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The Supreme Court's Myriad Effects on Scientific Research: Definitional Fluidity and the Legal Construction of Nature

Peter Lee
UC Davis School of Law

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The Supreme Court’s *Myriad* Effects on Scientific Research: Definitional Fluidity and the Legal Construction of Nature

Peter Lee*

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INTRODUCTION

Although patent law aims to promote technological progress,¹ its impact on scientific research—a key driver of such progress—is highly complicated. In analyzing this issue, context as well as definitions of key concepts such as “research” and even “nature” itself matter a great deal. Such is the case with evaluating the impact of the Supreme Court’s 2013 decision, *Association for Molecular Pathology v. Myriad Genetics*.² The decision culminated years of litigation over several patents held by Myriad Genetics, a Utah-based biotechnology company, covering two genes, BRCA1 and BRCA2. Mutations in these genes are correlated with an increased risk

* Professor of Law and Chancellor’s Fellow, UC Davis School of Law. I would like to thank Professor Dan Burk and UC Irvine School of Law for hosting “The Meaning of *Myriad*” symposium and conference participants for providing helpful feedback. I would also like to thank workshop participants at UC Berkeley School of Law, the Arizona State University Legal Studies Conference, and Willamette University College of Law for their valuable insights. Thanks as well to Dean Kevin Johnson and Senior Associate Dean Vik Amar of UC Davis School of Law for their generous institutional support of this project.

1. U.S. CONST. art. I, § 8, cl. 8.

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

of developing breast and ovarian cancer,³ and, based significantly on its patents, Myriad Genetics enjoyed exclusive rights on clinical genetic diagnostic tests related to these diseases. A consortium of plaintiffs, including medical research groups and women's health advocates, challenged the validity of Myriad's patents motivated by concerns that exclusive rights increased the cost of testing and decreased valuable access to these genes. This Article explores the subtle and important implications of the Supreme Court's decision for scientific research.

On its face, the case addressed the rather narrow technical issue of patentable subject matter: the threshold inquiry of what sort of *thing* is eligible for patenting.⁴ In particular, at issue was the validity of Myriad's patents on isolated DNA and complementary DNA (cDNA).⁵ Reversing decades of accepted legal practice, the Court held that isolated DNA, which is DNA that is separated from its genomic environment, does not comprise patentable subject matter.⁶ However, the Court held that cDNA, which entails synthetically created DNA that omits nucleotide sequences that do not code for proteins, remains eligible for patenting.⁷ Beyond this narrow technical holding, however, the case has significant ramifications for public health, biotechnological innovation, and, as this Article will explore, biomedical research.

Assessing the impact of the Supreme Court's decision is a complex task. For some, it represents a "narrow" holding that "will have a surprisingly small effect on the biotech industry."⁸ For others, the decision "may have a larger long-term impact on the role of intellectual property protection in modern genomic and medical science."⁹ Most policy, media, and popular attention has focused on the impact of Myriad's patents on the availability of diagnostic tests for breast and ovarian cancer, a matter of high personal and political salience.¹⁰ Indeed, the plaintiffs challenging

3. Myriad announced that it had sequenced and mapped BRCA1 and BRCA2 in 1994 and 1995, respectively. Shobita Parthasarathy, *Architectures of Genetic Medicine: Comparing Genetic Testing for Breast Cancer in the USA and the UK*, 35 SOC. STUD. SCI. 5, 19 (2005).

4. See 35 U.S.C. § 101 (2012) (stating that patentable subject matter encompasses "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof").

5. *Myriad*, 133 S. Ct. at 2111.

6. *Id.*

7. *Id.* Though nucleotide sequences excised in the creation of cDNA may not code for proteins directly, they play an important role in regulating the behavior of cells, organs, and other tissue. Gina Kolata, *Study Discovers Road Map of DNA; A Key to Biology*, N.Y. TIMES, Sept. 6, 2012, at A1.

8. Steven Seidenberg, *Supreme Court's Decision in Myriad Sends Shockwaves Through the Biotech Industry*, INSIDECOUNSEL (Aug. 5, 2013), <http://www.insidecounsel.com/2013/08/05/supreme-courts-decision-in-emmyriad-em-sends-shock> [<http://perma.cc/ND6B-2K4P>].

9. Kenneth Offit et al., *Gene Patents and Personalized Cancer Care: Impact of the Myriad Case on Clinical Oncology*, 31 J. CLINICAL ONCOLOGY 2743, 2743 (2013).

10. E. Richard Gold & Julia Carbone, *Myriad Genetics: In the Eye of the Policy Storm*, 12 GENETICS MED. S39, S39 (2010) ("It is perhaps because of the high profile of breast cancer that this test, patented by Myriad, struck a chord among politicians and the public.").

Myriad's patents argued that exclusive rights raised the cost of testing, hampered verification of test results, and limited the variety of tests offered.¹¹

A separate consideration throughout the litigation, however, focused on the effect of Myriad's isolated DNA patents on the progress of biomedical research itself. Although less immediately impacting human health than access to diagnostic tests, the prospect that Myriad's DNA patents could inhibit research may have greater long-term implications. After all, inhibited research could retard the expansion of biological knowledge and the development of future diagnostics and therapeutics. Furthermore, although some would argue that ensuring equitable access to diagnostics and other innovations is not the responsibility of the patent system,¹² the prospect of exclusive rights inhibiting scientific research directly implicates the patent system's constitutional objective of promoting the progress of science and useful arts.¹³ This Article focuses on the impact of the Supreme Court's decision on scientific research rather than access to diagnostics. One of its arguments, however, is that there is no clear distinction between diagnostic and research use of genes, and constraints on one activity inhibit the other.

The potential for isolated DNA patents to inhibit biomedical research was a significant issue throughout the *Myriad* litigation. Plaintiffs argued that Myriad's isolated DNA patents "impermissibly preempt scientific and medical work, far beyond what Myriad's contribution can justify."¹⁴ *Amici* challenging the patents, including the American Medical Association, the National Women's Health Network, and leading geneticist Eric Lander, argued similarly.¹⁵ Concerns over the ability of patents to deter research also permeated lower court decisions in this litigation. At the trial court, the Southern District of New York noted the "deep disagreement" between the parties regarding the impact of Myriad's patents on scientific progress.¹⁶ At the Federal Circuit, Judge Bryson viewed isolated DNA patents with skepticism, citing Justice Breyer's earlier statement in *Laboratory Corp.*

11. See generally Sandra S. Park, *Gene Patents and the Public Interest: Litigating Association for Molecular Pathology v. Myriad Genetics and Lessons Moving Forward*, 15 N.C. J.L. & TECH. 519 (2014).

12. Cf. Peter Lee, *Toward a Distributive Commons in Patent Law*, 2009 WIS. L. REV. 917, 995–97 (describing and critiquing the argument that the patent system should focus simply on maximizing productivity, leaving distributive and access concerns to other policy mechanisms).

13. U.S. CONST., art. I, § 8, cl. 8. This sentiment also informed the ACLU's decision to represent the plaintiffs in this case. See Park, *supra* note 11, at 521.

14. Brief for Petitioners at 41, *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013) (No. 12-398); *id.* at 43 ("The effect of the patents has been to prevent and deter research.").

15. See, e.g., Brief of Amici Curiae American Medical Association et al. in Support of Petitioners at 13, *Myriad*, 133 S. Ct. 2107 (2013) (No. 12-398) (arguing that patents on isolated DNA impede both research and diagnosis); Brief Amici Curiae of the National Women's Health Network et al. in Support of Petitioners at 27, *Myriad*, 133 S. Ct. 2107 (2013) (No. 12-398) ("Myriad's patents on the embodied information of the BRCA 1/2 genes inhibit important scientific work in biomedical research and treatment for breast and ovarian cancer . . ."); Brief for Amicus Curiae Eric S. Lander in Support of Neither Party at 24, *Myriad*, 133 S. Ct. 2107 (2013) (No. 12-398) ("Granting a monopoly on possessing a molecule that is a product of Nature authorizes a patent holder to wall off an entire domain of Nature from observation.").

16. *Ass'n for Molecular Pathology v. USPTO*, 702 F. Supp. 2d 181, 207–11 (S.D.N.Y. 2010).

of *America Holdings v. Metabolite Labs Inc.* that sometimes “*too much* patent protection can impede rather than ‘promote the Progress of Science and useful Arts.’”¹⁷

This Article argues that *Myriad Genetics* has subtle but important implications for enhancing freedom to operate for scientific research. In examining this complex question, several themes emerge. First, definitions matter. The question of whether Myriad’s isolated DNA patents burdened scientific research prior to their invalidation depends significantly on the definitions of “noncommercial,” “commercial,” “research,” and “diagnostic” uses of patented technologies, all of which are fraught with indeterminacy. Furthermore, how courts define “nature” for purposes of subject matter exclusions from patentability is highly discretionary and has important implications for the intersection of patents and scientific inquiry.

Second, in evaluating the impact of *Myriad* on scientific research, context matters. Accordingly, this Article examines the implications of the Supreme Court’s ruling on three levels.¹⁸ Part I considers the decision’s impact on Myriad Genetics itself and its attempts to control BRCA research. It explores the problematic nature of Myriad’s voluntary policy of allowing noncommercial research to proceed without a license, ultimately arguing that the Court’s ruling creates more real and perceived freedom to operate for scientists studying the BRCA genes. Part II expands the perspective, drawing on the *Myriad* opinion to revisit a longstanding debate over the potential for “upstream” patents on research inputs to stymie scientific inquiry. Although empirical studies reveal little chilling effect of such patents in the pure research context, they have been shown to constrain diagnostic testing. Given that diagnostic testing yields significant scientific insights, to the extent that the Court’s decision leads to greater diagnostic testing, it will promote research as well. Part III expands the perspective further and considers *Myriad*’s long-term doctrinal implications. It argues that the opinion reflects both a strong prudential interest in excluding “nature” from patentable subject matter as well as a remarkable degree of flexibility in defining nature for this purpose. It contends that *Myriad* is a highly pragmatic opinion that creates greater opportunity to challenge patents in research contexts going forward. Part IV examines outstanding issues and considers some additional long-term ramifications of the Court’s decision.

17. *Ass’n for Molecular Pathology v. USPTO*, 653 F.3d 1329, 1380 (Fed. Cir. 2011) (Bryson, J., concurring in part and dissenting in part); see Dianne Nicol, *Implications of DNA Patenting: Reviewing the Evidence*, 21 J. L. INFO. & SCI. 7, 28 (2011).

18. This Article focuses on the Supreme Court’s holding that isolated DNA does not comprise patentable subject matter, and it briefly addresses the Court’s holding that cDNA remains eligible for patenting. It does not address the important lower court holdings regarding the patent eligibility of Myriad’s patented *processes*. These patents, however, may be quite significant. Cf. Christopher M. Holman, *The Impact of Human Gene Patents on Innovation and Access: A Survey of Human Gene Patent Litigation*, 76 UMKC L. REV. 295, 314 (2007) (“In many cases the most dominating patent claims relating to human genetic sequences are process claims, particularly those that broadly claim methods for identifying mutations.”).

I. THE IMPACT OF *MYRIAD GENETICS* ON BRCA RESEARCH

This Part examines the impact of the Supreme Court's invalidation of isolated DNA patents on Myriad Genetics' own efforts to control BRCA research. This is a complicated issue, partly due to Myriad's self-professed policy of permitting noncommercial research on BRCA1 and BRCA2 to proceed without a license.¹⁹ Myriad's policy and efforts to enforce it reveal the importance of definitions in determining whether and to what extent patents impede research. After all, Myriad's definitions of "research" and "commercial" uses of genes were rather subjective and malleable. Furthermore, commercial diagnostic uses of BRCA, which never qualified for Myriad's exemption, may yield important research insights. Additionally, perceptions of the law or a patentee's willingness to enforce its rights may be more important than reality in shaping (and chilling) behavior in the research community. Among other implications, these observations reveal the tenuous nature of private ordering regimes wherein patentees selectively refrain from enforcing their patents. Taken together, the Court's invalidation of Myriad's isolated DNA patents creates greater real and perceived freedom to operate, thus encouraging more BRCA research to proceed.

At the outset, it is important to acknowledge that from several practical perspectives, the significance of the Supreme Court's ruling is quite modest. First, Myriad's patents in suit were set to expire in 2015.²⁰ Therefore, even if the Court upheld the validity of Myriad's isolated DNA claims, exclusivity would have only remained for two more years. Second, patentable subject matter was not the only doctrinal ground available for challenging Myriad's patents. For example, even if the Supreme Court had ruled that isolated DNA comprised patentable subject matter, Myriad's patents would still be vulnerable on nonobviousness grounds.²¹ Third, in the wake of the Supreme Court's decision, Myriad continued to assert other patents covering clinical genetic diagnostic tests. Indeed, about three-fourths of Myriad's BRCA-related patents are on cDNA, probes, and methods that the Supreme Court's ruling did not directly address, though subsequent litigation has invalidated several of these patents.²² Prior to the decision, Myriad even downplayed the importance

19. See Gold & Carbone, *supra* note 10, at S42.

20. Cf. Rose-Ellen Lessy, *What's at Stake in the Supreme Court Decision in 'AMP v. Myriad Genetics'*, NATION (June 5, 2013), <http://www.thenation.com/article/174681/whats-stake-supreme-court-decision-amp-v-myriad-genetics> [<http://perma.cc/234F-JGCJ>] (noting that Myriad's patents expire in 2015).

21. The ACLU considered challenging Myriad's patents on nonobviousness grounds but ultimately decided that "Section 101's prohibition on patenting laws and products of nature was best suited for asserting the larger public interest in opposing gene patents." Park, *supra* note 11, at 529; see *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009) (invalidating claims covering an isolated DNA encoding a particular protein as obvious); *infra* note 175 and accompanying text.

22. *In re BRCA1- & BRCA2-Based Hereditary Cancer Test*, 774 F.3d 755 (Fed. Cir. 2014) (drawing on the Supreme Court's *Myriad* decision to invalidate several patents on probes and methods related to BRCA genes).

of its isolated DNA patents and suggested that their potential invalidation would be rather insignificant.²³

Notwithstanding these considerations, the Court's decision remains significant as immediately eliminating an important and highly visible mechanism of exclusivity. It also provides an opportunity to assess the degree to which Myriad's isolated DNA patents inhibited or threatened to inhibit BRCA research. This is a complicated issue, for Myriad has long maintained that it allows "research" (presumably meaning "noncommercial research") uses of its patents to proceed without a license. This private ordering regime, however, faced several problems. First, as Myriad's own rather convoluted definitions illustrate, it is difficult to clearly distinguish between "research" and "commercial" uses of patents. This supposed dichotomy parallels in some ways the perceived distinction between basic research, which tends to be noncommercial, and applied research, which is associated with commercial activity.²⁴ Contemporary science, however, blurs these boundaries. These days, much biomedical research occurs in "Pasteur's Quadrant": it both strives for fundamental understanding and is intrinsically oriented toward practical application.²⁵ For example, discovery of the BRCA1 and BRCA2 genes advanced basic biological knowledge as well as led directly to diagnostic tests. Given that much research spans both the noncommercial and commercial realms, it would be difficult for scientists to understand the contours of Myriad's exemption for "research" use of its patents. Not surprisingly, this lack of definitional clarity led to interpretive disputes and chilling effects for scientists seeking to conduct BRCA research. Ultimately, it was difficult for scientists to know what constituted a "research" use of BRCA1 and BRCA2 that Myriad would permit.

Second and relatedly, Myriad's research exception never extended to "commercial" diagnostic testing, which also yields important research insights. Such

23. John Conley, Myriad, *Finally; Supreme Court Surprises by not Surprising*, GENOMICS L. REP. (June 18, 2013), <http://www.genomicslawreport.com/index.php/2013/06/18/myriad-finally-supreme-court-surprises-by-not-surprising/> [http://perma.cc/LC8S-Z8PF].

24. See Fiona Murray & Scott Stern, *Do Formal Intellectual Property Rights Hinder the Free Flow of Scientific Knowledge? An Empirical Test of the Anti-Commons Hypothesis*, 63 J. ECON. BEHAV. & ORG. 648, 651–52 (2007). This distinction has a long provenance and relates to the massive increase in federal science funding following World War II. See Lee, *supra* note 12, at 944 n.160. Vannevar Bush, chief scientific advisor to President Roosevelt and architect of postwar U.S. science policy, envisioned that federal funding of basic academic research would create a "reservoir of knowledge" that would facilitate downstream, applied research and innovation. Timothy L. Faley & Michael Sharer, *Technology Transfer and Innovation: Reexamining and Broadening the Perspective of the Transfer of Discoveries Resulting from Government-Sponsored Research*, 3 COMP. TECH. TRANSFER & SOC'Y 109, 110–11, 111 fig.1 (2005). See generally VANNEVAR BUSH, SCIENCE: THE ENDLESS FRONTIER (1945).

25. Francis Narin et al., *The Increasing Linkage Between U.S. Technology and Public Science*, 26 RES. POL'Y 317, 317 (1997); Richard R. Nelson, *The Market Economy, and the Scientific Commons*, 33 RES. POL'Y 455, 457 (2004); see Nicol, *supra* note 17, at 13; Katherine J. Strandburg, *User Innovator Community Norms: At the Boundary Between Academic and Industry Research*, 77 FORDHAM L. REV. 2237 (2009). See generally DONALD E. STOKES, PASTEUR'S QUADRANT: BASIC SCIENCE AND TECHNOLOGICAL INNOVATION (1997).

diagnostic testing can reveal previously unknown disease-causing mutations,²⁶ thus enhancing basic knowledge of the BRCA genes. There is thus no sharp distinction between “clinical” and “research” uses of the BRCA diagnostic test, for one informs the other. As Jon Merz testified to Congress,

There is no clear line to be drawn between clinical testing and research testing, because the state of the art of genetic tests is such that much more clinical study is necessary to validate and extend the early discovery of a disease gene. Thus, the restriction of physicians from performing clinical testing will directly reduce the knowledge about these genes.²⁷

Thus, assertions of patent rights against even obviously commercial uses of BRCA genes slowed scientific advances in the field.

Myriad’s conduct illustrates the difficulty of defining “research” uses of patented DNA and the scientific losses from inhibiting even clearly “commercial” uses of DNA. To understand this issue, some background on Myriad’s services is helpful. Myriad developed several genetic diagnostic tests based on its discoveries, including the Comprehensive BRACAnalysis, which comprises full sequence testing of BRCA1 and BRCA2,²⁸ as well as Single Site BRACAnalysis tests, which only test for a single mutation.²⁹ Myriad performed the Comprehensive BRACAnalysis at its own laboratory in Utah.³⁰ However, it granted licenses to several laboratories around the nation to perform single mutation testing.³¹ These licenses included special provisions permitting certain research activities, as defined by Myriad, though these policies evolved over time. According to Myriad, licensees were allowed to perform genetic tests for research purposes as long they did not charge fees or share results with patients.³² Furthermore, at some point Myriad agreed to perform diagnostic tests for all researchers funded by the National Institutes of Health (NIH) for \$1200 rather than the ordinary cost of \$2680 for patients.³³ If, however, researchers shared results with patients, then “it crosses over the line,” and such activity became unauthorized commercial use.³⁴

Myriad’s narrow conception of “research” use, however, created difficulties

26. Rochelle Cooper Dreyfuss, *Implications of the DNA Patenting Dispute: A US Response to Dianne Nicol*, 22 J.L. INF. & SCI. 1, 9 (2012).

27. John P. Walsh et al., *Effects of Research Tool Patents and Licensing on Biomedical Innovation*, in PATENTS IN THE KNOWLEDGE-BASED ECONOMY 285, 318–19 (Wesley M. Cohen & Stephen A. Merrill eds., 2003) (quoting testimony of Jon F. Merz before the House Judiciary Committee, July 13, 2000).

28. Gold & Carbone, *supra* note 10, at S42.

29. *Id.*; see also Parthasarathy, *supra* note 3, at 21.

30. Gold & Carbone, *supra* note 10, at S42–S43.

31. *Id.*

32. Walsh et al., *supra* note 27, at 318.

33. Kimberly Blanton, *Corporate Takeover Exploiting the US Patent System, a Single Company Has Gained Control over Genetic Research and Testing for Breast Cancer, and Scientists, Doctors, and Patients Have to Play by Its Rules*, BOSTON GLOBE, Feb. 24, 2002, at 10.

34. Walsh et al., *supra* note 27, at 318 (quoting Gregory Critchfield, Myriad Genetics); see Aaron S. Kesselheim & Michelle M. Mello, *Gene Patenting—Is the Pendulum Swinging Back?*, 362 NEW ENG. J. MED. 1855, 1857 (2010); Parthasarathy, *supra* note 3, at 23.

for scientists seeking to conduct BRCA research.³⁵ In May 1998, Myriad Genetics accused University of Pennsylvania cancer researchers Dr. Arupa Ganguly and Dr. Haig Kazazian of infringing five of its patents.³⁶ Myriad offered the researchers a license, but it was “of very limited scope,” as it would have prevented the scientists from completing diagnostic testing services for BRCA1 or conducting comprehensive research on the gene.³⁷ Ultimately, the researchers ceased “all *BRCA1* and *BRCA2* testing, whether for research or clinical purposes.”³⁸ In particular, the inability to share diagnostic results with test subjects made it more difficult for scientists to enlist patients in research studies.³⁹ This restriction especially discouraged the most important potential research subjects—those with a family history of breast cancer—from participating in studies.⁴⁰ Although Myriad offered to perform full-gene “research” sequencing at its own laboratory for a discount, the fee was still substantial.⁴¹ Furthermore, the requirement of submitting samples to Myriad would have foreclosed researchers from utilizing their own preferred sequencing techniques.⁴² Commentators suggest that chilled research on the BRCA1 and BRCA2 genes may have delayed important discoveries, such as the role of “big deletions” in developing breast cancer.⁴³

Further disputes reflect both the narrowness of Myriad’s research exception and the malleability of its key terms. In September 1998, Myriad wrote to the National Cancer Institute (NCI), alleging patent infringement based on NCI-funded BRCA1 and BRCA2 testing.⁴⁴ The University of Pennsylvania’s Genetics Diagnostic Laboratory (GDL) was to host several NCI-funded trials, and Myriad also informed GDL that it could only continue diagnostic tests upon agreeing to certain restrictions and paying a license fee.⁴⁵ Importantly, Myriad’s dispute with GDL depended centrally on “a question of how one defines research in deciding whether to enforce a patent.”⁴⁶

GDL initially refused to accede to Myriad’s request, claiming a “research

35. See Parthasarathy, *supra* note 3, at 23.

36. A. Lane Baldwin & Robert Cook-Deegan, *Constructing Narratives of Heroism and Villainy: Case Study of Myriad’s BRCA Analysis Compared to Genentech’s Herceptin*, GENOME MED., Jan. 31, 2013, at 4–5, <https://www.genomemedicine.com/content/pdf/gm412.pdf> [<https://perma.cc/5USE-TCD9>].

37. *Id.* at 5.

38. Declaration of Arupa Ganguly, Ph.D. ¶ 10, *Ass’n for Molecular Pathology v. USPTO*, 702 F. Supp. 2d 181 (S.D.N.Y. 2010) (No. 09-4515); see Baldwin & Cook-Deegan, *supra* note 36, at 5.

39. Blanton, *supra* note 33, at 10.

40. *Id.*

41. See *id.*

42. *Id.*

43. *Id.* Myriad’s initial diagnostic tests screened for relatively small point mutations rather than big deletions where long stretches of sequences are missing. See *id.*

44. Baldwin & Cook-Deegan, *supra* note 36, at 5.

45. Steve Bunk, *Researchers Feel Threatened by Disease Gene Patents*, SCIENTIST (Oct. 11, 1999), <http://www.the-scientist.com/?articles.view/articleNo/19605/title/Researchers-Feel-Threatened-by-Disease-Gene-Patents/>. In 1998, Myriad filed a lawsuit against the University of Pennsylvania, but the district court dismissed it because Myriad failed to serve process on the defendant. Holman, *supra* note 18, at 347.

46. Gold & Carbone, *supra* note 10, at S64.

exemption” because it was working under protocols from the NCI’s Cancer Genetics Network.⁴⁷ In response, Myriad modified its research policy and entered into an agreement with NCI in 1999 that articulated a rather complicated definition of “research use” that was permitted under Myriad’s license.⁴⁸ The agreement defined “research testing services as part of the grant supported research of an investigator, and *not in performance of a technical service for the grant supported research of another* (as a core facility, for example).”⁴⁹ Research testing services were further defined as paid for by grant funds and not by patients or insurance. Notably, if these conditions were satisfied, patients participating in research could obtain their test results. This was a “fairly narrow conception of what constituted acceptable research,”⁵⁰ and because GDL performed tests for other NCI-funded researchers, its activities did not qualify as “research testing” under the agreement.⁵¹ Unable to take advantage of Myriad’s research exemption, GDL found the prospect of paying royalties to Myriad to be financially untenable.⁵²

Myriad’s shifting policies and inconsistent public communications undermined certainty within the BRCA research community. The company maintains that it “[does] not require a research license for anybody” and that it is only concerned with commercial infringement.⁵³ It further states that it defines “noncommercial research” broadly.⁵⁴ However, these are debatable propositions. There appears to be some inconsistency in Myriad’s conception of noncommercial research; in some contexts, such activity was incompatible with sharing results with patients while in other contexts, such sharing was allowed.⁵⁵ Myriad has tried to corroborate its image as a “proresearch” company by reasoning that “[s]ince research performed on BRCA1 and BRCA2 could only confirm and expand the clinical utility of testing, it would have been counter productive to science or to Myriad’s commercial development to require researchers to obtain a license.”⁵⁶ However, this is a questionable assertion, as constraining research may have actually commercially benefitted Myriad. After all, a dearth of independent research on the BRCA1 and BRCA2 genes shored up the value of Myriad’s own (proprietary) database of identified mutations.⁵⁷

Further exacerbating difficulties were divergences between Myriad’s actual

47. *Id.* at S42; Baldwin & Cook-Deegan, *supra* note 36, at 5.

48. Additionally, Myriad entered into an MOU with NCI to allow for discounted testing for any researcher working under an NCI-funded project, as noted above. Gold & Carbone, *supra* note 10, at S42.

49. *Id.* (emphasis added).

50. Julia Carbone et al., *DNA Patents and Diagnostics: Not a Pretty Picture*, 28 NATURE BIOTECHNOLOGY 784, 785 (2010).

51. Gold & Carbone, *supra* note 10, at S42.

52. Bunk, *supra* note 45.

53. *Id.* (quoting Gregory C. Critchfield, President, Myriad Genetics).

54. Gold & Carbone, *supra* note 10, at S58.

55. *See supra* notes 34 & 49-50 and accompanying text.

56. Gold & Carbone, *supra* note 10, at S44.

57. *See* Bunk, *supra* note 45; *infra* notes 246–56 and accompanying text.

policies, which seemed to evolve, and perceptions by the research community. As in many areas of law, perception is sometimes more important than reality.⁵⁸ Although Myriad's policy regarding unlicensed research use of BRCA diagnostic tests was, at times, quite permissive, the company failed to articulate this message coherently.⁵⁹ GDL helped fan the flames by widely publicizing Myriad's cease-and-desist letter "with the accompanying message that Myriad was attempting to impede basic scientific research."⁶⁰ Indeed, news accounts of Myriad Genetics have been consistently unflattering.⁶¹ Due in part to these media accounts, some scientists were wary about identifying new BRCA mutations and depositing them in public databases; they were concerned that such actions would constitute evidence of patent infringement.⁶² Some investigators stopped BRCA research or at least stopped publicly disseminating their results.⁶³ Notably, Myriad has only recently formalized and publicized its policy of "not imped[ing] noncommercial, academic research that uses patented technology licensed or owned by us."⁶⁴ Although Myriad claims that it has always permitted noncommercial use of the BRCA1 and BRCA2 genes, it is far from clear what this means, and some scientists understandably felt that their research might expose them to liability.

Given this state of affairs, the Supreme Court's invalidation of Myriad's isolated DNA patents creates greater real and perceived freedom to operate for researchers. The impact of the decision operates on two levels. First, it ensures that direct research on isolated DNA can proceed without a license. Scientists need not parse the meaning of Myriad's distinction between noncommercial and commercial research; any researcher may study isolated BRCA1 and BRCA2 DNA without fear of liability (assuming, of course, that she does not infringe any other patents). This episode illustrates the limitations of "private ordering" or voluntary forbearance from suit as the foundation for accommodating research interests and patent rights. Because of deficiencies in formulating and communicating Myriad's research policy, some researchers were chilled in pursuing BRCA research. Notwithstanding Myriad's recent policy articulations, the Supreme Court's decision sends a powerful

58. Holman, *supra* note 18, at 359 ("[I]f academic researchers face little or no real threat of a lawsuit based on patent infringement but nevertheless avoid the use of certain patented genes and other technologies in their research, it is this misperception rather than patents *per se* that is having the impact.").

59. Gold & Carbone, *supra* note 10, at S44. *See id.* at S58 ("Much of the policy storm surrounding Myriad and its genetic test stemmed from Myriad's failure to communicate its position clearly, if indeed its position was clear and stable to itself.").

60. Gold & Carbone, *supra* note 10, at S44.

61. One study of English-language newspaper articles on Myriad Genetics and BRCA patents found that 77.6% of the articles had a negative tone. Timothy Caulfield et al., Myriad *and the Mass Media: The Covering of a Gene Patent Controversy*, 9 GENETICS MED. 850, 852 (2007).

62. Gold & Carbone, *supra* note 10, at S44.

63. *Id.* at S61.

64. Myriad's Pledge to Our Patients and the Research Community, MYRIAD, <https://www.myriad.com/responsibility/myriads-pledge> [<http://web.archive.org/web/20140626130039/https://www.myriad.com/responsibility/myriads-pledge/>] (last visited June 26, 2014); *see* Arti K. Rai, *Diagnostic Patents at the Supreme Court*, 18 MARQ. INTELL. PROP. L. REV. 1, 4 (2014).

message to the scientific community that research on isolated DNA corresponding to BRCA genes can proceed without any threat of patent infringement.

Second, to the extent that the Supreme Court's decision leads to greater diagnostic testing, such commercial use will also enhance scientific understanding of BRCA1 and BRCA2. Diagnostic use never qualified for Myriad's research exception, but it holds significant research value. As mentioned, widespread diagnostic testing will reveal more genetic variants and provide insights into their biological significance. Widespread testing will not only generate more mutation data, it will also ensure the public availability of such data. Based on its patents, Myriad Genetics has developed an exclusive database of BRCA mutations containing over 300,000 cases.⁶⁵ This resource is highly valuable for interpreting individual test results as well as characterizing the biology of the BRCA genes. It is particularly useful for cataloging and interpreting so-called variants of unknown significance.⁶⁶ Greater access to commercial diagnostic testing promises greater access to genetic data,⁶⁷ thus advancing scientific understanding of these genes.⁶⁸

Of course, even after invalidation of its isolated DNA patents, Myriad has still asserted some intellectual property rights over BRCA testing. In the wake of the Court's ruling, several companies began offering clinical genetic diagnostic tests for mutations on BRCA1 and BRCA2.⁶⁹ However, Myriad quickly filed patent infringement suits against several companies, including Ambry Genetics and Gene By Gene.⁷⁰ In so doing, it asserted other product and process patents not directly

65. Robert Nussbaum, *Corporate Genetics: Even Without Gene Patents, Companies are Monopolizing Genetic Data*, MIT TECH. REV., Sep. 2013, at 12; Offit et al., *supra* note 9, at 2746. Myriad stopped contributing to the public Breast Cancer Information Core in 2004. Baldwin & Cook-Deegan, *supra* note 36, at 8; Derek So & Yann Joly, *Commercial Opportunities and Ethical Pitfalls in Personalized Medicine: A Myriad of Reasons to Revisit the Myriad Genetics Saga*, 11 CURRENT PHARMACOGENOMICS & PERSONALIZED MED. 98, 104 (2013).

66. Robert Cook-Deegan et al., *The Next Controversy in Genetic Testing: Clinical Data as Trade Secrets?*, 21 EUR. J. HUM. GENETICS 585, 585–86 (2013). Interestingly, when Myriad finds a new variant of unknown significance, it provides free testing to the patient's family to determine the variant's effects. *Id.* at 586.

67. Mark Ratner, *Myriad Decision Aftershocks Ripple Through Biotech*, 31 NATURE BIOTECH. 663, 664 box 1 (2013).

68. *See* Cook-Deegan et al., *supra* note 66, at 586 (describing several non-Myriad databases of BRCA variations).

69. *See* Editorial, *Myriad Diagnostic Concerns*, 31 NATURE BIOTECH. 571, 571 (2013) ("Ambry Genetics, Bio-Reference Laboratories, Pathway Genomics and Gene by Gene all announced lower-priced *BRC41/BRC42* tests within 24 hours of the ruling . . .").

70. *See* Complaint, Univ. of Utah Research Found. v. Gene By Gene, No. 2:13cv-00643, 2013 WL 3810325 (C.D. Utah July 10, 2013); Complaint, Univ. of Utah Research Found. v. Ambry Genetics Corp., No. 2:13-cv-00640-RJS, 2013 WL 3810321 (C.D. Utah July 9, 2013); Brent Kendall, *Myriad Genetics Presses Ahead After High Court Ruling on Patents*, WALL ST. J. L. BLOG (July 12, 2013, 4:03 PM), <http://blogs.wsj.com/law/2013/07/12/myriad-genetics-presses-ahead-after-high-court-ruling-on-patents/>. Ambry Genetics and Gene By Gene countersued, alleging antitrust violations by Myriad. *Gene By Gene Joins Ambry in Countersuit Against Myriad Alleging Antitrust Violations*, GENOMEWEB (Aug. 15, 2013), <https://www.genomeweb.com/sequencing/gene-gene-joins-ambry-countersuit-against-myriad-alleging-antitrust-violations> [<https://perma.cc/EQA3-WU7P>].

addressed by the Supreme Court's decision.⁷¹ Although litigation with Gene By Gene settled largely in Myriad's favor,⁷² a court rejected Myriad's motion for a preliminary injunction against Ambry.⁷³ Furthermore, the Federal Circuit has invalidated some of Myriad's key remaining patents,⁷⁴ and several cases have been dismissed or settled in favor of defendants.⁷⁵ For the time being, such testing—and its research benefits—is available on a wider basis. In sum, the Supreme Court's ruling loosens the constraints of Myriad's patents and its research policy, allowing more direct research on BRCA as well as knowledge-producing commercial testing to proceed.

II. UPSTREAM-DOWNSTREAM DYNAMICS IN PATENT LAW

Moving beyond the immediate impact on Myriad Genetics, the *Myriad* decision provides an opportunity to revisit a longstanding debate regarding the potential chilling effects of “upstream” patents, including DNA patents, on scientific research. Although theoretical concerns abound that DNA patents may impede scientific inquiry, most empirical research reveals little to no inhibitory effect.⁷⁶ An important exception, however, pertains to diagnostics, a realm in which patentees (like Myriad Genetics itself) have aggressively asserted exclusive rights. Given the link between diagnostics and scientific knowledge, the Supreme Court's ruling may have more significance in accelerating scientific research than initially perceived.

In theory, there are several mechanisms by which patents on research inputs,⁷⁷ such as isolated DNA, could stymie scientific inquiry.⁷⁸ After all, scientific progress is cumulative, building on previous discoveries.⁷⁹ First, a patent on an indispensable

71. Myriad claimed that even after the Court's decision, it maintains 515 of 520 patent claims on the test. Brian Resnick, *Why is Myriad Genetics Still Filing Patent Suits for Breast-Cancer Tests?*, NAT'L J. (Aug. 8, 2013), <http://www.nationaljournal.com/healthcare/why-is-myriad-genetics-still-filing-patent-suits-for-breast-cancer-tests-20130808> [<http://perma.cc/XC3D-JRSB>].

72. See Lora Hines, *Local Company Settles Gene-Testing Patent Case*, HOUS. CHRON. (Feb. 7, 2014), <http://www.houstonchronicle.com/business/medical/article/Local-company-settles-gene-testing-patent-case-5216088.php> [<http://perma.cc/HUX6-LTAX>] (last updated Mar. 15, 2014). Under the settlement, Gene By Gene agreed to stop selling and marketing gene-based diagnostics in North America. However, it can still offer whole genome and exome products and services, plus custom products that test variants of BRCA genes. *Id.*

73. Andrew Pollack, *Patentholder on Breast Cancer Tests Denied Injunction in Lawsuit*, N.Y. TIMES, Mar. 11, 2014, at B3.

74. *In re BRCA1- & BRCA2-Based Hereditary Cancer Test*, 774 F.3d 755 (Fed. Cir. 2014) (invalidating several of Myriad's primer and process patents related to the BRCA genes).

75. *Utah Court Dismisses Two More BRCA Testing Patent Lawsuits Against Labcorp, Ambry*, GENOMEWEB, Jan. 27, 2015, <https://www.genomeweb.com/business-news/utah-court-dismisses-two-more-brca-testing-patent-lawsuits-against-labcorp-ambry>.

76. See *infra* notes 97–100 and accompanying text.

77. Such inputs are commonly referred to as “research tools.” Peter Yun-hyoung Lee, *Inverting the Logic of Scientific Discovery: Applying Common Law Patentable Subject Matter Doctrine to Constrain Patents on Biotechnology Research Tools*, 19 HARV. J.L. & TECH. 79, 80 & n.3 (2005).

78. See Rebecca S. Eisenberg, *A Technology Policy Perspective on the NIH Gene Patenting Controversy*, 55 U. PITT. L. REV. 633, 647 (1994).

79. See Walsh et al., *supra* note 27, at 289–90.

resource for which there are no substitutes may impede biomedical research.⁸⁰ For example, the Wisconsin Alumni Research Foundation's patents on extracted and purified human embryonic stem cells have attracted such concern, as there is no scientifically adequate substitute for this biological entity.⁸¹ Second, a proliferation of upstream exclusive rights can impede downstream productive activity, a concern articulated in Michael Heller and Rebecca Eisenberg's influential theory of the anticommons.⁸² Although Heller and Eisenberg originally emphasized the potential for upstream patents to inhibit downstream *commercial* development,⁸³ the anticommons phenomenon could also inhibit basic research.⁸⁴ BRCA research itself provides an illustration of this phenomenon given that by 2005, the BRCA1 gene was subject to "14 different patents owned by 12 different entities."⁸⁵ Third, analytically distinct from the anticommons theory is the phenomenon of patent thickets, in which multiple overlapping patents cover a single technology.⁸⁶ In theory, a patent thicket in biomedicine could inhibit lines of research that infringe multiple sets of exclusive rights.

An important background consideration that exacerbates the chilling potential

80. See Peter Lee, *Contracting to Preserve Open Science: Consideration-Based Regulation in Patent Law*, 58 EMORY L.J. 889, 903 (2009). See generally, Robert P. Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839 (1990); Suzanne Scotchmer, *Standing on the Shoulders of Giants: Cumulative Research and the Patent Law*, 5 J. ECON. PERSP. 29 (1991). In gauging the potential for an upstream patent to inhibit research, "it is obviously of interest how essential or 'foundational' a research tool is for subsequent innovation, both in the sense of whether the tool is key to subsequent research and in the sense of the breadth of innovation that might depend on its use." Walsh et al., *supra* note 27, at 332.

81. See Christopher D. Hazuka, *Supporting the Work of Lesser Geniuses: An Argument for Removing Obstructions to Human Embryonic Stem Cell Research*, 57 U. MIAMI L. REV. 157, 198 (2002); Lee, *supra* note 77, at 91–92.

82. Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698, 698–99 (1998); see also Lee, *supra* note 80, at 892; Lee, *supra* note 77, at 83–86; Arti K. Rai & Rebecca S. Eisenberg, *Bayh-Dole Reform and the Progress of Biomedicine*, 66 L. & CONTEMP. PROBS. 289, 295 (2003).

83. Heller & Eisenberg, *supra* note 82, at 699 ("Each upstream patent allows its owner to set up another tollbooth on the road to product development, adding to the cost and slowing the pace of downstream biomedical innovation.").

84. Indeed, the potential for aggressive patenting strategies to inhibit biomedical research informed the findings of an NIH working group on research tools, which was chaired by Professor Eisenberg. See NAT'L INSTS. OF HEALTH (NIH), MEDICAL RESEARCH AND HUMAN EXPERIMENTATION LAW (1998), <http://biotech.law.lsu.edu/research/fed/NIH/researchtools/Report98.htm> [<http://perma.cc/VRM8-XXLV>]; Rebecca S. Eisenberg, *Bargaining Over the Transfer of Proprietary Research Tools: Is This Market Failing or Emerging?*, in EXPANDING THE BOUNDARIES OF INTELLECTUAL PROPERTY: INNOVATION POLICY FOR THE KNOWLEDGE SOCIETY 223, 248–98 (Rochele Cooper Dreyfuss et al. eds., 2004) (describing the findings of the working group).

85. Louis M. Solomon & Gregory J. Sieczkiewicz, *Law, Ethics, and Gender: Impact of the US Patent System on the Promise of Personalized Medicine*, 4 GENDER MED. 187, 189 (2007).

86. See Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1627 (2003); Peter Lee, *Patents and the University*, 63 DUKE L.J. 1, 26 (2013); Carl Shapiro, *Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard Setting*, in 1 INNOVATION POLICY AND THE ECONOMY 119 (Adam B. Jaffe et al. eds., 2001).

of patents is the United States' lack of a robust research exception to infringement.⁸⁷ Since at least the nineteenth century, U.S. patent doctrine has recognized an exception for infringement for purely noncommercial, "philosophical" uses of a patented invention.⁸⁸ At least one twentieth-century case suggested that the exception may extend to a university's unlicensed use of a patented invention for academic purposes.⁸⁹ However, in the 2002 case of *Madey v. Duke University*,⁹⁰ the Federal Circuit construed the common law experimental use exception very narrowly.⁹¹ Notwithstanding earlier perceptions, as a doctrinal matter, the common law experimental use exception does not apply to the vast majority of university-based research. The absence of this "safe harbor" heightens the possibility that patents on inputs to scientific inquiry—including isolated DNA—may impede research.

Concern over the potential for patents to inhibit research has been particularly acute in biomedicine.⁹² Indeed, Heller and Eisenberg's primary example of the anticommons involved multiple patents on gene fragments that would be costly to clear.⁹³ This concern has even informed government policy, most notably in the Human Genome Project (HGP). Organizers of the project "emphasized that, in order to reap the maximum benefit from the HGP, human DNA sequence should be freely available in the public domain."⁹⁴ This sentiment was operationalized in the so-called Bermuda Principles from 1996, in which an international consortium of genomic scientists unanimously agreed that human genomic DNA sequence information should be deposited in public databases within twenty-four hours of discovery.⁹⁵ Rapid disclosure served several purposes, including preempting patents on DNA sequences.⁹⁶

Although provocative, the threat of upstream patents chilling scientific research has been subject to significant empirical challenge. Influential studies by

87. See Timothy Caulfield et al., *Patenting Human Genetic Material: Refocusing the Debate*, 1 NATURE REVIEWS: GENETICS 227, 229 (2000); Lee, *supra* note 77, at 86–87.

88. See *Whittemore v. Cutter*, 29 F. Cas. 1120, 1121 (C.C.D. Mass. 1813) (No. 17,600).

89. See *Ruth v. Stearns-Roger Mfg.*, 13 F. Supp. 697, 713 (D. Colo. 1935).

90. *Madey v. Duke Univ.*, 307 F.3d 1351 (Fed. Cir. 2002).

91. See Lee, *supra* note 86, at 57.

92. See, e.g., John J. Doll, *The Patenting of DNA*, 280 SCIENCE 689, 689 (1998); Jon F. Merz & Mildred K. Cho, *What Are Gene Patents and Why Are People Worried About Them?*, 8 COMMUNITY GENETICS 203, 207 (2005).

93. Heller & Eisenberg, *supra* note 82, at 698.

94. NAT'L HUMAN GENOME RESEARCH INST., POLICY ON AVAILABILITY OF GENOMIC DNA SEQUENCE FUNDED BY NHGRI (1999), <http://www.genome.gov/pfv.cfm?pageID=10001802> [<http://perma.cc/JN6Q-SUNZ>].

95. *Policies on Release of Human Genomic Sequence Data Bermuda-Quality Sequence—Summary of Principles Agreed Upon at the First International Strategy Meeting on Human Genome Sequencing*, HUMAN GENOME PROJECT INFO. ARCHIVE, http://web.ornl.gov/sci/techresources/Human_Genome/research/bermuda.shtml [<http://perma.cc/2LXE-FEYX>] (last visited Oct. 7, 2015); see Jorge L. Contreras, *Bermuda's Legacy: Policy, Patents and the Design of the Genome Commons*, 12 MINN. J.L. SCI. & TECH. 61, 64 (2011).

96. This effort was consistent with NIH's evolving policy of not seeking patents on cDNAs of unknown function. See Eisenberg, *supra* note 78, at 633–34.

John Walsh and his colleagues have cast doubt on the presence of an anticommons phenomenon in basic biomedical research.⁹⁷ One study found that only one percent of a random sample of academic scientists reported a project delay of more than one month due to patents on research inputs.⁹⁸ Another found “only limited support for the idea that negotiations over rights stymie precommercial research conducted in universities.”⁹⁹ A survey of the American Association for the Advancement of Science found “very little evidence of an ‘anticommons problem’” in the United States and Japan.¹⁰⁰ Although most empirical analyses find little or no evidence of an anticommons in biomedical research, this phenomenon has received some validation. For example, Fiona Murray and Scott Stern found that citations to scientific articles decline after a patent is granted on the research described in the article.¹⁰¹ They thus present “robust evidence for a quantitatively modest but statistically significant anti-commons effect.”¹⁰²

Several factors explain why patents may not inhibit research as much as anticipated. First, a de facto experimental use exception operates whereby patentees rarely sue basic researchers—especially university scientists—for patent infringement.¹⁰³ The absence of significant monetary damages, fear of undermining potential licensing relationships, and concerns about harming public relations all dissuade patentees from suing universities.¹⁰⁴ Indeed, some patentees welcome unlicensed use of their technologies by academics because those patentees stand to benefit from any new discoveries related to their invention.¹⁰⁵ This principle appears to have informed Myriad’s rather permissive approach to research use of BRCA1 and BRCA2 patents.¹⁰⁶ Similarly, Ariad Pharmaceuticals, which patented the NF- κ B molecular pathway, actively encouraged noncommercial use of its patent without a license.¹⁰⁷ Short of simply tolerating infringement, patentees also routinely

97. Walsh et al., *supra* note 27, at 289, 331; John P. Walsh et al., *Patents, Material Transfers and Access to Research Inputs in Biomedical Research*, in FINAL REPORT TO THE NATIONAL ACADEMY OF SCIENCES’ COMMITTEE INTELLECTUAL PROPERTY RIGHTS IN GENOMIC AND PROTEIN-RELATED INVENTIONS (2005), <http://www2.druid.dk/conferences/viewpaper.php?id=776&cf=8> [<http://perma.cc/4YZ7-9Y4H>] (finding minimal blocking effects from patents).

98. Walsh et al., *supra* note 97, at 2.

99. Walsh et al., *supra* note 27, at 317.

100. AM. ASS’N FOR THE ADVANCEMENT OF SCI., INTERNATIONAL INTELLECTUAL PROPERTY EXPERIENCES: A REPORT OF FOUR COUNTRIES 12 (2007).

101. Murray & Stern, *supra* note 24, at 683; *see also* Kenneth G. Huang & Fiona E. Murray, *Does Patent Strategy Shape the Long-Run Supply of Public Knowledge? Evidence from Human Genetics*, 52 ACAD. MGMT. J. 1193, 1198 (2009).

102. Murray & Stern, *supra* note 24, at 651.

103. Rai & Eisenberg, *supra* note 82, at 296 (characterizing the informal norm against suing nonprofit researchers as a form of price discrimination).

104. Walsh et al., *supra* note 27, at 325.

105. *Id.* at 326; *see* Dreyfuss, *supra* note 26, at 8 (“Until there are ways to translate the advances in the sciences of biotechnology into products, patent holders may be very happy to let researchers infringe, in the hope that the infringers will find therapies (or methods for developing them).”).

106. Gold & Carbone, *supra* note 10, at S64.

107. Walsh et al., *supra* note 97, at 30.

charge lower licensing fees for academic versus for-profit uses of their patents.¹⁰⁸ For example, as noted, Myriad discounted whole-gene testing for NIH-funded cancer researchers.¹⁰⁹

Second, in addition to patentees frequently not asserting their patents, university scientists routinely ignore patents when conducting their research.¹¹⁰ The norm of ignoring patents thus represents a “working solution” to the threat of patent holdup.¹¹¹ Notably, this norm continued even after *Madey v. Duke*, which articulated a very narrow formal experimental use exception.¹¹² The combined effect of most patentees as well as scientists ignoring patents in the research context means that in the vast majority of cases, patents do not obstruct university research. Some commentators, however, have questioned the long-term viability of this regime.¹¹³ Concerned by the fragility of “working solutions,” they have argued for a more robust, legally grounded experimental use exception.¹¹⁴ And it is important to keep in mind that “academic” uses of research inputs are not the only ones that bear scientific fruit. As discussed above, commercial diagnostic testing—which is not subject to the de facto experimental use exception—yields significant research insights as well.¹¹⁵

Within biomedical science, concerns over anticommons and chilling effects have particularly focused on “gene patents.”¹¹⁶ It has been estimated that twenty percent of human genes are patented,¹¹⁷ although that figure has been seriously questioned.¹¹⁸ The prevalence and fundamentality of gene patents has fueled concerns that exclusive rights may inhibit both patient access to diagnostic tests as well as basic research.¹¹⁹ Notably, much of this controversy has focused on Myriad

108. Walsh et al., *supra* note 27, at 302.

109. *Id.*

110. *Id.* at 324; Walsh et al., *supra* note 97, at 3; John P. Walsh et al., *View from the Bench: Patents and Material Transfers*, 309 SCI. & L. 2002, 2002 (2005).

111. See David E. Adelman, *A Fallacy of the Commons in Biotech Patent Policy*, 20 BERKELEY TECH. L.J. 985, 1000 (2005).

112. Walsh et al., *supra* note 97, at 15.

113. Rebecca S. Eisenberg, *Noncompliance, Nonenforcement, Nonproblem? Rethinking the Anticommons in Biomedical Research*, 45 HOUS. L. REV. 1059, 1097 (2008).

114. *See id.*

115. *See supra* notes 26–27 and accompanying text.

116. The term “gene patents” is highly contested. In one view, it encompasses a wide range of composition of matter patents on various forms of isolated DNA as well as patents on processes that involve isolated DNA. Offit et al., *supra* note 9, at 2744. *But see* Holman, *supra* note 18, at 315–19 (critiquing prevailing definitions of gene patents).

117. Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 SCIENCE 239, 239 (2005).

118. *See, e.g.,* Christopher M. Holman, *Debunking the Myth that Whole-Genome Sequencing Infringes Thousands of Gene Patents*, 30 NATURE BIOTECH. 240, 240–41 (2012).

119. Lori B. Andrews, *Genes and Patent Policy: Rethinking Intellectual Property Rights*, 3 NATURE REVIEWS: GENETICS, 803, 803 (2002); Timothy Caulfield et al., *Evidence and Anecdotes: An Analysis of Human Gene Patenting Controversies*, 24 NATURE BIOTECH. 1091, 1091 (2006); Susanne B. Haga & Huntington F. Willard, *Defining the Spectrum of Genome Policy*, 7 NATURE REVIEWS: GENETICS 966, 968 (2006).

Genetics and its isolated DNA and cDNA patents.¹²⁰ Here again, however, empirical studies specifically examining gene patents have found little inhibitory effect on research.¹²¹ A metastudy of gene patents concludes that “the effects predicted by the anticommons problem are not borne out in the available data.”¹²² Similarly, Timothy Caulfield notes that “despite all the noise, there is still no solid evidence that gene patents hurt basic research.”¹²³ Rebecca Eisenberg, revisiting the anticommons thesis a decade after her seminal coauthored article, observes that “patents appear to have a greater impact on downstream product development than on upstream academic research.”¹²⁴

Along these lines, studies suggest that gene patents do not seriously chill whole genome sequencing. Such sequencing has significant clinical and research value, but some observers worry that sequencing a person’s entire genome may infringe thousands of isolated DNA patents. Indeed, fears that isolated DNA patents could inhibit whole genome sequencing surfaced in the *Myriad* litigation itself. At the Federal Circuit, Judge Bryson argued in his partial concurrence that isolated DNA patents might inhibit this valuable activity.¹²⁵ Studies indicate, however, that isolated DNA patents do not significantly threaten whole genome sequencing.¹²⁶ Both existing methods for whole genome shotgun sequencing as well as next generation nanopore sequencing¹²⁷ do not generate significant numbers of gene fragments that are likely to infringe isolated DNA patents.¹²⁸

120. Baldwin & Cook-Deegan, *supra* note 36, at 2 (“While there have been gene patent controversies over the years, none has approached the intensity of public conflict over *BRC-A* patents.”); Caulfield et al., *supra* note 119, at 1091; Holman, *supra* note 18, at 299.

121. See Subhashini Chandrasekharan & Robert Cook-Deegan, *Gene Patents and Personalized Medicine—What Lies Ahead?*, 92 *GENOME MED.* x.1, x.1 (2009) (“Gene patents have generally not impeded biomedical research . . .”); Nicol, *supra* note 17, at 35 (“On the available evidence, the detrimental impact of DNA patents appears to be considerably lower than anticipated by many commentators, even in the contexts of research and consumer access to healthcare.”). *But see* Isaac Rabino, *How Human Geneticists in US View Commercialization of the Human Genome Project*, 29 *NATURE GENETICS* 15, 15 (2001) (reporting survey results finding that forty-nine percent of respondents from the American Society of Human Genetics said human-DNA patenting has at some time limited their research).

122. Caulfield et al., *supra* note 119, at 1092.

123. Timothy Caulfield, *Do Gene Patents Hurt Research? The Data Say They Don't*, *SCI. PROGRESS* (Oct. 29, 2009), <http://scienceprogress.org/2009/10/do-gene-patents-hurt-research/> [<http://perma.cc/2YPS-GTUJ>].

124. Eisenberg, *supra* note 113, at 1062. Some empirical evidence, however, does show that gene patents exhibit a chilling effect on research. Huang & Murray, *supra* note 101, at 1214 (“A strict interpretation of our results suggests follow-on genetic researchers forego about one in ten research projects . . . through the causal negative impact of a gene patent grant.”).

125. *See, e.g., Ass’n for Molecular Pathology v. USPTO*, 653 F.3d 1329, 1374 (Fed. Cir. 2011) (Bryson, J., concurring in part and dissenting in part) (“[S]ome of Myriad’s challenged composition claims effectively preempt any attempt to sequence the BRCA genes, including whole-genome sequencing.”).

126. W. Nicholson Price II, *Unblocked Future: Why Gene Patents Won’t Hinder Whole Genome Sequencing and Personalized Medicine*, 33 *CARDOZO L. REV.* 1601, 1606 (2012).

127. *Id.* at 1606.

128. Conley, *supra* note 23; Holman, *supra* note 118, at 242; Holman, *supra* note 18, at 326; Offit et al., *supra* note 9, at 2746.

Similarly, it is unlikely that gene patents significantly impede efforts to express therapeutic proteins. Such protein expression is one of the most important commercial applications of human DNA, but it also holds research interest as well. However, it may not be necessary to isolate DNA (and thus infringe isolated DNA patents) to express a protein, particularly based on new techniques of gene activation.¹²⁹ Furthermore, the trend in biotechnology is to produce synthetic varieties of therapeutic proteins rather than replicate naturally-occurring proteins. Scientists create such proteins by modifying sequences of genomic DNA, thus designing around isolated DNA patents.¹³⁰ As Christopher Holman observes, “as the chemical structure of therapeutic proteins continue to diverge farther from naturally-occurring human proteins, human gene patents will probably play a diminishingly important role in providing market exclusivity for these important products.”¹³¹

Diagnostics, however, are a different story. While gene patents do not seriously threaten whole genome sequencing or protein expression, they have significantly curtailed diagnostic testing.¹³² In this context, patentees have not voluntarily refrained from suit,¹³³ and they have even asserted their rights against university researchers.¹³⁴ Given that diagnostics produce relatively low profits, laboratories are likely to simply cease testing in the face of threatened patent enforcement.¹³⁵ One survey found that twenty-five percent of clinical laboratories stopped performing a clinical genetic test because of patent concerns, and fifty-three percent did not develop a new test because of such concerns.¹³⁶ In particular, when diagnostic research also comprises a commercial activity, “patent holders are more likely to assert and clinical researchers more likely to abandon infringing activities.”¹³⁷ Such behavior is illustrated by Myriad Genetics itself,¹³⁸ which curtailed clinical genetic diagnostic testing at the University of Pennsylvania GDL.¹³⁹ Another biotechnology firm, Chiron, has also developed a reputation for

129. Holman, *supra* note 18, at 327.

130. *Id.* at 339; *see generally* Sapna Kumar & Arti Rai, *Synthetic Biology: The Intellectual Property Puzzle*, 85 TEX. L. REV. 1745 (2007) (describing general techniques of synthetic biology).

131. Holman, *supra* note 18, at 356.

132. Caulfield et al., *supra* note 119, at 1092; *see* Chandrasekharan & Cook-Deegan, *supra* note 121, at x.2 (“Multi-gene diagnostic tests may infringe existing DNA-sequence or method claims . . .”).

133. Dreyfuss, *supra* note 26, at 8; *see also* John F. Merz, *Discoveries: Are there Limits on What May Be Patented?*, in WHO OWNS LIFE? 99, 101 (David Magnus et al. eds. 2002) (arguing that disease gene patents and exclusive licenses “restrict clinical observation and formal research”).

134. Eisenberg, *supra* note 113, at 1071–72; Walsh et al., *supra* note 27, at 317–18.

135. Carbone et al., *supra* note 50, at 788.

136. Mildred K. Cho et al., *Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services*, 5 J. MOLECULAR DIAGNOSTICS 3, 5 (2003).

137. Walsh et al., *supra* note 110, at 2002.

138. *See* Eisenberg, *supra* note 113, at 1081–82; Parthasarathy, *supra* note 3, at 22 (“Using a combination of threats and bargaining, [Myriad] forced the other testing providers out of the market by 1999.”); Jacob S. Sherkow & Christopher Scott, *Myriad Stands Alone*, 32 NATURE BIOTECH. 620, 620 (2014) (describing Myriad as “voraciously litigious”).

139. *See* Offit et al., *supra* note 9, at 2746; Walsh et al., *supra* note 27, at 312; *supra* Part I.

aggressively enforcing its patents.¹⁴⁰ Additionally, SmithKline Beecham Clinical Laboratories asserted its patents on hemochromatosis to shut down testing, thus “demonstrat[ing] how a gene patent, when enforced, can serve to stifle or hinder human genetics research.”¹⁴¹ Patentees have also asserted their rights to constrain diagnostic testing on genes related to Alzheimer’s disease, long-QT syndrome, cystic fibrosis, spinocerebellar ataxia type 1, and Canavan disease, among other conditions.¹⁴²

Because diagnostic testing also generates fundamental biological knowledge, patent-based chilling of such testing has the effect of inhibiting scientific research. As described above, widespread clinical testing reveals previously unrecognized mutations that may contribute to disease.¹⁴³ Significant clinical study is necessary to understand a newly discovered gene, and patent enforcement produces “fear that limiting clinical testing will inhibit further discovery as well as the understanding that emerges naturally from broad medical adoption.”¹⁴⁴ For instance, although many laboratories routinely offered genetic tests for haemochromatosis, thirty percent of surveyed labs discontinued services or did not develop tests when patent concerns came to light.¹⁴⁵ In countries where isolated DNA associated with haemochromatosis and Alzheimer’s disease is not patented, researchers have found new disease-contributing mutations that were previously undiscovered.¹⁴⁶ A study found that fourteen of twenty-seven owners of patents on genetic tests would require a license for a researcher to study the “penetrance and prevalence of the genetic mutation covered by their patent.”¹⁴⁷ Viewed in this light, the Supreme Court’s holding that isolated DNA is not patentable subject matter may accelerate genetic diagnostic testing more generally, thus producing valuable research insights. This is especially the case because other genes may not be subject to the same kind of overlapping exclusive rights as BRCA1 and BRCA2.¹⁴⁸ In such cases, isolated DNA patents may represent the primary barrier to widespread diagnostic testing, thus rendering elimination of such patents particularly impactful.

Of course, an opposing narrative exists in which maintaining the patent eligibility of isolated DNA would actually lead to a net *increase* in scientific research. Based on the traditional theory of patent protection, exclusive rights may encourage parties to invest the time, energy, and resources to “invent” isolated DNA

140. Walsh et al., *supra* note 27, at 312.

141. Andrew S. Robertson, *The Role of DNA Patents in Genetic Test Innovation and Access*, 9 NW J. TECH. & INTELL. PROP. 377, 384 (2011).

142. Blanton, *supra* note 33, at 3; Carbone et al., *supra* note 50, at 786 (explaining that patentees Athena Diagnostics and PGxHealth have prevented university laboratories from offering genetic tests for long-QT syndrome and Alzheimer’s disease, respectively).

143. Andrews, *supra* note 119, at 804; *see supra* notes 26–27 and accompanying text.

144. John F. Merz et al., *Diagnostic Testing Fails the Test*, 415 NATURE 577, 577 (2002).

145. *Id.*

146. Andrews, *supra* note 119, at 804.

147. Caulfield et al., *supra* note 87, at 230; Anna Schissel et al., *Survey Confirms Fears About Licensing of Genetic Tests*, 402 NATURE 118, 118 (1999).

148. *See generally* Sherkow & Scott, *supra* note 138.

sequences as well as develop them into useful applications like diagnostic tests. In some cases, “companies have invested heavily in developing the clinical evidence base for diagnostics to exploit a strong IP position based on exclusive licenses to DNA patents.”¹⁴⁹ In particular, biomarker patents may support “virtuous corporate behavior,” motivating significant private investment in new diagnostics.¹⁵⁰ Along these lines, it is possible that the absence of patent protection on isolated DNA following *Myriad Genetics* may actually *decrease* research.

More subtly, however, the patent eligibility of isolated DNA functions as a policy lever that toggles between encouraging two different types of research. Maintaining isolated DNA in the public domain may promote more basic research by the scientific community in general as well as facilitate research insights that arise from widespread diagnostic testing.¹⁵¹ While rendering isolated DNA eligible for patenting may inhibit this research, it may spur more targeted research by parties who are incentivized by exclusive rights to discover new gene sequences and perform applied research to translate them into commercial diagnostic tests.

The argument that maintaining the patent eligibility of isolated DNA would significantly enhance research, however, is questionable on several fronts. First, such patents play a relatively small role in the initial discovery and sequencing of genes, particularly given that a substantial amount of (patented) genetic discoveries arise from academic science.¹⁵² In such cases, public funding, professional rewards, and scientific norms of discovery already provide robust incentives for invention, thus undermining the justification for exclusive rights.¹⁵³ Second, exclusive rights also play a rather minimal role in translating existing genetic discoveries into commercial diagnostic tests.¹⁵⁴ Compared to developing new therapeutic agents, developing diagnostic tests tends to be faster, more technically certain, less costly, and less burdened by regulatory requirements.¹⁵⁵ Oftentimes, multiple entities independently develop the same or similar diagnostic tests, thus casting doubt on the need for patent exclusivity to drive such development. In the case of BRCA testing, for example, several public and private entities, including Myriad Genetics, OncorMed, the Genetics and IVF Institute, and GDL, offered BRCA diagnostic testing prior to Myriad’s assertions of patent exclusivity.¹⁵⁶ The Secretary of Health

149. Michael M. Hopkins & Stuart Hogarth, *Biomarker Patents for Diagnostics: Problem or Solution?*, 30 NATURE BIOTECH. 498, 499 (2012).

150. *Id.*

151. See *supra* notes 26–27 and accompanying text.

152. Offit et al., *supra* note 9, at 2745; cf. Rochelle C. Dreyfuss & James P. Evans, *From Bilski Back to Benson: Preemption, Inventing Around, and the Case of Genetic Diagnostics*, 63 STAN. L. REV. 1349, 1374 (2011) (“[T]he genetics case studies show that associations between genotype and specific diseases are most often identified by academics.”).

153. See generally Lee, *supra* note 80, at 893–94.

154. Heller & Eisenberg, *supra* note 82, at 698–99.

155. Robertson, *supra* note 141, at 390–95.

156. Fabienne Orsi & Benjamin Coriat, *Are “Strong Patents” Beneficial to Innovative Activities? Lessons from the Genetic Testing for Breast Cancer Controversies*, 14 INDUS. & CORP. CHANGE 1205, 1213 (2005); see Park, *supra* note 11, at 522.

and Human Services' Advisory Committee on Genetics, Health, and Society similarly concluded that patents were not necessary to ensure the development and dissemination of several diagnostic tests.¹⁵⁷

Ultimately, the question of whether the patent eligibility of isolated DNA promotes more research (by incentivizing invention and commercialization) or less research (by stymying use by others) is a complicated empirical inquiry. However, from a theoretical standpoint, it seems reasonable that more aggregate research would be performed by a broad scientific community unconstrained by patents than by a single patentee seeking to exploit exclusive rights to commercialize a discovery.¹⁵⁸ Furthermore, these patents may not be necessary to spur initial investigations or develop commercial applications, and evidence suggests that patentees do not even enforce them stringently (outside of the diagnostics context).

More broadly, patents on research inputs (including isolated DNA) have second-order effects aside from directly impeding research activities. Studies show that patents delay publication of new biotechnology discoveries.¹⁵⁹ Additionally, researchers are less likely to work in areas after significant findings have been patented, and more researchers enter a field and do more varied work after patents expire.¹⁶⁰ Furthermore, patents on inputs to scientific experimentation may contribute to a culture of secrecy within academia or skew university research toward more applied ends.¹⁶¹ These second-order effects may ultimately chill or distort research as well.

Although this Article has focused on the Supreme Court's invalidation of Myriad Genetics' isolated DNA patents, it will briefly consider the research implications of the Court's additional holding that cDNA remains eligible for patenting. In a somewhat simplified dichotomy, commentators tend to associate

157. U.S. DEP'T OF HEALTH & HUMAN SERVS., SECY'S ADVISORY COMM. ON GENETICS, HEALTH & SOCIETY, *GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON PATIENT ACCESS TO GENETIC TESTS 2* (2010). Historically, many types of diagnostics were not regulated by the Food and Drug Administration (FDA), which may have contributed to their relatively low development costs. This may change, however, as the FDA increases its regulation of companion diagnostics and laboratory developed tests. See Press Release, U.S. Food & Drug Admin., FDA Takes Steps to Help Ensure the Reliability of Certain Diagnostic Tests (July 31, 2013), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm407321.htm> [<http://web.archive.org/web/20151008064332/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm407321.htm>]. See generally, Editorial, *supra* note 69, at 571.

158. Cf. Merges & Nelson, *supra* note 80, at 872–80 (arguing that simultaneous development of a technological prospect by multiple parties yields more robust innovation than coordinated development by a single entity).

159. David Blumenthal et al., *Withholding Research Results in Academic Life Science: Evidence from a National Survey of Faculty*, 277 JAMA 1224, 1224 (1997).

160. Huang & Murray, *supra* note 101, at 1214.

161. Caulfield et al., *supra* note 87, at 230; cf. Huang & Murray, *supra* note 101, at 1197; Nicol, *supra* note 17, at 16 (describing commentary suggesting that patenting may alter “fundamental scientific norms at the upstream end of the research-development continuum”). But see Caulfield et al., *supra* note 119, at 1093 (questioning whether an increase in academic secrecy is attributable to patents); Walsh et al., *supra* note 27, at 305 (suggesting that redirecting scientific efforts toward more practical ends may be socially beneficial).

isolated DNA with diagnostics and research while viewing cDNA, which has noncoding nucleotides synthetically removed, as more important for commercially expressing therapeutic proteins.¹⁶² However, cDNA also has significant research uses, and the affirmation that cDNA is patentable subject matter may have “important consequences for research, including research to discover new disease treatments and create new genetic tests.”¹⁶³ For example, scientists often utilize cDNA to create animal models of disease,¹⁶⁴ such as fruit flies with cDNA disease genes that facilitate research on neurodegenerative conditions.¹⁶⁵ Some have speculated that the Court’s ruling may encourage researchers to patent cDNA as well as other forms of artificially synthesized DNA, perhaps simply to preserve freedom to operate.¹⁶⁶ It is difficult to assess the magnitude of this development, however, partly because the Court’s holding that cDNA comprises patentable subject matter merely maintains the status quo. Furthermore, even if more parties begin patenting cDNA, they are unlikely to assert these patents against researchers in noncommercial, academic contexts for the reasons described above.¹⁶⁷ Perhaps the largest implication of the Court’s “split decision” on the patent eligibility of isolated DNA and cDNA is the challenge of delineating when a natural substance is modified “enough” to become a patentable technology,¹⁶⁸ a challenge this Article explores further below.¹⁶⁹

In sum, the Court’s ruling that isolated DNA is not patentable subject matter is likely to create more freedom to operate not only for BRCA research but for genetic research more generally. Empirical studies find little general evidence that patents chill biomedical research. This suggests that the patent eligibility of isolated DNA has little impact on scientific inquiry. One of the consistent themes of this study, however, is that context and definitions matter. Diagnostics are an important exception where patentees have aggressively asserted their rights, and “commercial” testing can yield significant research insights. To the extent that the Court’s ruling increases diagnostic testing, it will also help accelerate scientific research about genes and disease-causing mutations.

162. See Brief for Amicus Curiae Eric S. Lander in Support of Neither Party, *supra* note 15, at 27–28 (arguing that “most medically and commercially important biotechnology products” depend on non-naturally occurring DNA molecules, such as cDNA); Arti K. Rai & Robert Cook-Deegan, *Moving Beyond “Isolated” Gene Patents*, 341 SCIENCE 137, 137 (2013).

163. Megan Krench, *New Supreme Court Decision Rules that cDNA is Patentable—What It Means for Research and Genetic Testing*, SCL. AM. (July 9, 2013), <http://blogs.scientificamerican.com/guest-blog/2013/07/09/new-supreme-court-decision-rules-that-cdna-is-patentablewhat-it-means-for-research-and-genetic-testing/> [<http://perma.cc/ZZ9V-XP6N>].

164. *Id.*

165. *Id.*

166. *See id.*

167. *See supra* notes 102–113 and accompanying text.

168. Krench, *supra* note 163; *see also* Seidenberg, *supra* note 8 (“The patent-eligibility of synthetic molecules will be an issue in the future.” (quoting Professor Rochelle Dreyfuss, N.Y.U. School of Law)).

169. *See infra* Section III.B.

III. BROADER DOCTRINAL IMPLICATIONS

Beyond its impacts on BRCA research and genetic research more generally, *Myriad* holds broader doctrinal implications for the intersection of patents and scientific inquiry. First, the opinion helps solidify patentable subject matter doctrine as a robust “policy lever” for policing the boundaries of exclusive rights.¹⁷⁰ Second, within the context of several recent Supreme Court patentable subject matter decisions, *Myriad* signals a strong prudential interest in carving out a zone of nonpatentability for natural phenomena. Here again, definitional fluidity plays an important role, for the opinion both reflects and reinforces significant judicial discretion in determining what constitutes “nature” for purposes of subject matter exclusions. Such a pragmatic, policy-oriented approach to patent eligibility creates greater flexibility to challenge patents in research contexts going forward.

A. Elevating Patentable Subject Matter Doctrine to Police Patentability

One of the significant implications of *Myriad* is that it helps galvanize 35 U.S.C. § 101 as a robust doctrinal lever for filtering out patents. As noted earlier, plaintiffs and their counsel deliberately chose patentable subject matter, rather than other doctrinal grounds, as the sole vehicle for challenging *Myriad*’s patents.¹⁷¹ From a macroscopic perspective, it is not clear that patent-eligibility doctrine—which operates as a blunt on-off switch—is the optimal mechanism for policing the boundaries of patentability.¹⁷² First, such categorical exclusions are difficult to define and apply, a matter discussed more fully below.¹⁷³ Second, other patentability doctrines may offer more nuanced, granular means for regulating patentability. For instance, courts have used the written description requirement to invalidate specific gene patent claims that the patent disclosure did not adequately support.¹⁷⁴ Nonobviousness doctrine offers another possibility; the now-routine nature of isolating and sequencing DNA, as well as discerning nucleotide sequences from known protein structures, is likely to render much isolated DNA obvious under 35 U.S.C. § 103.¹⁷⁵ Nonetheless, the *Myriad* decision demonstrates the effectiveness of

170. See generally Burk & Lemley, *supra* note 86.

171. See Park, *supra* note 11, at 529.

172. Cf. Rai, *supra* note 64, at 3 (“[P]atent validity is a blunt and over-inclusive mechanism for policing concerns about access.”).

173. See *infra* Section III.B.

174. See, e.g., *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1575 (Fed. Cir. 1997) (holding that claims covering cDNA that produced insulin in all vertebrates and mammals were invalid in light of written description that described cDNA that produced insulin only in rats).

175. Dreyfuss, *supra* note 26, at 3; see 35 U.S.C. § 103 (2012). Because *Myriad* filed for its patents before March 16, 2013, it was subject to the nonobvious requirements prior to the America Invents Act. Arguably, the nonobviousness hurdle is slightly higher under the AIA, as the date of prior art is pushed up to the date of filing a patent application rather than the date of invention. Additional developments in nonobviousness doctrine have also heightened this requirement of patentability. See *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 416–17, 421 (2007); *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009) (holding that obvious to try may, in some circumstances, indicate obviousness).

patentable subject matter doctrine as a vehicle for invalidating patents, which will likely encourage similar challenges going forward.

In addition to elevating the importance of patentable subject matter doctrine, *Myriad* also enhances judicial discretion in applying it. Some authorities, including Federal Circuit judges, counsel a rather modest role for § 101; they recommend that it operate as a “coarse eligibility filter”¹⁷⁶ that leaves more nuanced analyses of patentability to other doctrines. There have even been suggestions for courts to scrutinize other requirements of patentability first, analyzing patentable subject matter later only if necessary.¹⁷⁷ Although the *Myriad* Court considered patent eligibility to be simply a “threshold test,”¹⁷⁸ it elevated the importance of this doctrinal test as a substantive filter for patent law. In so doing, it intrinsically enhanced judicial discretion in patentability determinations. Given the rather subjective, malleable nature of patentable subject matter exclusions, courts will exercise greater discretion in determining patent validity, a development more fully explored below.

B. *Creating a Strong and Flexible Exception for “Nature” from Patent Eligibility*

In addition to elevating the robustness of patentable subject matter doctrine as a mechanism for challenging patents, *Myriad* helps expand its power and flexibility. As we will see, *Myriad* helps solidify both a strong exclusion for nature from patentable subject matter as well as significant judicial discretion in identifying natural phenomena for this purpose. To understand this development—as well as its potential impact on scientific research—it is necessary to situate *Myriad* within the context of several recent Supreme Court decisions addressing patentable subject matter.

Some of the foundations of *Myriad*’s invalidation of isolated DNA patents were laid in *Bilski v. Kappos*, a 2010 case addressing the patent eligibility of a business method for hedging risks in commodities trading.¹⁷⁹ The Supreme Court invalidated the claims at issue, reasoning that they covered patent-ineligible “abstract ideas.”¹⁸⁰ On its face, this case has little to do with *Myriad*’s holding regarding isolated DNA. However, *Bilski*’s concern with abstract ideas stemmed from a broader objective to prevent patents from “preempting” commonly used approaches and ideas that are

176. See *Research Corp. Tech., Inc. v. Microsoft Corp.*, 627 F.3d 859, 869 (Fed. Cir. 2010); Rebecca S. Eisenberg, *Wisdom of the Ages or Dead-Hand Control? Patentable Subject Matter for Diagnostic Methods After In re Bilski*, 3 J.L. TECH. & INTERNET 1, 34–35 (2012).

177. See Dennis Crouch & Robert P. Merges, *Operating Efficiently Post-Bilski by Ordering Patent Doctrine Decision-Making*, 25 BERKELEY TECH. L.J. 1673, 1674, 1676 (2010).

178. *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010).

179. *Id.* at 3218.

180. See *id.* at 3229–31. The Federal Circuit had invalidated the patents as failing the machine-or-transformation test, by which a process is only eligible for patenting if it meaningfully involves a machine or effectuates a transformation of one thing or state to another. *In re Bilski*, 545 F.3d 943, 954, 961, 963 (Fed. Cir. 2008). The Supreme Court, however, rejected the machine-or-transformation test as the sole test governing the patent eligibility of processes. *Bilski*, 130 S. Ct. 3229–31.

critical to wide swaths of technological development.¹⁸¹ In surprising ways, *Bilski*, a case about hedging risks in financial transactions, has important implications for the Court's treatment of nature. As Rochelle Dreyfuss and James Evans observe, "since science must deal with the natural world, the inability to invent around is also a clue to *Bilski*'s other exclusions: laws of nature and natural phenomena."¹⁸² Extrapolating from *Bilski* to the genetics context, the difficulty of inventing around claims to gene sequences as well as associations between sequences and disease heightens prudential interest in keeping these assets in the public domain.¹⁸³

In expressing concerns with preemption, *Bilski* left significant discretion to courts to identify instances of preemption and apply subject matter exclusions to prevent them. The majority opinion in *Bilski* does not offer much direct guidance for how to apply patentable subject matter doctrine or the policy objectives that the doctrine seeks to achieve.¹⁸⁴ This void leaves significant discretion to courts, and other authorities have weighed in to help guide application of patentable eligibility doctrine. Most notably, both concurring opinions in *Bilski* frame preemption analysis within concerns that patents on foundational assets may impede subsequent innovation. In his concurrence, Justice Stevens cites earlier precedent holding that laws of nature, natural phenomena, and abstract ideas are not eligible for patenting because they "are the basic tools of scientific and technological work."¹⁸⁵ Justice Breyer articulates a similar theme in his concurrence, which also emphasizes the public's need to access basic tools of innovation.¹⁸⁶

Similarly, commentators have focused on the innovation-enhancing objective of preemption doctrine to guide application of subject matter exclusions.¹⁸⁷ According to Mark Lemley and his coauthors, the exclusion of abstract ideas is really "about encouraging cumulative innovation and furthering societal norms regarding

181. Dreyfuss & Evans, *supra* note 152, at 1351; see JOHN R. THOMAS, CONG. RESEARCH SERV., NO. 7-5700, R42815, MAYO V. PROMETHEUS: IMPLICATIONS FOR PATENTS, BIOTECHNOLOGY, AND PERSONALIZED MEDICINE 6 (2012). The issue of preemption originally arose in *Gottschalk v. Benson*, a 1972 case in which the Supreme Court held that a process of converting numbers from one numerical system to another was not patentable subject matter. *Gottschalk v. Benson*, 409 U.S. 63, 71–72 (1972); see Dreyfuss & Evans, *supra* note 152, at 1351–52.

182. Dreyfuss & Evans, *supra* note 152, at 1361. This sentiment is also evident in the Federal Circuit's earlier adjudication of *Bilski*. In his dissent, Judge Rader stated, "Natural laws and phenomena can never qualify for patent protection because they cannot be invented at all." *In re Bilski*, 545 F.3d at 1013 (Rader, J., dissenting).

183. Dreyfuss & Evans, *supra* note 152, at 1371.

184. *Bilski v. Kappos*, 561 U.S. 593, 621 (2010) (Stevens, J., concurring) ("The Court, in sum, never provides a satisfying account of what constitutes an unpatentable abstract idea."); Eisenberg, *supra* note 176, at 7 ("In *Bilski v. Kappos*, the Court not only failed to offer clear guidance as to the boundaries of patentable subject matter, but also missed an opportunity to explain what patentable subject matter is about.").

185. *Bilski*, 561 U.S. at 649 (2010) (Stevens, J., concurring) (quoting *Gottschalk*, 409 U.S. at 67).

186. *Id.* at 658 (2010) (Breyer, J., concurring) (quoting *Gottschalk*, 409 U.S. at 67).

187. Mark A. Lemley et al., *Life After Bilski*, 63 STAN. L. REV. 1315, 1317 (2011). *But see* Katherine J. Strandburg, *Much Ado About Preemption*, 50 HOUS. L. REV. 563, 607 (2013) ("In fact, preemption had little to do with the questions truly at issue in *Bilski* itself, which centered around defining the boundaries of the per se abstract ideas exclusion.").

access to knowledge by preventing patentees from claiming broad ownership over fields of exploration rather than specific applications of those fields.”¹⁸⁸ In other words, courts should consider the “generative nature of the new technology” to help determine whether it comprises an abstract idea.¹⁸⁹ This functional approach suggests categorizing an asset as an abstract idea precisely because exclusive rights over it would foreclose much productive activity, a sentiment that applies as well to natural laws and physical phenomena.¹⁹⁰ This creates a significant amount of judicial discretion in determining the contours of patentable subject matter.

These themes of keeping foundational assets in the public domain as well as a functional approach to identifying such assets found greater expression in *Mayo Collaborative Services. v. Prometheus Laboratories*.¹⁹¹ Substantively, *Mayo* relates more directly to *Myriad Genetics*, as it addressed the patentability of a method of optimizing the therapeutic efficacy of a drug. The method comprised administering a drug to a patient and then determining the amount of metabolite in the patient’s blood, wherein various concentration thresholds indicated the likelihood of deleterious side effects or a lack of therapeutic effectiveness.¹⁹² In describing subject matter exclusions from patent eligibility,¹⁹³ the Court again expressed concerns with preempting access to productivity-facilitating assets.¹⁹⁴ It cited precedent characterizing laws of nature as “the basic tools of scientific and technological work”¹⁹⁵ and cautioned that “monopolization of those tools through the grant of a patent might tend to impede innovation more than it would tend to promote it.”¹⁹⁶ Underlying the subject matter exclusion for laws of nature is a *functional* concern that

188. Lemley et al., *supra* note 187, at 1329. *But see* Eileen M. Kane, *Patent Ineligibility: Maintaining a Scientific Public Domain*, 80 ST. JOHN’S L. REV. 519, 545 (2006) (“Rationales for the exclusion of the laws of nature, natural phenomena and abstract ideas cannot be described with precision.”).

189. Lemley et al., *supra* note 187, at 1339. *But see* Eisenberg, *supra* note 176, at 63 (“A policy of promoting unfettered access to the basic tools of scientific and technological work does not provide a fully coherent account of patentable subject matter doctrine.”).

190. *See, e.g.*, Peter Lee, *The Evolution of Intellectual Infrastructure*, 83 WASH. L. REV. 39, 62–67 (2008). An analogous dynamic applies to the idea-expression dichotomy in copyright. In some ways, courts identify an asset as an idea precisely because it facilitates wide downstream productivity. *See id.* *But see* Eisenberg, *supra* note 176, at 22 (disputing the doctrinal equivalence of “abstract ideas” and “phenomena of nature”).

191. *Mayo Collaborative Servs. v. Prometheus Labs*, 132 S. Ct. 1289, 1292 (2012).

192. *Id.* at 1290–91.

193. *Id.* at 1293 (citing *Diamond v. Diehr*, 450 U.S. 175, 185 (1981)).

194. *Cf.* Rai, *supra* note 64, at 5 (noting that the opinion focuses on “pragmatic consequences” related to preempting future research). *But see* Strandburg, *supra* note 187, at 613 (arguing that preemption was not central to the Court’s patentable subject matter determination in *Mayo*).

195. *Mayo*, 132 S. Ct. at 1301; *Gottschalk v. Benson*, 93 S. Ct. 253, 253 (1972).

196. *Mayo*, 132 S. Ct. at 1293; *see id.* at 1301 (“[T]here is a danger that the grant of patents that tie up their use will inhibit future innovation premised upon them.”); *id.* (“The Court has repeatedly emphasized this last mentioned concern, a concern that patent law not inhibit further discovery by improperly tying up the future use of laws of nature.”); *see also* *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.* 548 U.S. 124, 126 (2006) (Breyer, J., dissenting from dismissal of writ of certiorari) (“[S]ometimes *too much* patent protection can impede rather than ‘promote the Progress of Science and useful Arts.’”).

considers the amount of future innovation that would be foreclosed in comparison to the contribution of the inventor.¹⁹⁷

In addition to reiterating the importance of excluding laws of nature from patentability, *Mayo* maintained significant flexibility in defining what constitutes a law of nature. A principal challenge in applying subject matter exclusions is determining when enough transformation or manipulation has occurred such that an application of a natural law passes the threshold to become eligible for patenting.¹⁹⁸ Drawing from earlier precedent, the Court identified that “something more” as an “‘inventive concept,’ sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself.”¹⁹⁹ However, the Court did not define what constitutes “enough,”²⁰⁰ thus leaving ample room for discretion.

Indeed, one of the most important legacies of *Mayo* is the Court’s expansive and malleable conception of nature. According to the Court, the patents at issue “set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm.”²⁰¹ However, the Court recognized that this was a very narrow conception of a law of nature.²⁰² The specific correlation of thiopurine metabolite levels and therapeutic efficacy seems to be a far cry from more conventional, general laws of nature such as $E=MC^2$.²⁰³ Furthermore, the Court made the rather curious statement that the relationship between thiopurine and therapeutic efficacy “exists in principle apart from any human action.”²⁰⁴ Arguably, however, this relationship is not a natural law at all, given that the starting point of the process is a synthetic drug—thiopurine.²⁰⁵ Accordingly, one of *Mayo*’s most significant doctrinal innovations is the expansive manner in which the Court defined nature.²⁰⁶ According to Rebecca Eisenberg, “The decision could be read as

197. *Mayo*, 132 S. Ct. at 1303.

198. *Id.* at 1294.

199. *Id.*

200. Bernard Chao, *Moderating Mayo*, 107 NW. L. REV. 423, 424–25 (2012).

201. *Mayo*, 132 S. Ct. at 1296.

202. *Id.* at 1302 (“The laws of nature at issue here are narrow laws that may have limited applications . . .”).

203. For this and other reasons, Katherine Strandburg argues that *Mayo* is better understood as a case about per se exclusions for natural laws than about preventing patents from blocking wide swaths of downstream innovation. See Strandburg, *supra* note 187, at 613.

204. *Mayo*, 132 S. Ct. at 1297; see Rebecca S. Eisenberg, *Prometheus Rebound: Diagnostics, Nature, and Mathematical Algorithms*, 122 YALE L.J. ONLINE 341, 343 (2013) (“The Court’s characterization of the relationship between the observed metabolite levels and the need to adjust drug dosage as a ‘natural law’ is puzzling.”).

205. See Christopher Holman, *Preliminary Thoughts on the Implications of Prometheus v. Mayo for Biotechnology*, GENETIC ENGINEERING & BIOTECH. NEWS (Apr. 3, 2012), <http://www.genengnews.com/gen-articles/preliminary-thoughts-on-the-implications-of-prometheus-v-mayo/4392> [<http://perma.cc/H3JY-JY3U>] (“Of course, the correlation does not exist naturally, but only as a consequence of introducing a non-naturally occurring, man-made molecule into the human body.”).

206. Eisenberg, *supra* note 204, at 342.

expanding the scope of what is a natural law or natural phenomenon The court's conception of natural phenomena and natural law is huge."²⁰⁷

This strong interest in preventing patents on nature, as well as flexibility to define nature expansively, continued in *Myriad* itself. In a sense, *Myriad* culminates contemporary interpretations of the three traditional categories of nonpatentable subject matter: *Bilski* addresses abstract ideas, *Mayo* addresses laws of nature, and *Myriad* is largely framed as addressing physical phenomena.²⁰⁸ The opinion situates itself within the doctrinal and conceptual framework articulated by *Mayo*, expressing a strong prudential interest in maintaining a zone of nonpatentability for nature.²⁰⁹ It observes that “laws of nature, natural phenomena, and abstract ideas” are ineligible for patenting because they comprise the “basic tools of scientific and technological work.”²¹⁰ Subjecting these resources to exclusive rights would subvert the goals of the patent system by “inhibit[ing] future innovation premised upon them.”²¹¹ Although the Court does not delineate the exact relationship between the “natural law” and “products of nature” exclusions,²¹² it groups them together in a narrative about facilitating downstream applications of foundational resources. This is a further articulation of the functional, productivity-based approach to subject matter exclusions evident in *Mayo*.

Recognizing that natural laws and natural phenomena are not eligible for patenting leaves significant discretion to determine the contours and penumbras of these legal categories. In this regard, the Court exhibits some slipperiness in defining and conceptualizing *Myriad*'s invention. At times, the Court appears to concede that *Myriad* Genetics created something, but it did not add “enough” to the discovery

207. Steven Seidenberg, *New Laws of Nature Law: Ruling Questions Scientific Patents*, ABA J., July 2012, at 21 (quoting Rebecca Eisenberg). Interestingly, the Court briefly considers whether the patent eligibility of natural correlations will impact the progress of diagnostic research. *Mayo*, 132 S. Ct. at 1304. It recites familiar arguments about both the need to recoup research expenses as well as the dangers of patent thickets. *Id.* at 1304–05. The Court concludes that it “need not determine here whether, from a policy perspective, increased protection for discoveries of diagnostic laws of nature is desirable.” *Id.* at 1305. The Court is slightly disingenuous, however, as its analysis suggests that the absence of patent protection over natural correlations may best promote scientific progress.

208. There is some ambiguity here. At times, the Court characterizes *Myriad*'s claimed isolated DNA as a “product of nature” and “naturally occurring phenomena.” *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2111, 2116 (2013). At other times, it characterizes *Myriad*'s invention as encompassing a “law of nature.” *Id.* at 2117.

209. See Arti K. Rai, *Biomedical Patents at the Supreme Court: A Path Forward*, 66 STAN. L. REV. ONLINE 111, 111 (Oct. 11, 2013) (noting that the policy analyses in both *Mayo* and *Myriad* focus on innovation).

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

211. *Id.*

212. As Dan Burk observes, this is particularly odd because the Supreme Court had earlier remanded *Myriad* to the Federal Circuit for reconsideration in light of *Mayo*. See Dan L. Burk, *The Curious Incident of the Supreme Court in Myriad Genetics*, 90 NOTRE DAME L. REV. 505, 506 (2014). *But see* Brief for the United States as Amicus Curiae in Support of Neither Party at 16–17, *Myriad*, 133 S. Ct. 2107 (No. 12-00398) (“The law-of-nature and product-of-nature exceptions to Section 101 . . . reflect the same basic principle: a person should not receive a patent for simply discovering the existence and useful properties of something that already exists in nature.”).

of the BRCA1 and BRCA2 genes so as to warrant patent eligibility.²¹³ At other times, the Court suggests that Myriad's isolated DNA claims are not distinguishable from nature itself. Describing Myriad's isolated DNA claims, the Court states, "In this case . . . Myriad did not create anything. To be sure, it found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention."²¹⁴ This characterization, however, ignores the reality that Myriad created *something* when it cleaved various bonds to isolate the BRCA1 and BRCA2 genes.²¹⁵

Additionally, the Court's malleable conception of nature flies in the face of the longstanding practice of granting patents on isolated DNA and centuries of precedent holding that isolations and purifications of natural products may be eligible for patenting. The Court rather cursorily dismisses the importance of Patent and Trademark Office practice, citing among other factors the Solicitor General's recent change of position on the patent eligibility of isolated DNA.²¹⁶ Perhaps more remarkably, the Court does not address longstanding precedent holding that isolations and purifications of natural substances may be eligible for patenting. In the venerable case of *Parke-Davis & Co. v. H.K. Mulford Co.*, Judge Learned Hand ruled that purified and extracted human adrenaline was eligible for patenting.²¹⁷ This and other cases have provided doctrinal justification for decades of patents on isolated DNA as well as other isolations and purifications of natural substances.²¹⁸ The Federal Circuit had even assumed (without directly holding) that isolated DNA comprised patentable subject matter.²¹⁹ However, the Supreme Court's opinion does not mention or distinguish these cases.

Indeed, the Court takes great pains to characterize Myriad's claimed invention as not meaningfully distinguishable from nature itself. Regarding isolated DNA, the Court compares Myriad's contribution to that of the patent applicant in *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, in which the court rejected the patentability of a composition of naturally occurring bacteria.²²⁰ The Court noted that the "invention" in *Funk Bros.* fell within the law of nature exception, and so did Myriad's.²²¹ From a factual standpoint, however, isolated DNA appears to be more

213. See *Myriad*, 133 S. Ct. at 2117.

214. *Id.*

215. Although some amici argued that isolated DNA is itself a naturally occurring substance, the Court did not rely on this observation in its opinion. See Brief for Amicus Curiae Eric S. Lander in Support of Neither Party, *supra* note 15, at 12.

216. *Myriad*, 133 S. Ct. at 2118–19.

217. *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95 (C.C.S.D.N.Y. 1911), *aff'd in part, rev'd in part*, 196 F. 496 (2d Cir. 1912).

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

219. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212 (Fed. Cir. 1991) (examining whether isolated nucleotide sequences satisfied the enablement requirement of patentability).

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

221. *Myriad*, 133 S. Ct. at 2117. *But see* Burk, *supra* note 212, at 7 (observing that *Funk Bros.* was a case concerning the historical requirement of "invention," which is most analogous to the modern doctrine of nonobviousness, rather than patentable subject matter).

similar to the patent eligible isolations and purifications of *Parke-Davis* rather than the patent ineligible composition at issue in *Funk Bros.*

The oddity of the Court's reasoning is even more apparent in light of its discussion of Myriad's cDNA claims. cDNA is synthesized by excising non-protein-encoding nucleotides from protein-encoding nucleotides. According to the Court, "the lab technician unquestionably creates something new when cDNA is made."²²² However, this reasoning could apply equally well to isolating DNA from its genomic context, which also involves selectively breaking chemical bonds. The Court never explains why snipping bonds to make cDNA makes "something new" while snipping bonds to make isolated DNA does not. Commentators have rightfully criticized the decision as internally inconsistent on this point.²²³

Crucial to the Court's reasoning was its characterization of isolated DNA as an informational rather than chemical entity. The Court states that "Myriad's claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA."²²⁴ Rather, the opinion states that Myriad's "claim is concerned primarily with the *information* contained in the genetic sequence, not with the specific chemical composition of a particular molecule."²²⁵ This is a significant (re)characterization of Myriad's claimed invention. Myriad's patent clearly claims chemicals—isolated nucleic acids—albeit ones with valuable informational attributes.²²⁶ Nonetheless, the Court states that "genes and the information they encode are not patent eligible under § 101 simply because they have been isolated from the surrounding genetic material."²²⁷ This may be an example of what Christopher Holman describes as "genetic exceptionalism," in which lay observers (such as Supreme Court justices)

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

223. See, e.g., Dan L. Burk, *Are Human Genes Patentable?*, 44 IIC: INT'L REV. INTELL. PROP. & COMPETITION L. 747, 747 (2013) (characterizing this distinction as "puzzling and contradictory"); Rai, *supra* note 64, at 7; Rai & Cook-Deegan, *supra* note 162 ("The Court's analysis does not connect the dots as to why claims to information in the form of cDNA are less problematic than claims to information in the form of gDNA."). Indeed, AMP argued that "[t]here is no scientific or legal distinction between isolated genomic DNA and cDNA that warrants treating their patent eligibility differently." Brief for Petitioners, *supra* note 14, at 50. *But see* Brief for Amicus Curiae Eric S. Lander in Support of Neither Party, *supra* note 15, at 12 (arguing that isolated DNA fragments routinely occur in the human body and are thus products of nature); Brief for the United States as Amicus Curiae, *supra* note 212, at 23–24 (acknowledging that isolated DNA is structurally different from native DNA but not "markedly different" so as to warrant patent eligibility).

224. *Myriad*, 133 S. Ct. at 2118.

225. *Id.* (alteration in original) (emphasis added).

226. *Cf.* Robertson, *supra* note 141, at 381 ("DNA has an inherent duality, both as tangible material and intangible information, posing both practical and legal problems for gene patenting and patent enforcement.").

227. *Myriad*, 133 S. Ct. at 2120. This view, of course, is not without support. See, e.g., Jordan Paradise et al., *Patents on Human Genes: An Analysis of Scope and Claims*, 307 SCIENCE 1566, 1566 (2005) ("In the case of a human gene sequence . . . the 'invention' is the information."); Justine Pila, *Bound Futures: Patent Law and Modern Biotechnology*, 9 B.U. J. SCI. & TECH. L. 326, 337 (2003); Arti K. Rai, *Addressing the Patent Gold Rush: The Role of Deference to PTO Patent Denials*, 2 WASH. U. J.L. & POL'Y 199, 204 (2000) (describing genes as "carriers of information").

view genes as more than chemicals and apply specialized rules accordingly.²²⁸ However, this emphasis on information reveals another inconsistency: cDNA is also valuable for its informational properties, yet the Court regards it as patentable subject matter.²²⁹ Ultimately, *Myriad* reflects both a strong emphasis on exempting nature from patent eligibility as well as a high degree of malleability in construing claimed inventions and nature itself to apply that exemption.

Before considering the implications of these trends for research, it is interesting to note that these principles continued to play a prominent role in the Supreme Court's most recent patent eligibility decision. In *Alice Corp. v. CLS Bank International*, the Court addressed the patent eligibility of method and system claims encompassing a computerized scheme for mitigating "settlement risk" in financial transactions.²³⁰ *Alice* reiterates the familiar preemption rationale for the common law exclusions of laws of nature, natural phenomena, and abstract ideas from patentable subject matter.²³¹ Additionally, it acknowledges the difficulty of clearly identifying these entities,²³² and it articulates a two-part framework for patent eligibility analyses based on *Mayo*. First, courts must ascertain whether a patent claim covers one of the three patent-ineligible categories. Second, it must determine whether there is something more—an inventive concept—that elevates the claim beyond simply covering patent-ineligible subject matter.²³³ Although the Court emphasizes that patentable subject matter analyses are not "like a nose of wax which may be turned and twisted in any direction,"²³⁴ it provides little concrete guidance for determining when exactly a claim contains "enough" to render it eligible for patenting. The Court's patentable subject matter jurisprudence ensures that the "nose of wax" remains quite malleable.

These twin principles of excluding nature from patentable subject matter and allowing significant judicial discretion to define nature (and what is "close enough" to nature) when applying this exclusion have significant implications for research. Nature, after all, is the essential object of scientific research, and *Myriad* and its related cases enhance doctrinal flexibility to challenge patents that appear to cover natural phenomena. First, these cases help affirm that productivity concerns—such as the potential gains of unfettered research—are legitimate factors that can limit patentable subject matter. Within this narrative of promoting productivity, nature assumes an almost talismanic quality. Nature is both difficult if not impossible to invent around (thus raising preemption concerns) and facilitates significant

228. Holman, *supra* note 18, at 360.

229. See Burk, *supra* note 223, at 748; Burk, *supra* note 212, at 508 ("[M]olecules with the same coding information as a native molecule are *also* both excluded from and included within patentable subject matter."); Rai, *supra* note 209, at 114.

230. *Alice Corp. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2351–52 (2014). Settlement risk refers to the risk that a party to a financial transaction will not follow through on its obligations.

231. *Id.* at 2354.

232. *Id.*

233. *Id.* at 2355.

234. *Id.* at 2360.

downstream productivity.²³⁵ *Myriad* and its doctrinal siblings create more opportunity for courts and litigants to challenge patents that they can frame as encompassing nature.

Second and relatedly, *Myriad* reflects significant flexibility in characterizing assets as natural laws or natural phenomena. The decision draws rather questionable distinctions between patent-ineligible natural phenomena and patent-eligible technologies, a practice that will likely embolden litigants seeking to challenge science-related patents. Going forward, appeals to nature and the natural may have significant rhetorical force in arguments before courts.²³⁶ As one commentator observes, “[T]he Supreme Court positioned medical genetics under the framework of natural resource law and, in effect, recast medical genetics as an extractive, rather than inventive, industry.”²³⁷ The notion that one merely extracts rather than invents isolated DNA helped undergird the Court’s decision that such DNA does not comprise patentable subject matter.²³⁸ The Court’s flexible approach to defining nature is likely to encourage similar challenges by future litigants.

Indeed, the Court’s treatment of isolated DNA casts doubt on the patent eligibility of a host of additional entities of high research interest. In the pharmaceutical industry, many important drugs (that are currently patented) are derived from molecules isolated from their natural context.²³⁹ For example, the immune suppressor rapamycin is isolated from the bacterium *Streptomyces hygroscopicus*.²⁴⁰ And Taxol, an anticancer drug, is isolated from the bark of the Pacific yew tree.²⁴¹ Furthermore, many nanotechnology patents cover compositions of matter isolated from natural products.²⁴² For instance, scientists create carbon nanotubes by isolating them from graphite. *Myriad* creates greater opportunity to challenge patents on such assets on the theory that the inventor has not added “enough” to differentiate them from natural products.²⁴³ Of course, the relevance

235. Although the laws of nature at issue in *Mayo* were admittedly narrow, the Court observed that they still implicated the policy concern of tying up valuable downstream activity. *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289, 1302 (2012).

236. Cf. Jason Karlawish, *Your Genes Are Not for Sale*, SCI. PROGRESS (June 24, 2013), <http://scienceprogress.org/2013/06/your-genes-not-for-sale/> [<http://perma.cc/XSD9-R3M7>] (“[D]espite the relentless march of science that all but banished nature from its textbooks, laboratories, and clinics, the appeal to nature and the natural still evoke [sic] deep convictions in the nonscientists.”).

237. Barbara J. Evans, *Mining the Human Genome After Association for Molecular Pathology v. Myriad Genetics*, 16 GENETICS MED. 504, 504 (2014).

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

239. Seidenberg, *supra* note 8.

240. *Id.* But see Rai & Cook-Deegan, *supra* note 162, at 138 (noting that rapamycin was claimed in terms of chemical structure—rather than informational content—and might thus avoid analogy to the isolated DNA claimed in *Myriad*).

241. Ratner, *supra* note 67, at 663; see also Burk, *supra* note 212, at 5–6 (observing that *Myriad* casts doubt on the patent eligibility of a wide range of macromolecules as well as other organic molecules extracted from native sources).

242. Seidenberg, *supra* note 8.

243. Indeed, *Myriad* has helped motivate challenges to patents on extracted and purified human embryonic stem cells on patentable subject matter grounds. Ratner, *supra* note 67, at 663; see also Seidenberg, *supra* note 8 (discussing nanotubes).

of *Myriad* to such contexts is mitigated to the extent that it was a relatively narrow case dealing with isolated DNA. The Court emphasized that *Myriad* claimed isolated DNA in the context of its informational content (i.e., its sequence) rather than as a chemical composition.²⁴⁴ Nevertheless, this is largely an issue of framing, and patents on assets close to natural substances are more vulnerable following *Myriad*.

Of course, as discussed above, it is not immediately clear whether the reduced likelihood of patent eligibility for assets characterized as “natural” is a net positive or negative development for research. The familiar narrative of patent law applies here as elsewhere, and perhaps patent protection for isolated DNA, medicines derived from natural products, and nanotubes would enhance incentives to conduct research in these areas. Alternatively, perhaps the absence of patent protection following *Myriad* will lead to a net gain in research, as the scientific community will enjoy greater freedom to study these resources. As a corollary, perhaps the availability of patent protection for more “downstream” applications closer to the market will preserve adequate commercial incentives for research while still leaving ample room for unfettered upstream scientific inquiry. Of course, determining which of these narratives most closely reflects reality is a complicated empirical question that is likely to be highly contextually sensitive. *Myriad* and its related cases, however, send a consistent message that the Court is increasingly sensitive to the threat that upstream patents may inhibit rather than promote scientific and technological progress.²⁴⁵

Ultimately, this analysis reaffirms the importance of definitions and context in determining the impact of patentable subject matter doctrine on scientific research. In the private ordering realm, differing and nuanced definitions of “noncommercial research use” in *Myriad*’s corporate policy significantly impacted

244. Among other implications, this suggests that entities such as DNA are more likely to be eligible for patenting if claimed as chemicals. *See* Seidenberg, *supra* note 8 (“The Supreme Court seemed to express a more favorable view of patents on ‘specific chemical compositions.’” (quoting Professor Arti Rai, Duke School of Law)).

245. In this regard, it is useful to place *Myriad* and other decisions narrowing patentable subject matter within the broader context of patent cases that tend to narrow patentability, or at least push patentability downstream toward the more commercial end of the R&D spectrum. *See, e.g.*, *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007) (raising the nonobvious requirement of patentability); *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 193 (2005) (applying a statutory exemption from patent infringement to apply to preclinical research reasonably related to information submissions to the Food and Drug Agency); *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990) (interpreting that same statutory exemption from patent infringement to apply to certain research on medical devices); *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010) (en banc) (denying the patentability of a foundational molecular pathway on written description grounds); *id.* at 1353 (“Much university research relates to basic research, including research into scientific principles and mechanisms of action . . . and universities may not have the resources or inclination to work out the practical implications of all such research, i.e., finding and identifying compounds able to affect the mechanism discovered. That is no failure of the law’s interpretation, but its intention.”); *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009) (applying *KSR* to invalidate a patent on isolated DNA as obvious to try); *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997) (holding that claims covering cDNA that produced insulin in all vertebrates and mammals were invalid in light of a written description that only described cDNA that produced insulin in rats).

the degree to which Myriad's patents threatened BRCA research. Additionally, definitional distinctions between "commercial" and "research" use are somewhat illusory; Myriad's research policy always prohibited commercial diagnostic use, but such use can yield important scientific insights. More generally, empirical arguments that gene patents do not chill research must be sensitive to context, as patentees have aggressively enforced exclusive rights in the diagnostics context, thus hampering research. In the doctrinal realm, courts exercise significant discretion in determining whether certain assets qualify as nature (or close enough to nature) for purposes of subject matter exclusions.

IV. ONGOING CHALLENGES AND LONG-TERM RAMIFICATIONS

Although *Myriad* has both short-term and long-term implications for the intersection of patents and research, it leaves significant issues unaddressed. From the perspective of patients seeking wider access to BRCA testing, the Supreme Court's invalidation of Myriad's isolated DNA patents was only a partial victory. Although several firms began offering diagnostic testing following the Court's decision, Myriad promptly sued them for infringement. While many of the cases have settled in favor of defendants,²⁴⁶ the prospect that Myriad has continued to assert intellectual property claims over BRCA testing suggests that more widespread testing—and the research gains that it produces—may face some obstacles.

Relatedly, as mentioned earlier, Myriad Genetics maintains an exclusive database of BRCA mutations including over 300,000 cases.²⁴⁷ Although the Court's ruling on patentable subject matter does not address the database directly, this resource played a small role in the litigation. According to plaintiffs, "[b]ecause the patents have authorized Myriad to maintain a monopoly on clinical testing, they have permitted Myriad to control huge amounts of data on the nature and significance of variants in the BRCA1 and BRCA2 genes."²⁴⁸ Although Myriad initially contributed such information to the publicly-accessible Breast Cancer Information Core mutation database, it ceased major deposits in 2004.²⁴⁹ The inability of outside researchers to access Myriad's proprietary database prevents them from independently characterizing missense variants. This database, which Myriad protects as a trade secret, may be its "most valuable asset," and it represents an important research resource that is not fully open to the scientific community.²⁵⁰

246. See *supra* note 74 and accompanying text.

247. See *supra* note 65 and accompanying text.

248. Brief for Petitioners, *supra* note 14, at 47; see Cook-Deegan et al., *supra* note 66, at 586 ("[A] proprietary database gives Myriad indefinite exclusivity independent of patent protection."); Parthasarathy, *supra* note 3, at 23.

249. Baldwin & Cook-Deegan, *supra* note 36, at 8; So & Joly, *supra* note 65, at 104.

250. Conley, *supra* note 23; see Krench, *supra* note 163 ("By sharing the rich dataset Myriad has collected from patients, collaborative research efforts from many labs could lead to better cancer detection and treatments."); Rai & Cook-Deegan, *supra* note 162, at 138 ("Keeping data proprietary confers an advantage when interpreting the small percentage of BRCA test results whose clinical importance cannot be discerned from public data sources.").

In the short term, there is little that patent doctrine can do to enhance access to this resource. In the long term, however, more widespread BRCA testing can facilitate greater public access to valuable mutation data.

From the macroscopic perspective of reconciling patents and research, the Supreme Court's invalidation of Myriad's isolated DNA patents represents just one piece of a large policy puzzle. As noted, patentable subject matter is but one doctrinal lever among many (and perhaps not the optimal one) for regulating patents in the context of scientific research.²⁵¹ Other policy tools, such as the written description and nonobviousness requirements, may represent more granular regulatory mechanisms.²⁵² Additionally, policy levers outside of traditional patent doctrine are also available. In particular, public funding and the Bayh-Dole Act may help balance research interests and exclusive rights.²⁵³ Here, the ecosystem of biomedical innovation is highly relevant, as much of the research that produces gene patents arises from federal funds.²⁵⁴ Indeed, NIH contributed about \$4.6 million to the research leading to the sequencing of BRCA1 and engaged in an inventorship dispute with the University of Utah and Myriad Genetics.²⁵⁵ Under the Bayh-Dole Act, which allows recipients of public funds to patent the results of federally-funded research, NIH maintains certain rights in subject inventions.²⁵⁶ In theory, government rights in Myriad Genetics' isolated DNA patents as well as other federally-funded inventions provide another mechanism for enhancing access to such resources for research purposes.²⁵⁷ Although these rights are difficult to assert,²⁵⁸ any macroscopic approach to balancing patents and open science should take them into account.²⁵⁹

Statutory reforms are also a possibility. For example, the proposed 2007 Genomic Research and Accessibility Act would have prohibited the patenting of any "nucleotide sequence, or its functions or correlations, or the naturally occurring products it specifies."²⁶⁰ Although this act was overly broad and rightfully rejected, other jurisdictions have devised more measured, targeted approaches. For instance, France, Belgium, and Switzerland authorize compulsory licenses for diagnostic patents.²⁶¹ In sum, legal and regulatory mechanisms beyond traditional patent doctrine may also help reconcile patents and research interests.

251. See Rai, *supra* note 64, at 3.

252. See *supra* notes 173–174 and accompanying text.

253. See Lee, *supra* note 80.

254. See Cook-Deegan et al., *supra* note 66, at 585; Rai, *supra* note 64, at 3.

255. Baldwin & Cook-Deegan, *supra* note 36, at 3 ("Myriad's work was partially funded by government grants to the University of Utah."); Robert Dalpé et al., *Watching the Race to Find the Breast Cancer Genes*, 28 SCI. TECH. & HUM. VALUES 187, 196 (2003).

256. 35 U.S.C. §§ 200–212 (2000); see Lee, *supra* note 80, at 921–24.

257. See Lee, *supra* note 80.

258. Rai & Eisenberg, *supra* note 82, at 310.

259. See Rai, *supra* note 64, at 8.

260. H.R. 977, 110th Cong. (2007).

261. Hopkins & Hogarth, *supra* note 149, at 498; see Carbone et al., *supra* note 50, at 786 (describing compulsory licensing laws in France and Belgium).

Ultimately, perhaps the most enduring legacy of *Myriad* for the intersection of patents and research is a deep, policy-oriented pragmatism that engenders a malleable approach to doctrine and science. In addition to seeking to clarify patentable subject matter, the Supreme Court likely granted certiorari in *Myriad* because of the enormous political, social, and economic interests at stake, which spanned women's health, access to diagnostics, breast cancer research, and the financial viability of the biotechnology industry. The result achieved by the Court is not particularly doctrinally or scientifically rigorous, especially in its imprecise distinctions between isolated DNA and cDNA. Nonetheless, it reaches a pragmatic middle ground. Isolated DNA, which is most relevant for diagnostic and research purposes, is no longer patentable subject matter, but cDNA, which is more closely tied to commercial therapeutics, remains eligible for patenting.²⁶² *Myriad* is a highly pragmatic opinion that bends doctrine and science to achieve a political and legal compromise.²⁶³

This type of pragmatism has a long history in patent law.²⁶⁴ It even manifested itself in earlier stages of the *Myriad* litigation at the Federal Circuit, when Judge Moore cautioned that patentable subject matter should be sensitive to the "settled expectations of the biotechnology industry."²⁶⁵ In past generations, pragmatic considerations and sensitivity to the needs of industry led to doctrinal innovations tending to expand patentability. For example, Judge Learned Hand's epochal holding in *Parke Davis* that purified adrenaline constituted patentable subject matter substantially benefitted the nascent U.S. chemical industry.²⁶⁶ In the contemporary landscape, the pendulum has swung in the opposite direction. Attentive to growing concerns over patent holdup and the anticommons, the Supreme Court in *Myriad* consistently emphasized that upstream patents may ultimately subvert rather than promote innovation, including scientific research.²⁶⁷ After all, "[p]atent protection

262. See Burk, *supra* note 212, at 6 ("So it appears that the Supreme Court split the baby, giving something to the plaintiffs but also reserving the possibility of cDNA patents for the biotechnology industry."); cf. Brief for Amicus Curiae Eric S. Lander in Support of Neither Party, *supra* note 15, at 24, 27 (arguing that patents on isolated DNA would stymie scientific research and that patents on non-naturally occurring DNA such as cDNA are more important for commercial applications); Rai, *supra* note 64, at 1. But see *supra* notes 161–164 and accompanying text (discussing the importance of cDNA for research purposes).

263. However, in his notable concurrence, Justice Scalia refused to join the portions of the majority opinion discussing the details of molecular biology because he was "unable to affirm those details on my own knowledge or even my own belief." *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2120 (2013) (Scalia, J., concurring in part and concurring in the judgment).

264. Pila, *supra* note 227, at 339 ("[T]he success of patent law's accommodation of modern biotechnology ultimately reflects the success of legal expediency over legal reasoning.")

265. *Ass'n for Molecular Pathology v. USPTO*, 653 F.3d 1329, 1368 (Fed. Cir. 2011) (Moore, J., concurring in part), *vacated, appeal reinstated*, 467 Fed. App'x. 890 (Fed. Cir. 2012).

266. See GRAHAM DUTFIELD, *INTELLECTUAL PROPERTY RIGHTS AND THE LIFE SCIENCES INDUSTRIES* 85–89, 108–09 (2d. ed. 2009).

267. *Myriad*, 133 S. Ct. at 2116 ("[T]here would be considerable danger that the grant of patents would 'tie up' the use of such tools and thereby 'inhibit future innovation premised upon them.'" (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1301 (2012))).

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.’”²⁶⁸ Balancing these interests, the Court rejected the patent eligibility of isolated DNA. Whether or not the Court is ultimately correct in its analysis, its opinion reflects a willingness to flexibly frame law and science to achieve practical objectives. Ultimately, the longstanding impact of *Myriad* on research hinges considerably on one’s institutional confidence in courts to understand innovation dynamics in various fields and balance relevant policy interests correctly.

CONCLUSION

The Supreme Court’s decision in *Myriad* has several significant and underappreciated implications for the intersection of patents and research. Part of the complexity of this issue derives from the ambiguous and subjective definitions of the terms of debate. This Article has elucidated the impact of *Myriad* on research in three contexts. First, on the immediate level of BRCA research, *Myriad* creates more actual and perceived freedom to operate for scientists working with isolated DNA. Although Myriad Genetics maintains that it has always permitted noncommercial research use of isolated DNA covered by its patents, its policy was convoluted, inconsistent, and poorly communicated. More importantly, Myriad’s noncommercial research exception never covered diagnostic use, which yields valuable scientific knowledge. To the extent that *Myriad* leads to more research and diagnostic testing utilizing BRCA1 and BRCA2, it will help generate new insights about these genes and their biological function.

This phenomenon, moreover, extends beyond BRCA research. Although fears of patent holdup and the tragedy of the anticommons initially attracted significant attention, empirical research has found little direct evidence of chilling effects in the research context. An important exception, however, is diagnostics, where patentees have aggressively enforced their exclusive rights. In this context, the Court’s holding that isolated DNA is not patentable subject matter is likely to increase diagnostic testing for a host of genes related to other conditions. Given that diagnostic testing generates scientific knowledge, such testing has meaningful research benefits.

Beyond these effects, *Myriad* and its related cases exhibit both a strong prudential interest in keeping “nature” outside the domain of patent eligibility as well as a high degree of discretion in defining what comprises nature (and what comes close enough). The flexible character of the Court’s patentable subject matter test leaves ample room to bend doctrine and science to advance broader policy objectives related to promoting innovation. Such flexibility creates more opportunity to challenge patents in research science forward, which will likely have a net positive impact on efforts to study nature, however courts define it.

268. *Id.* (quoting *Mayo*, 132 S. Ct. at 1305).

