision in *Chakrabarty* is central to this inquiry.” *Myriad IV*, 133 S. Ct. at 2116. The Court continued:

In *Funk Brothers* . . . this Court considered a composition patent that claimed a mixture of naturally occurring strains of bacteria that helped leguminous plants take nitrogen from the air and fix it in the soil. . . . [This] patent claim thus fell squarely within the law of nature exception. So do Myriad’s.

Id. at 2117.

176. *Myriad IV*, 133 S. Ct. at 2117 (citing *Chakrabarty*, 447 U.S. at 310).

claims “[did] not disclose an invention or discovery within the meaning of the patent statutes.”¹⁷⁷ Similarly, Myriad’s “discovery [of the BRCA genes], by itself, [did] not render the BRCA genes ‘new . . . composition[s] of matter’ that are patent eligible.”¹⁷⁸ The degree of inventiveness required to clone DNA clearly falls somewhere between mixing three strains of bacteria and creating a new species.¹⁷⁹ However, the Court’s inconsistent scientific and brief legal analyses shed little light on where to place the complex process of cloning DNA molecules on the spectrum of inventiveness as related to patent eligibility.

The last paragraph of the opinion cites “what is *not* implicated by this decision.”¹⁸⁰ It notes that no method claims were before the Court in *Myriad*. Thus, “innovative method[s] of manipulating genes,” “new applications of knowledge” about the claimed isolated gDNA strands, and synthetic DNA strands “in which the order of the naturally occurring nucleotides has been altered” all would present “a different inquiry.”¹⁸¹ The Court concludes by emphasizing its reliance on DNA’s information content and seems to limit *Myriad*’s applicability beyond DNA molecules: “We merely hold that genes and the information they encode are not patentable under § 101 simply because they have been isolated from the surrounding genetic material.”¹⁸² The *Myriad* Court drew a line between two very similar molecules: gDNA is not patent eligible because it has the same nucleotide sequence and carries the same genetic information as naturally occurring chromosomal DNA. cDNA, on the other hand, is patent eligible because it does not share this chemical and informational identity with chromosomal DNA.¹⁸³

177. *Funk Bros.*, 333 U.S. at 132.

178. *Myriad IV*, 133 S. Ct. at 2117 (citation omitted). Note the ongoing confusion regarding Myriad’s claimed molecules. As discussed in Section I.C, *supra*, and as reflected in the language of the claims examined by the Court, Myriad’s patents were written on isolated DNA molecules, not on “genes.”

179. The *Chakrabarty* Court held that Chakrabarty “produced a new bacterium. . . .” *Chakrabarty*, 447 U.S. at 310. In contrast, the *Funk Brothers* Court held that the putative inventor had merely “provided a mixed culture of [bacteria] . . . belonging to several cross-inoculation groups.” *Funk Brothers*, 333 U.S. at 130.

180. *Myriad IV*, 133 S. Ct. at 2119.

181. *Id.* at 2119–20.

182. *Id.*

183. Despite its reliance on the importance of gDNA’s informational equivalence with naturally occurring chromosomal DNA, the *Myriad* Court does not address the informational equivalence of cDNA with naturally occurring mRNA.

IV. SUBSEQUENT DEVELOPMENTS

Ten months after *Myriad* was handed down, Dr. Ostrer, the lone remaining plaintiff, does not offer a BRCA test that competes with Myriad's genetic test aimed at determining the presence of BRCA1 or BRCA2 gene mutations, the so-called "BRCAAnalysis test."¹⁸⁴ Myriad is involved in MDL with five of its competitors regarding whether their competing tests do or might infringe its patents, and the USPTO has issued new guidelines for the evaluation of patents that appear to have been written on natural products.¹⁸⁵ These facts make it difficult to interpret the impact of the decision on the parties to the suit, much less on the patent system as a whole.

A. ONGOING LAWSUITS CONCERNING MYRIAD'S PATENTS

Unsurprisingly, given the financial stakes and Myriad's position that the Court only "invalidated five [of its 520] patent claims covering isolated naturally occurring DNA, . . . thereby reducing [its] patent estate to 24 patents and 515 patent claims," Myriad and its potential competitors disagree on the reach of the decision.¹⁸⁶ Myriad has sued each large company that has announced its entry into the lucrative arena of BRCA testing.¹⁸⁷ The first of these cases was settled out of court under terms that prohibit the alleged infringer from offering standalone BRCA testing in North America.¹⁸⁸ However, Myriad lost its bid for a preliminary injunction enjoining Ambry Genetics from selling or offering to sell genetic tests, including a BRCA1 or BRCA2 panel.¹⁸⁹ Judge Shelby, who oversees the ongoing MDL, denied the

184. Telephone Interview with Dr. Harry Ostrer, Professor, Albert Einstein College of Medicine (Apr. 16, 2014).

185. See *infra* Sections IV.A, IV.C.

186. See Complaint, Univ. of Utah Research Found. v. Ambry Genetics Corp., Case No. 2:13-cv-00640-RJS (D. Utah July 9, 2013).

187. Less than one month after the Supreme Court issued its opinion, Myriad began to sue competitors that had entered the BRCA testing market, prompting an additional wave of countersuits and declaratory judgment actions from accused or potential infringers. See *Myriad Legal Consequences Stem from Supreme Court Gene Case*, NEWLEGALREVIEW (Jan. 16, 2014), <http://newlegalreview.cpaglobal.com/myriad-legal-consequences-stem-supreme-court-gene-case>. In February 2014, the U.S. Judicial Panel on Multidistrict Litigation combined five actions relating to fourteen of Myriad's patents for MDL management in the District of Utah. *In re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litig.*, No. 2:14-MD-2510, 2014 WL 690559 (J.P.M.L. Feb. 19, 2014). At the time of writing, litigation is still ongoing.

188. See Press Release, Gene by Gene, Ltd. & Myriad Genetics, Inc., BRCA Patent Owners and Gene by Gene, Ltd. Resolve Patent Suit (Feb. 7, 2014), *available at* <http://online.wsj.com/article/PR-CO-20140207-907847.html>.

189. *In re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litig.*, MDL No. 2:14-MD-2510, 2014 WL 931057, at *4 (D. Utah Mar. 10, 2014).

petition in part because Myriad was “unable to establish that [it is] likely to succeed on the merits of [its] claims.”¹⁹⁰

B. EARLY CASES CITING *MYRIAD*

Two district court cases have relied on *Myriad* to evaluate subject matter eligibility of DNA-related patents. In *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, Judge Illston of the Northern District of California extended *Myriad*'s reasoning to method patents.¹⁹¹ She granted summary judgment to an alleged infringer of a patent written on methods of testing for cell-free DNA, one of the many types of DNA not explicitly under review by the *Myriad* Court.¹⁹² In a decision that frequently cited *Myriad*, Judge Illston held that “even though *Myriad* involved composition claims rather than method claims,” it also supports the conclusion that the plaintiff's claims were written on patent-ineligible subject matter.¹⁹³

Genetic Technologies Ltd. v. Agilent Technologies, Inc. involved a method patent that implicates another type of DNA not fully analyzed by the *Myriad* Court: chromosomal DNA corresponding to “noncoding” intronic regions.¹⁹⁴ In denying the alleged infringer's motion to dismiss, Judge Seeborg, also of the Northern District of California, again referred to *Myriad*:

Agilent argues that, unlike cDNA, amplified DNA is not patent eligible under *Myriad*. Even so, [Genetic Technologies] does not

190. *Id.* at *4 (D. Utah Mar. 10, 2014); see also Andrew Pollack, *Patentholder on Breast Cancer Tests Denied Injunction in Lawsuit*, N.Y. TIMES, Mar. 10, 2014, <http://www.nytimes.com/2014/03/11/business/patentholder-on-breast-cancer-tests-denied-injunction-in-lawsuit.html> (last accessed March 14, 2014).

191. No. C 11-06391 SI, 2013 WL 5863022 (N.D. Cal. Oct. 30, 2013).

192. *Id.* at *1–2.

193. As in Section IV.C, *supra*, and in the immediately following discussion of *Genetic Technologies v. Agilent*, the *Myriad* Court expressly limited its holding to Myriad's composition of nature claims. Judge Illston, however, reasoned:

Even though *Myriad* involved composition claims rather than method claims, that decision also supports the [*Ariosa*] Court's conclusion. . . . Although the Supreme Court was not presented with method claims, the Court explained “[h]ad Myriad created an innovative method of manipulating genes while searching for the BRCA1 and BRCA2 genes, it could possibly have sought a method patent. But the processes used by Myriad to isolate DNA were well understood by geneticists at the time of Myriad's patents” Similarly, had the inventors of the [Sequenom] patent created an innovative method of performing DNA detection while searching for paternally inherited cfDNA, . . . those claims would be patentable.

Id. at *10 (internal citations omitted.).

194. No. CV 12-01616 RS, 2014 WL 941354 (N.D. Cal. Mar. 7, 2014).

purport to have patented the amplified DNA itself, but rather methods utilizing amplified DNA. The Court in *Myriad* was careful to point out that its decision did not reach any method claims or applications of natural laws.¹⁹⁵

The degree to which district courts and, more importantly, the Federal Circuit will choose to extend *Myriad*'s logic clearly remains to be seen.

C. USPTO GUIDELINES FOR DETERMINING SUBJECT MATTER ELIGIBILITY

The USPTO seems to have a much clearer view of *Myriad*'s ramifications vis-à-vis the patent eligibility of isolated DNA molecules and the evaluation of patent claims written on “natural products.” Arguably, it takes a more expansive view than may be justified by the language of the ruling. On the day the *Myriad* decision was released, the USPTO's deputy commissioner interpreted *Myriad* as holding that “claims to isolated DNA are not patent eligible under 35 U.S.C. § 101” and instructed patent examiners to “reject product claims drawn solely to naturally occurring nucleic acids or fragments thereof, whether isolated or not, as being ineligible subject matter under 35 U.S.C. § 101.”¹⁹⁶

Nine months later, the USPTO issued a more comprehensive Guidance to its examiners covering the examination of “all claims (i.e., machine, composition, manufacture and process claims) reciting or involving laws of nature/natural principles, natural phenomena, and/or natural products.”¹⁹⁷ This Guidance supersedes the June Memorandum and “addresses the impact

195. *Id.* at *7 n.17. Note that this case does not implicate the product of nature doctrine. Rather, involves the validity of a patent written on technology alleged to be patent ineligible because it implicates a law of nature, another of the three judicial carve-outs cited by the *Myriad* Court.

196. Memorandum from Andrew H. Hirschfeld, Deputy Comm'r for Patent Examination Policy, USPTO, to Patent Examining Corps, Supreme Court Decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, United States Patent and Trademark Office (June 13, 2013) [hereinafter June Memorandum], available at http://www.uspto.gov/patents/law/exam/myriad_20130613.pdf. The June Memorandum does seem partially to retract its overly inclusive first sentence when it states in its second paragraph that “[c]laims clearly limited to non-naturally-occurring nucleic acids, such as a cDNA or a nucleic acid in which the order of the naturally-occurring nucleotides has been altered (e.g., a man-made variant sequence), remain eligible.” *Id.*

197. Memorandum from Andrew H. Hirschfeld, Deputy Comm'r for Patent Examination Policy, USPTO, to Patent Examining Corps, Guidance For Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena, & Natural Products, United States Patent and Trademark Office (Mar. 4, 2014) [hereinafter Guidance], available at http://www.uspto.gov/patents/law/exam/myriad-mayo_guidance.pdf.

of [*Myriad*] . . . on the Supreme Court’s long-standing ‘rule against patents on naturally occurring things.’”¹⁹⁸ It establishes a three-step algorithm procedure that examiners are to use in determining whether a claim is drawn to patent-eligible subject matter. The inquiry requires examiners to ask whether “the claim as a whole recite[s] something significantly different than the judicial exception(s)” and then establishes twelve factors that examiners are to weigh in deciding whether a claim “as a whole recites something significantly different than the [natural product] itself.”¹⁹⁹

Both the June Memorandum and the newly promulgated Guidance likely were intended to clarify the USPTO’s interpretation of the *Myriad* decision and to increase the uniformity of the patent examination process. However, it is not clear that either document accurately reflects the content of the *Myriad* decision.²⁰⁰

V. CONCLUSION

Myriad establishes a bright-line rule concerning the patent eligibility of two types of DNA molecules: gDNA is not patent eligible, but some cDNA is.²⁰¹ The Supreme Court based this distinction on an incomplete and seemingly contradictory scientific understanding of the chemistry, and on

198. *Id.*

199. *Id.*

200. The June Memorandum clearly misstated the Court’s holding in its first sentence: “Today in *Association for Molecular Pathology v. Myriad Genetics, Inc. (Myriad)*, the Supreme Court held that claims to isolated DNA are not patent-eligible under 35 U.S.C. § 101.” June Memorandum, *supra* note 196. However, as discussed in note 196, *supra*, the June Memorandum subsequently retreats from this overly broad interpretation. The Guidance tasks examiners with assessing whether a patent application covers something “significantly different than what exists in nature” as a prerequisite for subject matter eligibility, although the term “significantly different” is not used in the *Myriad* decision. Guidance, *supra* note 197, at 5. *Myriad*, in dictum, does refer to the *Chakrabarty* “markedly different” dictum: “The *Chakrabarty* bacterium was new ‘with markedly different characteristics from any found in nature.’” *Ass’n for Molecular Pathology v. Myriad Genetics, Inc. (Myriad IV)*, 133 S. Ct. 2107, 2117 (2013) (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980)). For early analysis of some troubling aspects of the USPTO’s Guidance, see, e.g., Courtenay C. Brinkerhoff, *United States: Do Pharmaceutical Compositions Have Patent Subject Matter Eligibility Under the New USPTO Guidelines?*, MONDAQ (Mar. 14, 2014), <http://www.mondaq.com/unitedstates/x/299892/Life+Sciences+Biotechnology/Do+Pharmaceutical+Compositions+Have+Patent+Subject+Matter+Eligibility+Under+the+New+USPTO+Guidelines>; Paul Cole, *USPTO Patent Eligibility Guidelines: A Topsy Turvy Approach for Natural Products*, IPWATCHDOG (Mar. 10, 2014), <http://www.ipwatchdog.com/2014/03/10/uspto-patent-eligibility-guidelines-natural-products/id=48451>.

201. cDNA molecules corresponding to chromosomal DNA that does not cross an intron-exon boundary may not be patent-eligible. See *supra* note 158.

limited and vaguely articulated legal reasoning. Taken together, these shortcomings of the *Myriad* opinion seem likely to restrict the applicability of the *Myriad* decision beyond its specific holding that isolated gDNA and some other analogous forms of DNA are not patent eligible. District courts may interpret *Myriad* in a number of different ways, each of which likely would be consistent with the Court's reasoning. They may regard *Myriad* as having added a "markedly different" requirement to the language of § 101 for subject matter patentability. They may see the *Myriad* Court as having followed the product of nature doctrine by stating that, based on the underlying science, gDNA does not qualify for the "isolated and purified" exception. They may surmise that *Myriad* added a new judicially created "information content" exception to § 101 patent-eligible subject matter: a composition of matter that is informationally identical to a naturally occurring product is not patent eligible. Finally, they may construe *Myriad* as having created a *sui generis* exception to the "isolated and purified" exception to the product of nature doctrine, which applies only to nucleic acids. Although the USPTO seems to have embraced the "markedly different" concept, the Federal Circuit, the de facto final arbiter of *Myriad*'s reach, may be more inclined to view *Myriad* as a *sui generis* exception that applies only to nucleic acids.

Regarding the "markedly different" interpretation of *Myriad*, the Court quoted language from *Chakrabarty* regarding the patent ineligibility of naturally occurring substances, but it did not thoroughly analyze either gDNA or cDNA to explain how the former is different but not "markedly different" from naturally occurring compositions, whereas the latter is "markedly different." Rather, in its analysis of cDNA, the Court merely stated that cDNA was "unquestionably . . . something new."²⁰² The Court did not give any meaningful guidance regarding what specific differences in structure, function, and utility make a claimed molecule "markedly different" from a similar naturally occurring molecule and thus patent eligible. The Court also did not clearly elucidate this standard, and it did not distinguish prior circuit court jurisprudence regarding either the product of nature exception to subject matter patentability or the "isolated and purified" exception. This lack of guidance makes it likely that lower courts' analyses of these matters, except as specifically regards the patent eligibility of DNA molecules, largely will continue to be based on prior Federal Circuit case law.

The degree to which the Court embraced Judge Sweet's DNA-as-information paradigm also is somewhat unclear. The Court did emphasize its

202. *Myriad IV*, 133 S. Ct. 2107, 2119 (2013).

interpretation that Myriad's "claim is concerned primarily with . . . information."²⁰³ However, it did not illuminate exactly what it meant by genetic information, what criteria could be used when examining a composition patent in order to determine whether the molecular structure or informational content predominated in a given claim, or which chemicals other than DNA are amenable to an information-content analysis in determining their patent eligibility. Thus, it may be difficult for a lower court to take meaningful direction from *Myriad* when analyzing a patent claim under this new paradigm.

It therefore appears that *Myriad* will be significant to current holders of isolated DNA patents but that its reach will be limited to its specific holding: gDNA is not patent eligible, and some cDNA is. The Court's unwillingness to expound on its scientific analysis and legal reasoning gives little motivation for the Federal Circuit to extend *Myriad's* precedential reach beyond DNA molecules. Furthermore, the Court failed to grapple with Federal Circuit precedent commenting on other purified isolated biological chemicals that have been held patent eligible. These facts, coupled with the Court's reliance on DNA's unique properties as an information-carrying molecule, are likely to relegate *Myriad's* legacy to having merely created a new carve out precluding the patent eligibility of some synthetic DNA molecules.

203. *Id.* at 2118.

