

IS THE SKY REALLY FALLING?: *MYRIAD* AND ITS IMPACT ON THERAPEUTIC DEVELOPMENT

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In 2013, the Supreme Court held in Association for Molecular Pathology v. Myriad Genetics that isolated products of nature are not patentable subject matter. Researchers believe that many pharmaceutical advances reside in natural products, so commentators worry that if products of nature cannot be patented, then promising innovation in this area will not be pursued. Because of these fears, Congress has recently focused on reforming the patent eligibility statute to abrogate the Court's recent limiting case law. But even after congressional hearings and public comment periods, there is still little rigorous evidence of how Myriad has affected innovation. This Note seeks to fill this gap by contributing new evidence to the debate, paying particular attention to therapeutics derived from natural products.

The evidence of affected innovation post-Myriad is presented through a review of lower court decisions that handle natural therapeutics under a Myriad standard, analysis of Department of Commerce, Patent and Trademark Office (USPTO) Patent Trial and Appeal Board (PTAB) decisions addressing the same category of inventions, and first-hand stories of deterred innovation due to Myriad-related concerns. Included in these stories is the case of Mambalgin-1, a snake toxin that possesses painkilling attributes with little-to-no negative side effects. The case of Mambalgin-1 answers the call by intellectual property academics for more evidence of discontinued projects due to patent eligibility concerns.

In short, with regard to therapeutics, Myriad has made a drop in the ocean in lower courts, a splash at the USPTO, and waves at biotechnology companies where encouraging natural therapeutics have been discovered, yet remain commercially unpursued. This does not mean, however, that Myriad has been an in-

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herently negative development; Myriad has positively influenced privacy and bodily autonomy, collaborative research, and access to quality healthcare. But in their assessment of patentable subject matter jurisprudence, Congress must balance both the strengths and weaknesses of Myriad, in order to honor the concerns that led to Myriad's holding while simultaneously spurring innovation. In order to do so, non-patent incentives, such as longer periods of regulatory exclusivity, increased grants and direct funding, and tax credits for natural therapeutics should be pursued as the government seeks impactful reform that will ensure that the sky does not fall on future therapeutic innovation.

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INTRODUCTION

For those affected by chronic illnesses, such as cancer or multiple sclerosis, prolonged pain management is critical.¹ Unfortunately, however, there are not

1. See Amy Butchart et al., *Experience and Management of Chronic Pain Among Patients with Other Complex Chronic Conditions*, 24 CLINICAL J. PAIN 293, 293 (2010) ("Managing . . . chronic health conditions is a significant challenge. . . . Better management of chronic pain among complex patients could lead to significant improvements in health status,

great options to control serious and long-term discomfort. Given the widespread addiction epidemic that plagues our country² and the many uncomfortable side effects associated with narcotic painkillers,³ doctors are hesitant to prescribe opioid medications for longer than brief periods of time.⁴ This leaves non-narcotic pain medications, such as acetaminophen, ibuprofen, and aspirin, for long-term pain control.⁵ Yet these drugs are not as powerful as their narcotic counterparts, such as hydrocodone or oxycodone, that can treat moderate to severe pain.⁶

Researchers estimate that about twenty percent of all U.S. adults experience chronic pain every day, leading to a loss of productivity estimated at about \$300 billion per year.⁷ Thus, the healthcare community and government have a vested interest in developing a non-narcotic pain therapy that does not lead to uncomfortable side effects and can attack moderate to severe pain. Subsequently, innovation is necessary to meet the need for a non-addictive pain management option that will simultaneously address our country's chronic illness and opioid epidemics.⁸ This example highlighting the need for a non-narcotic pain medication elucidates the importance of medical innovation, but represents just one of many areas where society would benefit from pharmaceutical advancement.

One potential avenue to search for these advances is in repurposing natural products for therapeutic use. Many therapeutic drugs are already derived from nature,⁹ and researchers emphasize that natural products remain a promising area for future research, particularly in the field of pain management.¹⁰ But in 2013,

functioning and quality of life and possibly also improve the management of their other major chronic health conditions.”).

2. See *What is the U.S. Opioid Epidemic?*, DEP'T HUM. HEALTH SERVS. (Oct. 27, 2021), <https://perma.cc/JKC2-Q3DN?type=image>.

3. See *Besides Addiction, Opioids Have Negative Side Effects*, AVANOS, <https://perma.cc/M2BB-AX97> (archived Apr. 7, 2023).

4. See Kelly K. Dineen & James M. DuBois, *Between a Rock and a Hard Place: Can Physicians Prescribe Opioids to Treat Pain Adequately While Avoiding Legal Sanctions*, 42 AM. L. J. MED. 7, 7-8 (2010).

5. *Non-Opioid Treatment*, AM. SOC'Y ANESTHESIOLOGISTS, <https://perma.cc/KD5T-358Q> (archived May 20, 2023).

6. See *generally Alternatives to Opioids*, FLA. DEP'T HEALTH, <https://perma.cc/ZTY9-KK8N> (archived May 20, 2023).

7. Jason Young, Peter M. Mullins, & Neil Bhattacharyya, *Prevalence of Chronic Pain Among Adults in the United States*, 163 PAIN 328, 330-32 (2021).

8. Keith Humphreys et al., *Responding to the Opioid Crisis in North America and Beyond: Recommendations of the Stanford-Lancet Commission*, 399 LANCET 555, 589 (2022) (“Innovation is also needed in pain management particularly in the development of effective medications that do not carry risk of addiction.”).

9. Atanas G. Atanasov et al., *Natural Products in Drug Discovery: Advances and Opportunities*, 20 NATURAL REV. DRUG DISCOVERY 200, 200 (2020) (“Historically, natural products (NPs) have played a key role in drug discovery, especially for cancer and infectious diseases, but also in other therapeutic areas . . . NPs offer special features . . .”).

10. See Wen Chen & D. Craig Hopp, *Research Workshop Will Delve Into Search for New Pain Treatments in Natural Products*, NAT'L CENTER FOR COMPLEMENTARY AND INTEGRATIVE HEALTH BLOG (Jan. 25, 2019), <https://perma.cc/A2EY-RV7R>.

the Supreme Court sharply limited the patentability of natural products in *Association for Molecular Pathology v. Myriad Genetics*,¹¹ leading some to worry that natural product innovation would subside—particularly with regard to therapeutics, where patents have played an important role in development.¹² Patents are so crucial to the development of pharmaceutical therapeutics because of the need to conduct rigorous and expensive clinical trials before even applying for drug approval from the FDA. Because of this historic relationship between patents and pharmaceutical therapies, academics and researchers alike have proclaimed that post-*Myriad*, “the sky is falling” on the development of future therapeutics derived from natural products.¹³

Because of fears that *Myriad* and other recent patentable subject matter eligibility cases will lead to less innovation as patents become harder to come by, there has been a great deal of recent focus on reforming the patent eligibility statute to abrogate the Court’s recent case law.¹⁴ In 2019, Senate hearings were held to assess the impact of *Myriad* and related cases, and in 2021, the Department of Commerce, Patent and Trademark Office (USPTO) requested public comments to assess the impact of current patent eligibility jurisprudence on innovation.¹⁵ But there is still little rigorous evidence of how *Myriad* and its family of cases have affected innovation in general, and of promising therapeutics derived from products of nature in particular.

This Note seeks to fill this gap by contributing new evidence to the debate. It does not, however, make broad conclusions, such as recommending that *Myriad* be reversed. Instead, it simply aims to add facts to the conversation about *Myriad*’s actual impact and show that post-2013, there has been at least *some* negative impact on therapeutic innovation. While a review of lower court decisions may suggest that *Myriad*’s impact has been negligible, the case has made a greater impact during initial patent examination. A review of post-2013 cases before the USPTO’s Patent and Trial Appeal Board (PTAB) shows that there are patent applications being rejected under a *Myriad* standard.

Additionally, through investigative research, this Note presents the case of Mambalgin-1, a novel contribution that answers the call by intellectual property academics for more evidence of discontinued projects due to patent eligibility concerns. A peptide found in Black Mamba venom that possesses painkilling

11. 569 U.S. 576 (2013).

12. Iain Cockburn & Genia Long, *The Importance of Patents to Innovation: Updated Cross-Industry Comparisons with Biopharmaceuticals*, 25 LANCET 739, 739 (2015) (“Patents have long been considered essential incentives to foster innovation, particularly the development of new prescription drugs, due to the lengthy, costly, and risky nature of the research and development (R&D) process as compared to the lower levels of investment and risk associated with generic drug entry.”).

13. See *infra* Part I.C.

14. See generally KEVIN J. HICKEY, CONG. RSCH. SERV., R45918, PATENT-ELIGIBLE SUBJECT MATTER REFORM IN THE 116TH CONGRESS 2-4 (2019).

15. *Id.* at 4.

qualities and little-to-no patient side effects, Mambalgin-1 was not pursued as a commercial therapeutic because of *Myriad*-related concerns.¹⁶ Therefore, while the sky has not fallen *en mass*, this new case study shows that at least a few chunks have left the atmosphere. Or put differently, there is specific evidence that *Myriad* has negatively impacted at least some innovation and development. How significant these impacts are, and whether these negative impacts outweigh *Myriad*'s benefits, remain questions for future research.

This Note proceeds in three parts. Part I describes recent judicial limits placed on patentable subject matter and unpacks the *Myriad* decision and reactions to its holding. Part II evaluates *Myriad*'s actual impact in three ways. Part II.A addresses current views on the patent system's general impact on research and development. Part II.B contributes the first review of *Myriad*'s impact in lower courts and at the PTAB, with a specific focus on therapeutics derived from natural products. Part II.C highlights new comments submitted to the USPTO from concerned members of the biotech community with regard to *Myriad*'s impact on therapeutic development. It also offers the story of Mambalgin-1, an unpursued natural therapeutic with the potential to alter chronic pain management. While the novel case study presented is but one instance of *Myriad* deterrence, it is concrete evidence that *Myriad* has had an impact on therapeutic development and that patents do impact innovation. Part III provides non-patent options, such as longer periods of regulatory exclusivity, increased grants and direct funding, and tax credits, that can be used to spur natural therapeutic innovation under the shadow of *Myriad*.

I. MYRIAD'S LIMITS ON PATENTING PRODUCTS OF NATURE

While *Myriad* is the focus of this Note, it is but one string in the web of patentable subject matter restraints. Part I delineates the current statutory and judicial limits placed on patent eligibility and describes where *Myriad* falls in this legal environment. It also describes the *Myriad* holding in detail and the reactions that followed this decision.

A. Recent Judicial Limits on Patent Eligibility

In exchange for the right to exclude others from their invention, the U.S. Patent Act imposes a number of requirements for obtaining a patent.¹⁷ In partic-

16. Telephone Interview with Thomas Mathers, President and CEO, Allievex Corp. (Feb. 8, 2022) [hereinafter Mathers Interview].

17. See generally 35 U.S.C. §§ 1-389 (1952).

ular, four statutory provisions outline the core legal requirements for patentability.¹⁸ Section 102 requires that the claimed invention is novel.¹⁹ Section 103 establishes a non-obviousness condition, demanding that the claim in question does not cover trivial alterations to previously known inventions.²⁰ And Section 112 necessitates a clear disclosure of the invention, including information that will allow a person having ordinary skill in the art (PHOSITA) to make and use the claimed invention without undue experimentation.²¹ But it is Section 101 that is of primary relevance to this Note's inquiry: the requirement of subject matter eligibility.²²

Even if an invention is new, non-obvious, and adequately disclosed, a patent will be denied if the claimed invention does not fall within one of four broad statutory categories, as a "process, machine, manufacture, or composition of matter."²³ The broad statutory language of Section 101 may appear all-embracing, but since the Patent Act's ratification, a number of implicit judicial limits have been attached to restrict the apparent breadth of the four patentable subject matter categories.

The Supreme Court has long struggled to clarify what is patentable subject matter and what is not; in so doing, they created unclear boundaries of subject matter limits.²⁴ In an attempt to provide a modern and coherent framework for delineating the extremities of patentable subject matter, the Court specifically addressed Section 101 in 1981 when it excluded "[l]aws of nature, natural phenomena, and abstract ideas" from the safe harbor of patentability, regardless of whether claimed inventions fall under one of the four Section 101 categories.²⁵

18. *See id.* at §§ 101-03, 112.

19. *Id.* at § 102.

20. *Id.* at § 103.

21. *Id.* at § 112. Section 112 does include other requirements beyond enablement, such as requiring that "the specification shall . . . set forth the best mode contemplated by the inventor . . . of carrying out the invention." *Id.* Additionally, there are other sections of the Patent Act (which includes three hundred eighty-nine sections) that cover patentability requirements, but Sections 102, 103, 112, and 101 highlight the core considerations that inventors face when contemplating patentability.

22. *Id.* at § 101. Section 101 also requires that patents seeking approval are "useful," a seemingly low hurdle, but an important one ground in the U.S Constitution's goal to promote "useful arts." *Id.*; U.S. CONST. art. I, § 8, cl. 8.

23. 35 U.S.C. § 101 (1952). The Federal Circuit has emphasized that these "four categories together describe the exclusive reach of patentable subject matter. If a claim covers material not found in any of the four statutory categories, that claim falls outside the plainly expressed scope of Section 101, even if the subject matter is otherwise new and useful. In re Nuijten, 500 F.3d 1346, 1354 (Fed. Cir. 2007).

24. For a full history of the Supreme Court's jurisprudence on patent subject matter eligibility, see generally Peter S. Menell, *Forty Years of Wondering in the Wilderness and No Closer to the Promised Land: Bilski's Superficial Textualism and the Missed Opportunity to Return Patent Law to Its Technology Mooring*, 63 STAN. L. REV. 1289 (2011).

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

The Court has justified this Section 101 carve out as necessary to avoid the “monopolization of [the basic tools of scientific and technological work that] . . . might tend to impede innovation more than it would tend to promote it.”²⁶ While the Court intended to protect the “progress of science,”²⁷ their attempt to promote ingenuity led to an unclear understanding of what “laws of nature, natural phenomena, and abstract ideas” include.

Beginning in 2010 and ending in 2014, the Court attempted to further clarify when “laws of nature, natural phenomena, and abstract ideas” are sufficiently transformed and thus “significantly more” than the unpatentable subject matter the claimed invention builds off of.²⁸ The Court took on four subject matter cases during this five-year period: *Bilski v. Kappos*,²⁹ *Mayo Collaborative Services v. Prometheus Laboratories*,³⁰ *Ass’n for Molecular Pathology v. Myriad Genetics*,³¹ and *Alice Corp. v. CLS Bank Int’l*,³² now affectionately called the “Alice Quartet.”³³ In doing so, the Court quickly altered the landscape of patent subject matter eligibility.

Bilski and *Alice* handled the patentability of business methods. In *Bilski*, a 2010 case, the Court (1) rejected the rigid Machine-or-Transformation Test;³⁴ and (2) affirmed the Patent Office’s rejection of an application because the claimed invention—a method for “managing the . . . risk costs of a [sale]”³⁵—was an “abstract idea.”³⁶ The Court reasoned that the patent’s claim was indistinguishable from “a fundamental economic practice [that has long been accepted as an abstract idea] prevalent in our system of commerce.”³⁷ Here, the Court proved their unwillingness to allow inventors to preempt the public from using basic abstract concepts long utilized by society. In 2014, the Supreme Court again found a business method, in addition to a system for managing risk, to be an ineligible “abstract idea” in *Alice v. CLS Bank*.³⁸ The Court found the financial

26. *Mayo Collaborative Servs. v. Prometheus Lab’ys, Inc.*, 566 U.S. 66, 71 (2012).

27. U.S. CONST. art. I, § 8, cl. 8.

28. See MANUAL OF PATENT EXAMINING PROCEDURE (NINTH) § 2106.05 (2019) (“Does the claim recite additional elements that amount to *significantly more* than the judicial exception?”(emphasis added)).

29. 561 U.S. 593 (2010).

30. 566 U.S. 66 (2012).

31. 569 U.S. 576 (2013).

32. 573 U.S. 208 (2014).

33. Robin Feldman, *The Arc of History in Patent Subject Matter*, 11 HASTINGS SCI. TECH. J. 1, 1 (2020).

34. *Bilski*, 561 U.S. at 594. The Machine-or-Transformation Test approved of claims as patentable subject matter if they 1) were implemented by a machine in a non-trivial and non-conventional manner and 2) transformed an article from one state to another entirely. See *Gottschalk v. Benson*, 409 U.S. 63, 71 (1972)

35. 561 U.S. at 615.

36. *Id.* at 609.

37. *Id.* at 611 (citing *In re Bilski*, 545 F.3d. 943, 1013 (2008) (Rader, J., dissenting)).

38. 573 U.S. 208 (2014); *see id.* at 214.

method and system to be abstract ideas made up of “purely conventional” steps.³⁹ The fact that these generic steps could be performed on a computer was not enough to make the inventions eligible for patent protection.⁴⁰ The *Bilski* and *Alice* decisions have remained particularly controversial and relevant in a software context.⁴¹

Mayo moved beyond business and technology and deeper into the world of science, handling diagnostics and products of nature. In *Mayo*, the patent at issue was a diagnostic test used to decide how to treat a gastrointestinal disorder.⁴² Again, the Court ruled the patent application ineligible due to subject matter concerns, finding that the claimed invention was a “law of nature” in every practical sense.⁴³ The relationship between metabolite levels and the ideal drug dosage was found to solely reiterate “well-understood, routine, [and] conventional activity” that was inherent in a law of nature (how an afflicted body naturally responds to the innate components of a drug and how this reaction should be handled to cure illness).⁴⁴ It was thus clarified that a “patent . . . [can]not simply recite a law of nature” and apply it at a high level of generality, but must also supply a sufficiently inventive concept.⁴⁵ In effect, *Mayo* “set forth a framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts.”⁴⁶ This framework for determining Section 101 patent eligibility was further solidified in the form of a two-step test in *Alice*: First, the court must decide whether the claims at issue are directed to a patent-ineligible concept. Then, the court must look to whether the claim’s elements, considered both individually and combined, transform the nature of the claims into a new patent-eligible subject matter.⁴⁷

B. The *Myriad* Decision

At issue in *Myriad* was a patent that “claimed isolated human genes related

39. *Id.* at 222.

40. *Id.*

41. With regard to “the patentability of software . . . patents, the decision in *Bilski* marked the beginning of the end, and *Alice* was its death knell . . .” Kim Jordahl, *Ten Years From Bilski: The Beginning of the End, With No Improvement in Sight*, IP WATCHDOG (June 28, 2020, 12:15 PM), <https://perma.cc/NAX2-KBEJ>.

42. The patent in question claimed the administration of a medication, the subsequent measuring of the metabolite levels associated with the administered drug, and the decision to increase or decrease the patient’s drug dosage depending on the results of the diagnostic test. *Mayo Collaborative Servs. v. Prometheus Lab ‘ys, Inc.*, 566 U.S. at 74-75 (citing U.S. Patent No. 6,355,623, col. 20, ll. 10–20 (filed Apr. 8, 1999)).

43. *Id.* at 67.

44. *Id.*

45. *Id.* at 72, 78.

46. *Alice Corp. vs. CLS Bank Int’l*, 573 U.S. 208, 217 (2014).

47. *Id.* at 221.

to breast and ovarian cancer.”⁴⁸ The case was brought by twenty plaintiffs who were backed by the American Civil Liberties Union. They ranged from geneticists and doctors to medical organizations and cancer patients.⁴⁹ The invigorated plaintiffs were concerned that Myriad Genetics’ claim to BRCA1 and BRCA2 (the human genes (gDNA) at issue) had led to a monopoly over the female cancer diagnostics market.⁵⁰

Myriad elicited remarkable attention within the legal, medical, and biotechnology communities, as well as with the general public; over fifty amicus briefs were filed⁵¹ and nearly every major news publication covered the litigation.⁵² Debate over *Myriad*’s impact on medical research,⁵³ health care,⁵⁴ patent innovation,⁵⁵ and bodily autonomy ensued.⁵⁶

48. Megan M. La Belle, *Standing to Sue in the Myriad Genetics Case*, 2 CAL L. REV. CIRCUIT 68, 68 (2011); Ass’n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 584 (2013) (“The first claim asserts a patent on ‘[a]n isolated DNA coding for a BRCA1 polypeptide,’ which has ‘the amino acid sequence set forth in SEQ ID NO:2.’” (quoting U.S. Patent No. 5,747,282, col. 153, ll. 56–58 (filed June 7, 1995))).

49. *Myriad*, 569 U.S. at 584.

50. In 2013, the actress Angelina Jolie “announced that she had undergone a preventive double mastectomy after testing positive for BRCA1.” Amelia Smith Rinehart, *Myriad Lessons Learned*, 5 UC IRVINE L. REV. 1147, 1149 (2015). Jolie expressed that “[t]he cost of testing for BRCA1 and BRCA2, at more than \$3,000 in the United States, remains an obstacle for many women.” Angelina Jolie, Opinion, *My Medical Choice*, N.Y. TIMES (May 14, 2013), <https://perma.cc/223J-UBQB>. While Jolie did not name the diagnostic provider whose test cost her \$3,000, she suggested that diagnostic tests in general were prohibitively expensive for the general population. While this was, and is still, certainly true, scholars have expressed concern that *Myriad*’s pricing of its diagnostic test was not unique and that the solution to inaccessible diagnostics has always been healthcare and insurance reform. Jorge L. Contreras, Association for Molecular Pathology v. Myriad Genetics: *A Critical Reassessment*, 27 MICH. TECH L. REV. 1, 52 (2020) (“Yet these sums [related to BRCA testing] pale in comparison to the staggering figures that are being charged for the latest gene therapies, including the record-breaking \$2.1 million price tag that Novartis recently announced for Zolgensma, a gene-based treatment for spinal muscular atrophy (SMA). The key, of course, is insurance coverage.”).

51. *Association for Molecular Pathology v. Myriad Genetics, Inc.*, SCOTUSBLOG, <https://perma.cc/NX4Y-R6TT> (archived May 14, 2023).

52. See, e.g., Andrew Pollack, *Ruling Upholds Gene Patent in Cancer Test*, N.Y. TIMES (July 29, 2011), <https://perma.cc/VL8J-B5ED>; Nathan Koppel, *Genetic Research Spurs Fight Over Patents Tied to the Body*, WALL ST. J. (Dec. 10, 2009, 12:01 AM ET), <https://perma.cc/VD9B-46PA>.

53. See generally Brief for Phar. Rsch. and Mfrs. of Am. as Amici Curiae Supporting Respondents, *Myriad*, 569 U.S. 576 (2013) (No. 12-398), 2013 U.S. S. Ct. Briefs LEXIS 1520.

54. During the *Myriad* oral arguments, protesters held signs outside the Supreme Court that read, “Your corporate greed is killing my friends.” Bill Mears, *Justices at Odds Over Patents for Human Genes*, CNN (updated Apr. 17, 2013, 6:15 PM EDT), <https://perma.cc/Y5K4-6PYF>.

55. See generally Brief for The Boston Pat. L. Ass’n as Amici Curiae Supporting Respondents, *Myriad*, 569 U.S. 576 (2013) (No. 12-398), 2013 U.S. S. Ct. Briefs LEXIS 1455.

56. Jim Dwyer, *In Patent Fight, Nature, 1; Company, 0*, N.Y. TIMES (Mar. 30, 2010), <https://perma.cc/3222-ZLUR> (“But for many people, it is impossible to understand how genes—the traits we inherit from our parents and pass along to our children—could become a

Ultimately, the Court unanimously found the genomic DNA at issue to be ineligible for patent status because it claimed a “product of nature” that was not created by invention.⁵⁷ Merely extracting and purifying DNA sequences from human cells found in nature would not make them patentable subject matter.⁵⁸ Thus, it followed that isolating any “product of nature” from its innate environment would not yield patentability. In deciding this, the Court demonstrated 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”⁵⁹

In *Myriad*, the Court also found that complementary DNA (cDNA), which was synthesized through a process that would not normally happen without human intervention, was patentable subject matter because it was distinct from anything that could be found in nature.⁶⁰ Yet “[t]he exclusion of gDNA from patentable subject matter has garnered much of the attention directed to the *Myriad* decision; the inclusion of cDNA less so,” given that the exclusion of isolated gDNA from patentable subject matter was the most shocking and unpredictable part of the Court’s analysis.⁶¹ Consistent with this trend, this Note focuses on the language of *Myriad* which excludes gDNA and future isolated products of nature from patentable subject matter.

C. Reactions to *Myriad*

The *Myriad* decision led many legal scholars and biotechnology professionals to claim that “the sky [was] falling.”⁶² In other words, critics asserted that if natural products were no longer patentable, then fewer biotechnology therapeutics derived from isolated natural products would be pursued, since a loss of patent protection would result in less investor interest.

For example, Jeffrey Lefstin testified at a Senate Judiciary Committee hearing that current requirements have “virtually eliminated patent protection for many new diagnostics and other discovery-based inventions.”⁶³ Similarly, the

company’s intellectual property.”).

57. *Myriad*, 569 U.S. at 595-96.

58. *Id.*

59. Peter Lee, *The Supreme Court’s Myriad Effects on Scientific Research: Definitional Fluidity and the Legal Construction of Nature*, 5 UC IRVINE L. REV. 1077, 1113 (2014).

60. *Myriad*, 569 U.S. at 580.

61. Dan L. Burk, *The Curious Incident of the Supreme Court in Myriad Genetics*, 90 NOTRE DAME L. REV. 505, 510 (2014).

62. See Gene Quinn, *Why SCOTUS Myriad Ruling Overrules Chakrabarty*, IP WATCHDOG (July 14, 2013, 8:30 AM), <https://perma.cc/TB69-CJ25>.

63. Jared B. Rifis, Courtenay C. Brinckerhoff, George C. Beck & Gilberto M. Villacorta, *The State of Patent Eligibility—Report on Senate Hearings*, FOLEY (June 19, 2019), <https://perma.cc/E39K-2SNG>.

American Intellectual Property Law Association (AIPLA), a community comprised of academics and interested practitioners, has expressed that “the current state of patent eligibility jurisprudence adversely affects the public by decreasing incentives to invest in the development of products that will improve individuals’ quality of life and the public health.”⁶⁴

The biotechnology community agrees with these concerns. Because many biotechnological products are not novel chemical structures, but naturally occurring products,⁶⁵ biotech companies emphasize that, particularly for start-up companies, “patents covering such products are incredibly important.”⁶⁶

But although legal academics and biotechnology companies alike have claimed that *Myriad*’s impact has been profound, “empirical research has found little direct evidence of chilling effects.”⁶⁷ Claims of acute influence on biotechnology innovation have typically lacked evidence, supporting anecdotes, or concrete examples of deterrence. In other words, “a lot of ink has been spilled speculating on the impact of the decision, yet many questions remain unanswered,” including whether *Myriad* has impacted health care in the way many have claimed.⁶⁸

One of the only concrete examples of *Myriad*’s genuine impact on biotechnology development was provided at the Berkeley Center for Law & Technology Section 101 Workshop, which addressed patent eligibility challenges.⁶⁹ At this conference, participants explicitly discussed *Myriad*’s isolated impact on research and development. Attendees lamented about “how the loss of patent protection for isolated and purified natural products further limits the range of bio-science advances where investors can[] expect rewards from their

64. AIPLA Submits Comments to USPTO Regarding Request for Information to Assist Preparation of Patent Eligibility Jurisprudence Study, AM. INTELL. PROP. L. ASS’N (Oct. 15, 2021), <https://perma.cc/WS6L-PYFP>.

65. Both small molecule drugs and complex biologics regulated by the FDA are commonly products of nature or derived from natural products. See David J. Newman & Gordon M. Cragg, *Natural Products as Sources of New Drugs over the 30 Years from 1981 to 2010*, 75 J. NAT. PROD. 311, 312 fig.1 (2012) (revealing that between 1981 to 2010, four percent of the 1355 therapeutics approved by the FDA were completely unchanged natural products, six percent were vaccines typically made from products of nature, fifteen percent were biological, and twenty-two percent were derived from a natural product).

66. Susan McBee & Bryan James, *The Supreme Court Should be Mindful of Naturally Derived Products other than Nucleic Acids when Deciding Myriad*, SCOTUSBLOG (Feb. 7, 2013, 10:16 AM), <https://perma.cc/H3YS-ZP3P> (“Between 1981 and 2006, approximately forty percent of all pharmaceuticals approved for use by the FDA were a biologic, natural product, or derived from a natural product.”).

67. Lee, *supra* note 59, at 1113.

68. Rinehart, *supra* note 50, at 1147.

69. See generally Jeffrey A. Lefstin, Peter S. Menell & David O. Taylor, *Final Report of the Berkeley Center for Law & Technology Section 101 Workshop: Addressing Patent Eligibility Challenges*, 33 BERKELEY TECH. L. REV. 551 (2018).

investments.”⁷⁰ Additionally, according to the final report derived from the conference:

An attorney with a strong bioscience background provided several concrete examples of important scientific research that was experiencing funding difficulties as a result of the shift in patent eligibility standards: cytotoxins derived from sea organisms (purified natural products) that could be used in treating tissue sarcoma; genes relating to particular genetic mutations; and snake toxins used for treating multiple sclerosis.⁷¹

However, beyond the comments made by this undisclosed conference attendee, reference to *Myriad*'s impact has been largely speculative and inconclusive.⁷² “In general, commentators agree[] that the Court decisions in *Bilski*, *Mayo*, *Myriad*, and *Alice* have had a significant impact on the scope of patent eligible subject matter.”⁷³ But what is not clear is whether they have affected anything that matters, such as innovation outcomes in the real world. This uncertainty is substantiated by congressional findings. In the recently published USPTO report to Congress titled *Patent Eligible Subject Matter: Public Views on the Current Jurisprudence in the United States*, it is clear that there are varying views on how *Myriad* (and other patentable subject matter cases) has affected innovation and investment.⁷⁴ This Note seeks to begin to fill this gap by addressing whether *Myriad* has directly influenced biotechnology development, particularly with regard to therapeutics.

70. *Id.* at 583.

71. *Id.* at 584.

72. See, e.g., Feldman, *supra* note 33, at 2; Mike Sikora, Note, *Mayo, Myriad, and a Muddled Analysis: Do Recent Changes to the Patentable Subject Matter Doctrine Threaten Patent Protections for Epigenetics-Based Inventions?*, 102 MINN. L. REV. 2229, 2229-31 (2018); Jacob S. Sherkow, Essay, *Preliminary Injunctions Post-Mayo and Myriad*, 67 STAN. L. REV. ONLINE 1, 1-3 (2014); Madison R. LeDuc, *Patent Eligibility of Natural Products: A Growing Problem*, 66 DRAKE L. REV. 229, 239-42 (2018).

73. U.S. PAT. & TRADEMARK OFF., *Patent Eligible Subject Matter: Report on Views and Recommendations From the Public*, USPTO (July 2017), <https://perma.cc/J9UL-NPJ6>.

74. In 2021, in response to an uncertain legal landscape following the *Alice* Quartet, Congress directed the USPTO to conduct an examination of the current state of patent eligibility jurisprudence in the United States. Patent Eligibility Jurisprudence Study, 86 Fed. Reg. 36, 257 (July 9, 2021), <https://perma.cc/63MP-TL3A>. This study, titled the Patent Eligibility Jurisprudence Study, elicited many comments from the public on their perception of current jurisprudence concerning patent-eligible subject matter, some of which are included in this Note. See, e.g., *infra* notes 110 and 124. Comments from the study also comprise much of the findings presented in the official Report to Congress, first introduced in Part I.C of this Note. See U.S. PAT. & TRADEMARK OFF., REPORT TO CONGRESS: PATENT ELIGIBLE SUBJECT MATTER: PUBLIC VIEWS ON THE CURRENT JURISPRUDENCE IN THE UNITED STATES 20 (June 2022), <https://perma.cc/6K88-K3T3> (“[C]ommenters generally agreed that a healthy, robust patent system promotes economic development through incentivizing innovation and investment . . . However, views differed considerably on whether and how the current state of the law on eligibility is furthering those objectives.”).

II. MYRIAD'S IMPACT ON THERAPEUTIC DEVELOPMENT

The impact of *Myriad* and other patent eligibility cases cannot be resolved from prior theoretical or empirical work with regard to the patent system's impact on innovation outcomes. Thus, Part II will highlight *Myriad*'s isolated impact on therapeutic development. First, the patent system's ambiguous impact on innovation in general will be addressed, followed by the first look into *Myriad*'s impact in lower courts and at the USPTO on therapeutics derived from natural products. Part II will then conclude with stories of therapeutic innovation that was deterred because of *Myriad*, most prominently the newly uncovered story of Mambalgin-1, a snake toxin with healing properties left unpursued. This case study is a novel contribution and a direct answer to the question of whether the patent system affects innovation results.

A. But First, the Patent System's Ambiguous Impact on Innovation

Evaluating whether *Myriad* has affected innovation outcomes in the biotechnology community is a difficult question to isolate, as it is situated within a broader, unanswered inquiry: whether patents impact research investment at all.

Scholars are not clear whether limits on patent eligibility, such as *Myriad* and its family of subject matter cases, affect innovation.⁷⁵ Not only is the answer to this question “theoretically ambiguous,”⁷⁶ but attempts to resolve it through empirical evidence have produced mixed results.⁷⁷

For example, Michele Boldrin and David K. Levine argue that there is no evidence that patents increase innovation.⁷⁸ In their book *Against Intellectual Monopoly*, they use many case studies to suggest that patents actually discourage research and development.⁷⁹ Similarly, Petra Moser has offered evidence that

75. See generally Maya Durvasula, Lisa Larrimore Oullette & Heidi L. Williams, Comment on Patent Eligibility Jurisprudence Study, (Sept. 7, 2021), <https://perma.cc/N2XS-TMVV>.

76. As Durvasula, Oullette, and Williams recount:

Theoretical models of patents originally focused on one central trade-off: society tolerates the cost of higher prices for patented products or processes in the short term (during the life of the patent) in exchange for these higher prices increasing the incentives for inventors to develop new technologies. These types of theoretical models generate the intuitive prediction that stronger—that is, longer or broader—patent terms will induce additional research investments. However, work by Suzanne Scotchmer and others considered the more realistic case where patents not only affect incentives for the development of an initial invention, but also affect subsequent innovation. In markets where innovation is cumulative—in the sense that inventions are themselves inputs into later follow-on discoveries—it is theoretically ambiguous whether stronger patents will increase or decrease innovation.

Id. at 1-2 (citations omitted)

77. *Id.* at 2.

78. Michele Boldrin & David K. Levine, *AGAINST INTELLECTUAL MONOPOLY* 6-7 (2007).

79. See generally *id.*

many world-changing innovations came from countries without patent protection, suggesting that patents are not necessary for innovation.⁸⁰

Yet other evidence suggests that the patent system does encourage new developments. Jacob Moscona provides causal evidence that the promise of a patent increased development in the plant biotechnology industry.⁸¹ Additionally, there is research that shows a potential relationship between patents and cancer drug development, although this evidence is not conclusive.⁸²

After synthesizing the limited and inconclusive empirical evidence regarding the patent system's impact on innovation, Maya Durvasula, Lisa Ouellette, and Heidi Williams suggest that "given the very small number of studies offering a rigorous causal test of how patents affect research investments . . . we currently lack sufficient evidence to inform the question of whether strengthening the patent system . . . would increase research investments and innovation."⁸³ They further this observation by claiming that "[i]t is unclear whether patent eligibility limits increase or decrease innovation in biomedical markets."⁸⁴ Their sentiments push back against those in the biotechnology field who claim that "the sky is falling" post-*Myriad*. In fact, they suggest that in order to evaluate the impact of patentable subject matter case law "observed changes must be benchmarked against a 'counterfactual' scenario: what would investments have looked like *had there been no policy change?*"⁸⁵ Of course, they concede that true counterfactuals are impossible to witness, but their logic inspires a goal of identifying "plausible [if not probable] counterfactuals . . . from which we can disentangle the effects of patentability restrictions from other trends in the economy."⁸⁶

Evidence arguing that *Alice* and *Mayo* have both encouraged and harmed biomedical innovation has been contemplated,⁸⁷ but has not yielded definitive results with regard to *Myriad* in isolation. With respect to this potential inquiry, Durvasula, Ouellette, and Williams note that:

Such survey data and anecdotes are valuable insofar as they provide practitioner

80. Durvasula, Ouellette & Williams, *supra* note 75, at 2 (citing Petra Moser, *How Do Patent Laws Influence Innovation? Evidence from Nineteenth-Century World's Fairs*, 95 AM. ECON. REV. 1214 (2005); Petra Moser, *Patents and Innovation: Evidence from Economic History*, 27 J. ECON. PERSP. 23, 24 (2005) ("In fact, survey data for the late twentieth century indicate that commercial research and development labs in most industries deem alternative mechanisms, such as secrecy and lead-time (being the first firm to offer a new product) to be more effective than patents . . .") (parenthetical added)).

81. See generally Jacob Moscona, *Flowers of Invention: Patent Protection and Productivity Growth in US Agriculture* (Sept. 20, 2021), <https://perma.cc/F5PE-VMU8>.

82. See generally Eric Budish, Benjamin N. Roin & Heidi Williams, *Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials*, 105 AM. ECON. REV. 2044 (2015).

83. Durvasula, Ouellette & Williams, *supra* note 75, at 2.

84. *Id.* at 4.

85. *Id.*

86. *Id.*

87. *Id.* at 5.

perspectives on the patent system. However, survey data and anecdotes are unable to provide a counterfactual, and thus cannot support a causal conclusion about how *Alice/Mayo* [or *Myriad*] has affected research investments. For example, historical investments into medicines derived from natural sources were made at a time when such inventions were eligible for patent protection, but that fact is insufficient to demonstrate that patent protection was *necessary* for their development. Furthermore, patent protection is still available on a number of aspects of therapeutics derived from natural sources. More comprehensive analysis of projects that were discontinued due to patent eligibility concerns would provide a promising avenue for future empirical work.⁸⁸

This Note intends to answer the call for “[m]ore comprehensive analysis of projects that were discontinued due to patent eligibility concerns,”⁸⁹ specifically with regard to *Myriad* and its impact on the development of therapeutics derived from natural products. The uncovered story of Mambalgin-1, highlighted in Part II.C.2, particularly adds empirical depth to the question posed in this Note; it provides an explicit counterfactual that *can* support a causal conclusion about how *Myriad* has affected research investments.

B. Applying *Myriad* to Therapeutics Derived from Natural Products in the Lower Courts and at the USPTO’s Patent Trial and Appeal Board

Contrary to some expectations, *Myriad* has made little impact in the courts so far with regard to therapeutic inventions. In the lower courts, *Myriad* has hardly made a drop in the ocean. A slightly larger splash has been made at the USPTO’s Patent Trial and Appeal Board (PTAB), but nothing significant in comparison to the impact some commentators expected *Myriad* to have on therapeutic development in the courts.⁹⁰

Mark Lemley and Samantha Zyontz recently created a dataset that coded “every district court decision and subsequent appeal[] to the Federal Circuit involving patentable subject matter” post-*Alice* by inventive category.⁹¹ One of their dataset’s categories is “biotech/life science” decisions.⁹² From the *Alice* decision in 2014 to June 2019, Lemley and Zyontz noted eighty-five biotech/life

88. *Id.* at 5-6.

89. *Id.* at 6.

90. It is important to note that parties may bring their claims to the USPTO over the appropriate district court for a variety of procedural or strategic reasons not mentioned in this Note. However, the choice of venue for patent cases, in general, is outside the scope of my research.

91. Mark A. Lemley & Samantha Zyontz, *Does Alice Target Patent Trolls?*, 18 J. EMPIRICAL LEGAL STUD. 47, 48 (2021).

92. *Id.*

science decisions that relied on *Mayo*, *Alice*, and/or *Myriad* as primary authority.⁹³ Of these eighty-five decisions, most addressed diagnostic claims ruled unpatentable under *Mayo*.⁹⁴ And of the few cases directed at non-diagnostic claims, all but one confronted medical techniques, processes, or methods.⁹⁵ The sole federal case to address claims of therapeutics derived from isolated natural products during this period was *Natural Alternatives International v. Allmax Nutrition*, and it only addressed the isolated nature of the product in question as dictum.⁹⁶ Additionally, the supplement in question, while intended to improve health, was a dietary supplement that could be marketed without evidence of efficacy, in contrast to drug products that require FDA approval on the basis of costly clinical trials.⁹⁷ The economics of developing a new dietary supplement thus do not parallel the types of pharmaceutical therapies this Note is focused on, including therapies that have the potential to significantly impact modern medicine and the care we provide to patients with chronic illness.

In *Natural Alternatives*, the claim at issue is an amino acid called beta-alanine in “human dietary supplement” form.⁹⁸ Here, the plaintiff claimed that the inventive concept was placing “a specific dosage of beta-alanine into a human dietary supplement.”⁹⁹ The Court, however, found that “placing a natural substance into a dietary supplement is a conventional activity, [and therefore] employing a dietary supplement to administer the beta-alanine, a natural phenomenon, is insufficient to render claim 1 patent eligible.”¹⁰⁰ The plaintiff also tried to argue that “when beta-alanine is isolated from the dipeptide, carnosine, beta-alanine has different properties than carnosine.”¹⁰¹ But the court struck down this

93. Zyontz graciously sent me a truncated version of their dataset which only included the coded biotech/life science decisions. E-mail from Samantha Zyontz, Research Fellow, Stan. L. Sch., to Taylor Beardall, Student, Stan. L. Sch. (Jan. 4, 2022, 9:36 PM PST) (on file with author).

94. See, e.g., *Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 915 F.3d 743 (Fed. Cir. 2019); *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015); *23andMe, Inc. v. Ancestry.com DNA, LLC*, 356 F. Supp. 3d 889 (N.D. Cal. 2018).

95. See, e.g., *Oxford Immunotec Ltd. v. Qiagen, Inc.* 271 F. Supp. 3d 358 (D. Mass. 2017); *Idexx Labs., Inc. v. Charles River Labs., No. 15-668-RGA*, 2016 U.S. Dist. LEXIS 87888 (D. Del. July 1, 2016); *INO Therapeutics LLC v. Praxair Distrib. Inc.*, 782 Fed. Appx. 1001 (Fed. Cir. 2019).

96. See *Natural Alternatives Int'l, Inc. v. Allmax Nutrition, Inc.*, 258 F. Supp. 3d 1170, n.13 (S.D. Cal. 2017).

97. *Id.* at 1181; *FDA 101: Dietary Supplements*, U.S. FOOD & DRUG ADMIN., <https://perma.cc/LA4R-HBJR> (archived May 20, 2023) (“Under the [Federal Food, Drug, and Cosmetic Act], it is the responsibility of dietary supplement companies to ensure their products meet the safety standards for dietary supplements and are not otherwise in violation of the law.”).

98. *Natural Alternatives*, 258 F. Supp. 3d at 1182.

99. *Id.* at 1183.

100. *Id.*

101. *Id.* at n.13.

secondary argument with a quick reference to *Myriad*, albeit in a footnote.¹⁰²

Since June 2019, only one other federal decision has focused on therapeutics derived from products of nature—and it also involved a dietary supplement rather than a pharmaceutical therapy.¹⁰³ In *Chromadex v. Elysium Health*, the court relied on *Myriad* to invalidate a claim covering “isolated nicotinamide riboside (NR), a naturally occurring form of vitamin B3.”¹⁰⁴ The plaintiff asserted that their claim could be distinguished from *Myriad* in that “[t]he characteristics of the claimed compositions dramatically distinguish those compositions from naturally occurring NR”¹⁰⁵ because the isolated NR is “stable, bioavailable, and sufficiently pure,”¹⁰⁶ which allows it to “reach the bloodstream, enter the cell, and

102. *Id.*

103. To find federal cases handling the patentability of therapeutics derived from products of nature under *Myriad* post-June 2019, I used Westlaw’s online search function. I used the following search terms: “Ass’n for Molecular Pathology v. Myriad Genetics, Inc., 566 U.S. 902,” “natural product!,” and “product! #of nature.” Then, I further limited the results to federal courts and cases post-June 2019. Seven cases fit these filters. (There were twelve initial results, but this included: one duplicative decision for *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, *Barton v. Pret A Manger (USA) Limited*, which was a false advertising case about natural food products, *In re MCP No. 165* which was an OSHA employment case focusing on a “myriad of workplace policies,” *Collins v. Quincy Bioscience* which was a class action lawsuit that used the adjective *myriad* in excess, and *In re MCP No. 165, Occupational Safety and Health Administration, Interim Final Rule: COVID-19 Vaccination and Testing*, which was a faulty search result and did not cite *Myriad* once.) From there, I read the patent claims at issue in each case to find the cases that handled therapeutics derived from products of nature. From the remaining seven cases that handled natural product patent claims, I excluded method, system, and diagnostic claims, leaving *Chromadex v. Elysium* as the sole case focusing on therapeutics derived from natural products. For the five false results, see *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 952 F.3d 1367 (Fed. Cir. 2020); *Barton v. Pret A Manger (USA) Ltd.*, 535 F. Supp. 3d 225, 229 (S.D.N.Y. 2021); *In re MCP No. 165*, 21 F.4th 357, 384 (6th Cir. 2021); *Collins v. Quincy Bioscience, LLC*, No. 19-CV-22864-COOKE/GOODMAN, 2020 WL 3268340, at *7-21 (S.D. Fla. Mar. 19, 2020); *In re MCP No. 165, Occupational Safety and Health Administration, Interim Final Rule: COVID-19 Vaccination and Testing*, 20 F.4th 264, 269 (6th Cir. 2021). For the six cases that cited *Myriad* and handled non-therapeutic natural product patents, see *Genetic Veterinary Sciences, Inc. v. LABOKLIN GmbH & Co. KG*, 933 F.3d 1302, 1315 (Fed. Cir. 2019) (“in vitro methods for genotyping a Labrador Retriever”); *Cedars Sinai Medical Center v. Quest Diagnostic Incorporated*, No. CV 17-5169-GW(FFMx), 2019 WL 8884101, at *2 (C.D. Cal. Aug. 8, 2019) (a “system for diagnosing irritable bowel syndrome”); *ThermoLife Int’l, LLC v. Hi-Tech Pharm, Inc.*, No. 1:15-CV-00892-ELR, 2020 WL 9601785, at *1 (N.D. Ga. May 29, 2020) (“method claims covering administration of those compositions for increasing vasodilation, athletic performance, bioabsorption, solubility, and distribution of amino acids”); *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 967 F.3d 1319, 1323 (Fed. Cir. 2020) (a “method for preparing a deoxyribonucleic acid (DNA) fraction from a pregnant human female useful for analyzing a genetic locus involved in a fetal chromosomal aberration”); *DUSA Pharm., Inc. v. Biofrontera Inc.*, 495 F. Supp. 3d 21, 25 (D. Mass. 2020) (“[a]n illuminator for diagnosing or treating a patient”); *Abbott Laboratories v. Grifols Diagnostic Solutions Inc.*, No. 19 C 6587, 2020 WL 7042891, at *4 (N.D. Ill. Dec. 1 2020) (“a method for replicating DNA specific for HIV”).

104. *Chromadex v. Elysium Health Inc.*, 561 F. Supp. 3d 460, 462 (D. Del. 2021).

105. *Id.* at 464.

106. *Id.*

provide therapeutic effect.”¹⁰⁷ The district court, however, relied on *Myriad* to shut down this reasoning, stating that “the Supreme Court unanimously rejected this line of argument”¹⁰⁸

Beyond these two references to *Myriad*—one cursory and one more substantive—no other lower court decisions have used *Myriad* to reject (or uphold) the patentability of a therapeutic derived from a natural product. And there have been *no* cases addressing the patent eligibility of pharmaceutical products derived from nature. There simply has not been a tsunami—or even a trickle—of litigation eliminating patents for naturally derived therapeutics as some feared. Thus, the sky is certainly not falling in the federal courts.

There is evidence, however, that *Myriad* has made a slightly larger splash at the USPTO. The PTAB, the adjudicative body of the USPTO, *is* affirming rejections of patent application claims of therapeutics derived from natural products on patent eligibility grounds under *Myriad*.¹⁰⁹ This is clear from a search of post-*Myriad* PTAB decisions and recently submitted comments to the USPTO regarding Congress’s Patent Eligibility Jurisprudence Study.¹¹⁰

In terms of post-*Myriad* PTAB cases that have addressed therapeutics derived from natural products, two hundred eight results appear.¹¹¹ Certainly not all of these cases dealt with therapeutics or led to the rejection of patents solely under a *Myriad* analysis, but some did. Therapeutic cells capable of repairing cardiac tissue,¹¹² an amino acid protein able to regenerate healthier cells,¹¹³ and a potato protein that possesses pharmaceutical and therapeutic enzymes¹¹⁴ are all examples of therapeutic inventions derived from natural products that have been rejected as patent ineligible at the PTAB.

107. *Id.* at 465.

108. *Id.*

109. The PTAB “decides appeals from the decisions of patent examiners, and adjudicates the patentability of issued patents challenged by third parties . . .” Janet Gongola, *The Patent Trial and Appeal Board: Who Are They and What Do They Do?*, USPTO, <https://perma.cc/97CM-S3CP> (archived May 20, 2023). Searching patent examination decisions directly would be a fruitful avenue for future research, as not all patent application rejections are appealed to the PTAB.

110. See *infra* Part II.C; Novartis, Comment in Response to USPTO’s “Patent Eligibility Jurisprudence Study Request for Information” (Oct. 15, 2021), <https://perma.cc/W47N-WZ3V>.

111. To find the PTAB cases handling the patentability of therapeutics derived from products of nature under *Myriad*, I used Westlaw’s online search function. I used the following search terms when searching among “Patent Trial & Appeal Board (PTAB) Decisions”: “Ass’n for Molecular Pathology v. Myriad Genetics, Inc., 566 U.S. 902,” “natural product!,” and “product! #of nature.” This led to two hundred eight results. I further narrowed this search by filtering decisions including “therap!” to target therapeutic inventions. This narrowed the results down to sixty-eight cases.

112. Ex Parte Marban, 2020 Pat. App. LEXIS 8028, at *6 (P.T.A.B. June 19, 2020).

113. Ex Parte Levine, 2018 WL 4739995, at *7 (P.T.A.B. Sept. 14, 2018).

114. Ex Parte Giuseppin, 2018 WL 1621788, at *1 (P.T.A.B. Mar. 22, 2018).

Comments submitted to the USPTO add to the list of patent applications for therapeutics that have been rejected by patent examiners under *Myriad*. For example, Novartis, one of the largest pharmaceutical companies in the world,¹¹⁵ claims that they have been denied therapeutic patents because of *Myriad*-induced Section 101 issues.¹¹⁶ One of their rejected inventions includes:

a novel “pharmaceutical composition” to treat osteoarthritis, made up of a modified protein that does not exist in nature, which was found to be an ineligible “product of nature,” despite the fact that the sequence was different from that of any natural protein, and that the desired medical effect was present only in our modified product.¹¹⁷

Given the example provided by Novartis, as well as the other apparent PTAB rejections available on Westlaw, it is clear that patents for therapeutics derived from natural products are being rejected more frequently than patents in federal courts. For companies and investors contemplating whether to pursue clinical trials for promising natural therapies, rejection by the USPTO might be cause for concern and influence eventual commercial development.

The sky is certainly not falling for therapeutics post-*Myriad* in federal courts. And while the effect of *Myriad* has been felt more acutely during patent examination, the impact has not been overwhelming, as some critics expected. This review, however, does not address *Myriad*'s impact on innovation, as the rejected patents at issue claimed creations that were still invented under a *Myriad* regime. To capture whether *Myriad* has deterred innovation, this Note turns to first-hand accounts of unpursued therapies.

C. Unpursued Therapeutic Innovation

1. Stories Submitted to the USPTO

While a review of federal judicial decisions shows that the most worrisome concerns about *Myriad*'s effect on innovation have not been realized,¹¹⁸ this does not mean that *Myriad*'s impact has been non-existent. As evidenced in Part II.B, there are claims to natural therapeutics being rejected by the USPTO because of *Myriad*, even though they may represent novel and nonobvious inventions. Additionally, members of the biotech community have shared stories that represent concern with how *Myriad* and other Supreme Court Section 101 patent eligibility cases have affected innovation.

Most recently, this discontent was shared with the USPTO in 2021 during the comment period for Congress's Patent Eligibility Jurisprudence Study, an

115. See *Top Ten Pharma Companies in 2020*, PHARM. TECH. (Oct. 1, 2020), <https://perma.cc/4VA4-AXY3>.

116. Novartis, *supra* note 110, at 4.

117. *Id.*

118. See *supra* Part II.B.

inquiry into how “the current jurisprudence has adversely impacted investment and innovation in critical technologies like . . . precision medicine, diagnostic methods, and pharmaceutical treatments.”¹¹⁹ Approximately twenty-two submissions came from the life sciences community, many noting innovation and development concerns.¹²⁰

Corey Salsberg, Vice President of Global Head IP Affairs, submitted a comment on behalf of Novartis.¹²¹ He noted that his company has “been denied patent claims through Section 101 rejections on a range of technologies of potential benefit to patients that plainly fit the statutory categories of eligible subject matter, and that should have granted under any sensible approach to eligibility.”¹²² These rejected patents include the modified protein capable of treating osteoarthritis previously mentioned in Part II.B.

Salsberg added that:

Losing patents and claim scope can have significant impact on innovation. While we rarely make investment decisions solely on the basis of a single patent, the accumulated loss of patents in a field or project over time significantly undermines our ability to continue to devote substantial resources to that field or project. At a minimum, such losses—particularly if they involve a patent that proves important for the protection of a commercial form of an invention—represent one more risk in a field where the scientific, technological, regulatory and market odds are already stacked significantly against us.¹²³

Genentech, the self-proclaimed “first biotechnology company, with a long history of solving the toughest medical problems”¹²⁴ submitted an eleven-page letter to the USPTO expressing concern that U.S. patent jurisprudence has unduly restricted life science innovations, “including those deliberately engineered to be closer to nature—that are the future of medicine.”¹²⁵ The company wrote:

For example, our personalized cancer therapeutics that are currently in development are a promising form of treatment that use nucleic acid sequences encoding a portion of a patient’s own tumor to stimulate the patient’s immune system to fight the tumor. Because they are tailored to a specific patient, these more natural treatments have the potential to be more effective and less harmful than conventional therapeutics, leading to more positive, long-lasting health outcomes for patients. Yet under the current patent eligibility jurisprudence, these revolutionary therapeutics may not be patent eligible.¹²⁶

119. Patent Eligibility Jurisprudence Study, 86 Fed. Reg. 129 (July 9, 2021).

120. Victoria T. Carrington & Jorge L. Contreras, *Guest Post: Assessing Responses to the PTO’s 2021 Patent Eligibility Study*, PATENTLYO (Feb. 1, 2022), <https://perma.cc/G4AK-5LBH>.

121. Novartis, *supra* note 110, at 1.

122. *Id.*

123. *Id.* at 4.

124. Genentech, Comment in Response to USPTO’s “Patent Eligibility Jurisprudence Study Request for Information” (Oct. 15, 2021), <https://perma.cc/XH2W-QVZR> at 1.

125. *Id.* at 4.

126. *Id.*

Genentech also added that “microbiome [the study of behavior, interactions, and functions of microbial communities within a specified environment¹²⁷] is another emerging area in biology and medicine.”¹²⁸ They continued that:

Only in the last several years has it become clear that the complex collections of bacteria found on our skin, in our gut, and elsewhere can play a vital role in our physical health and our reaction to certain medicines. Our scientists are researching medicines based on gut microbiome bacteria taken from patients which can then be carefully selected, and used to create medicines for patients—for example, for the treatment of inflammatory bowel disease. “Obtaining patent protection is essential for the development of [microbiome] therapeutics,” yet the ability to do so has been affected profoundly by the state of patent eligibility jurisprudence simply because these medicines are derived from natural products.¹²⁹

The Wisconsin Alumni Research Foundation (WARF), the University of Wisconsin’s patenting and licensing branch, also submitted a comment of particular interest to this Note.¹³⁰ They claimed that they:

have already begun to encounter the consequences of this uncertainty in our collaborations with UW-Madison researchers who are studying the naturally occurring substances that could generate the next generation of antibiotics. We have begun to explore foregoing domestic patenting in favor of foreign patent protections, and our contacts with industry suggest operations based overseas will be more likely to attract investors.¹³¹

Of course, it should be acknowledged that these comments were submitted to the USPTO with a strong agenda of rolling back patentable subject matter jurisprudence. But these newly released comments still represent stories of obstructed innovations from leaders in the biotechnology industry and add empirical depth and rigor to this discussion. They add to the limited evidence of *Myriad*’s impact on innovation, including the anonymous comments made at the Berkeley Section 101 workshop.¹³² However, just like the Berkeley 101 comments, the USPTO claims of unpursued therapeutics are each no longer than a paragraph, if one sentence. Thus, claims of hampered innovation due to *Myriad*-related concerns have been limited in detail and have lacked the in-depth recounting and explicit facts likely to move the public and Congress. There is a lack of

127. Chad M. Cullen et al., *Emerging Priorities for Microbiome Research*, 11 FRONTIERS IN MICROBIOLOGY 1, 2 (2020).

128. Genentech, *supra* note 124, at 4.

129. *Id.* at n.10 (citing Mark J. FitzGerald & Erik J. Spek, *Microbiome Therapeutics and Patent Protection*, 38 NATURE BIOTECHNOLOGY 806, 808 (2020) (“After the *Mayo* and *Myriad* decisions, patent prosecution of composition claims of natural products came to a halt . . .”).

130. Wisconsin Alumni Research Foundation, Comment in Response to USPTO’s “Patent Eligibility Jurisprudence Study Request for Information” (Oct. 14, 2021), <https://perma.cc/6RXX-FPPQ>.

131. *Id.*

132. See *supra* Part I.C.

stories that detail promising therapeutics unpursued because of the status of patentable subject matter jurisprudence. This Note seeks to begin to fill this gap and add greater empirical depth to the inquiry concerning *Myriads* direct effect.

2. *The Story of Mambalgin-1*

At the Berkeley 101 workshop, the most specific examples of patent eligibility case law having a negative effect on research investments were the mentions of “cytotoxins derived from sea organisms . . . that could be used in treating tissue sarcoma” and “snake toxins used for treating multiple sclerosis” that were “experiencing funding difficulties” because of *Myriad* and patent eligibility jurisprudence.¹³³ However, while these were listed as “concrete examples” of scientific research that encountered challenges because of *Myriad* concerns, the workshop report lacked supplemental evidence that might have a greater influence on conversations regarding the current status of patent eligibility standards and the potential changes that ought to be considered because of *Myriad*’s unintended failures.¹³⁴ I therefore sought out the details that would turn one of these exciting “examples” of deterrence into a comprehensive story of lost potential and social impact.

By emailing attendees of the Berkeley 101 workshop, I was able to track down Thomas Mathers, the now President and CEO of the clinical stage biotech company, Allievex Corporation, and the original source of the snake toxin example.¹³⁵ Mathers is also a partner at Pappas Capital, a venture capital firm “laser focused on the life science sector.”¹³⁶ Mathers generously agreed to expound on the “snake toxin” story through an interview. The following case study is derived from my interview with Mr. Mathers, supplemented by independent investigative research to fill small gaps in his otherwise-precise memory.¹³⁷

133. Lefstin, Menell & Taylor, *supra* note 69, at 584.

134. *Id.*

135. Dr. Hans Sauer was listed as an attendee of the Berkeley 101 workshop. During my interview with Sauer, he claimed the snake toxin quote, but attributed the story to Thomas Mathers. Sauer reached out to Mathers to confirm that he could connect me with the biotech CEO. Mathers agreed to discuss the failed venture with me. *Our Team*, ALLIEVEX, <https://perma.cc/U2N7-WSY7> (archived May 17, 2023). Allievex focuses primarily on developing novel therapies for treatment of rare pediatric neurodegenerative diseases. *Our Focus*, ALLIEVEX, <https://perma.cc/9LX5-Z79N> (archived May 17, 2023).

136. *Home*, PAPPAS CAPITAL, <https://perma.cc/KHU9-MVXA> (archived May 17, 2023).

137. Mathers Interview, *supra* note 16. Mathers still possessed a strong recollection of the story presented in this Note. My intervention was necessary, however, to add detail to his decade-old account. For example, Mathers said that he “came upon this literature from this . . . scientist at University of Nice named Eric . . . ugh I forget his last name.” I then researched scientists named Eric, who worked for the University of Nice during the relevant time period, and published research on snake venom to deduce that Mathers was referring to Eric Lingueglia. I only added detail of this nature to the thorough facts supplied by Mr. Mather or to describe the complex scientific terms used by Mathers during our interview; I did not alter,

In 2010, Mathers was the Director of Peptimmune, Inc, a life sciences company that provides products and services to prevent and treat multiple sclerosis, Chron's Disease, and Rheumatoid arthritis.¹³⁸ At the time, this company had expertise in making long peptides in solid phase synthesis and designing these peptides for development as therapeutics.¹³⁹ It was during this year that Mathers became interested in research emerging from the University of Nice Sophia Antipolis in France under the direction of Eric Languaglia, a faculty member at the University's Institute of Molecular and Cellular Pharmacology.¹⁴⁰ Mathers explained that the University did "a lot of work looking at venom derived peptides in acid sensing ion channels."¹⁴¹ He further described how ion channels in the spinal cord—that are heavily populated with venomous peptides—can be used to curb pain in the spinal region.¹⁴²

Until this point, venoms from marine snails were the primary focus of venom derived peptides and spinal pain reduction.¹⁴³ During the early 2010s, venom of the *Conus* species (conopeptides) was thought to be the richest source of naturally occurring peptides.¹⁴⁴ Researchers worked to develop and improve a safe and effective therapy to reduce patient's spinal pain, but toxicity remained a concern throughout development of sea snail venom.¹⁴⁵ The therapeutic window of the conopeptides remained close to zero, meaning that with every patient, it was uncertain whether the drug would solely reduce pain or also introduce symptoms associated with toxicity.¹⁴⁶ This research was ultimately used to develop and

enhance, or exaggerate the story presented.

138. Thomas Mathers, LINKEDIN, <https://perma.cc/7FGH-HQ2D> (archived May 25 2023); Peptimmune, MPM CAPITAL, <https://perma.cc/GTE3-AYGA?type=image> (archived Jan. 21, 2021).

139. Peptimmune, *supra* note 138. Peptides are short chains of amino acids linked by peptide bonds. Sara C. Hull, *Peptide*, NAT'L HUM. GENOME RSCH. INST. (Apr. 18, 2023), <https://perma.cc/ZHT7-QEWC?type=image>. Long peptides, also known as polypeptides, are longer and continuous peptide chains. *Id.* Solid phase synthesis is "the synthesis of chemical compounds whereby the reactant molecule is chemically bound to an insoluble material" *Solid-Phase Synthesis*, NATURE PORTFOLIO, <https://perma.cc/3W3Z-SZ7X> (archived May 17, 2023).

140. Mathers Interview, *supra* note 16. See Sylvie Diocot et al., *Black Mamba Venom Peptides Target Acid-Sensing Ion Channels to Abolish Pain*, 490 NATURE 552 (2012) for the research that piqued Mathers' interest.

141. Mathers Interview, *supra* note 16.

142. *Id.*

143. *Id.*

144. *Id.* See also Phillippe Favrea et al., *A Novel μ -conopeptide, CnIIIIC, Exerts Potent and Preferential Inhibition of NaV1.2/1.4 Channels and Blocks Neuronal Nicotinic Acetylcholine Receptors*, 166 BRIT. J. PHARMACOLOGY 1654, 1655 (2012).

145. See Max Chalmers & Laura Brierly Newton, *Sea Snail Venom Could Be "The Holy Grail" in Therapeutics*, ABC NEWS AUSTRAL. (Apr. 3, 2018, 10:18 PM), <https://perma.cc/DSL9-HEQU> ("[I]t is difficult to administer the correct dose without inducing bad side effects.")

146. *Id.* (The dose required for sea snail "toxicity [is] about the same dose as the dose that relieves the pain, making it difficult to adjust the dose based on a patient's response.")

commercialize the drug Prialt, a non-opioid pain reliever synthetically derived from marine snail venom,¹⁴⁷ but this medication still had (and has) side-effects, including hallucinations.¹⁴⁸ It was clear that peptide pain therapies could still benefit from further research and development. Thus, when looking for the next great peptide therapy to support, Lingueglia's research looked promising to Mathers.¹⁴⁹

Mathers ultimately reached out to Lingueglia and his team to learn more about the potentials of snake venom.¹⁵⁰ The university team explained that they had identified a venom drive peptide from the Black Mamba snake called Mambalgin-1.¹⁵¹ When a snake bites its prey, it envenomates it with all kinds of chemical structures,¹⁵² including peptides such as Mambalgin-1. This peptide is included in the Black Mamba's venom to ensure that its victims don't feel pain during envenomation; this allows a prolonged period of venom pumping.¹⁵³ The University of Nice researchers shared that they had isolated the peptide, studied it in rats, compared it to Prialt, and concluded that Mambalgin-1 could treat rats better than the current market option *and* with fewer side effects.¹⁵⁴ This led to Mather's conclusion that if Mambalgin-1 had survived natural selection, then it was fit for a greater medicinal purpose. He believed it could fill the demand for a non-opioid pain reliever that induced less side-effects than the current commercial option.¹⁵⁵

Given Mambalgin-1's potential as a commercial pain therapy, Mathers and Peptimmune got involved in the product's licensing and development around 2015, planning to quickly pitch the discovery to biotech investors.¹⁵⁶ This was two years after the Court handed down the *Myriad* decision, which Mathers and his legal team read to mean that Mambalgin-1's development as a natural product therapy would be unpatentable. Mathers knew that without the promise of patentability, investors would not take on the risk of Mambalgin-1's development and commercialization.¹⁵⁷

During our interview, Mathers described the way he has seen capital formation work in the biotech space, a topic he is uniquely qualified to speak on as he has had a long career on both sides of venture capital, as a CEO and investor.

147. Joe Palca, *Snail Venom Yields Potent Painkiller, But Delivering the Drug Is Tricky*, NPR (Aug. 3, 2015, 3:30 PM), <https://perma.cc/5SRX-JV5S>.

148. *Prialt*, RxLIST, <https://perma.cc/PKN2-RBGZ> (archived Apr. 6, 2023).

149. Mathers Interview, *supra* note 16.

150. *Id.*

151. *Id.*; see Lefstin, Menell & Taylor, *supra* note 69, at 584.

152. Mathers Interview, *supra* note 16.

153. *Id.*

154. *Id.*

155. *Id.*

156. *Id.*

157. *Id.*

He explained that without the promise of a patent, investors will not be willing to take on the risk of new projects, particularly in the biotech and life science industry where there is about a ninety-percent likelihood of failure.¹⁵⁸ He believes that this percentage, combined with zero promise of commercial exclusivity derived from a patent, will not entice any biotech investors, because venture capital firms search for opportunities that will promise commercial exclusivity for an extensive period of time. Mathers was resolute that no investor would invest tens of millions of dollars (the amount he estimated would be necessary to bring Mambalgin-1 to the market as a safe and successful pain medication), taking all of the risk, when a patent would not be provided at the end of the development process.¹⁵⁹

For these reasons, Mathers knew that he needed to find a *Myriad* workaround to ensure that his potential therapy derived from natural snake venom peptides could be patented in the U.S. With this purpose in mind, he arranged a meeting with Michelle K. Lee, the then-Director of the USPTO.¹⁶⁰ During his meeting with Lee, he made a passionate plea for an exception that would allow Mambalgin-1 to be patented as a new therapeutic. He promoted his natural sequence as a life-altering medicine that would not be pursued if denied patentability. Mathers described this meeting with Lee as unsuccessful. Therefore, he and his team at Peptimmune made the decision to pull the plug on successive Mambalgin-1 development and end the search for interested investors.¹⁶¹

During our interview, Mathers declared that he is convinced “to this day that Mambalgin-1 could be a very interesting therapeutic,” but that no one will develop it because there is no promise of the lengthy commercial exclusivity period that a patent can provide.¹⁶² He believes that nature is efficient at optimizing its natural products for certain restorative purposes and expressed his admiration for the Black Mamba and how over its existence and evolution, the Mambalgin-1 peptide has not been deleted. To Mathers, this means that it is clearly fit for a greater social purpose, but a purpose that will stay unpursued by biotech companies searching for lucrative and commercially exclusive opportunities as long as *Myriad* is good law.¹⁶³

158. *Id.* Patent expert Benjamin Roin’s academic research supports Mathers’ belief. He writes that “[g]iven the immense investment needed to fund clinical trials on drugs and the ability of generic manufacturers to rely on those tests to secure regulatory approval for their own products, pharmaceutical companies are rarely willing to develop drugs without patent protection.” He adds that “[t]he harm to the public from the loss of these drugs is potentially quite significant.” Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 503 (2009).

159. Mathers Interview, *supra* note 16.

160. *Id.*; Michelle K. Lee, USPTO, <https://perma.cc/YX35-6CKP> (archived May 17, 2023).

161. Mathers Interview, *supra* note 16.

162. *Id.*

163. *Id.*

Mathers concluded our interview by sharing that as a biotech CEO and life science investor, he “stays away from naturally derived products.”¹⁶⁴ He has faith that naturally derived products hold the key to safe and effective therapies—as evidenced by successful methods of Chinese medicine—but that isolating active compounds to create natural medicine is not an investible strategy in the biotech space. He labeled this an unfortunate, but “natural consequence [of] *Myriad*.”¹⁶⁵

While this case study is subject to the counterfactual concerns that plague all instances of reflection, I believe it is less prone to hindsight bias *because* Mathers visited the USPTO in search of a *Myriad* exception for Mambalgin-1 and then, having not found a workaround, ceased work on the natural product therapeutic. This is evidence that *but for Myriad*, Mambalgin-1 would have been pursued by Peptimmune as an exciting new development.

This story is not presented as evidence that *Myriad* was wrongly decided or should be reversed. Instead, it is offered as thorough evidence of a specific and promising innovation that was not pursued explicitly because of *Myriad*. Given the substantial uncertainty of whether *Myriad* has had any effect on therapeutic development at all, this Note presents evidence that it has in fact deterred innovation in *at least* one concrete instance. The story of Mambalgin-1 begins to plug the hole that can only be filled with “[m]ore comprehensive analysis of projects that were discontinued due to patent eligibility concerns.”¹⁶⁶

III. WHAT NOW?: A MYRIAD OF OPTIONS

Myriad was championed by the ACLU with good intent. They believed the case to be a pro-women’s-health “fight to take back our genes.”¹⁶⁷ Additionally, one of the ACLU’s primary underlying themes of the case was a fear that granting patents for genes would “limit scientific research, learning and the free flow of information.”¹⁶⁸

The public carried their own host of concerns during the *Myriad* litigation. Angelina Jolie had just publicly shared her preemptive and successful testing for the BRCA1 and BRCA2 genes, as well as her concern about private companies creating monopolies over genetic testing.¹⁶⁹ In theory, a genetic testing monopoly would prevent competition, leaving crucial diagnostics inaccessible and unaffordable. During this time, readers were also devouring *New York Times* Best-

164. *Id.*

165. *Id.*

166. Durvasula, Ouellette & Williams, *supra* note 75, at 6.

167. *The Fight to Take Back Our Genes*, ACLU, <https://perma.cc/BT88-B9XW> (archived May 14, 2023).

168. *Id.*

169. Rinehart, *supra* note 50, at 1149.

seller *The Immortal Life of Henrietta Lacks*, which highlighted the ethical questions surrounding genetic information belonging to private entities.¹⁷⁰ Various public interest groups submitted amicus curia briefs to the Court outlining concerns regarding bodily autonomy,¹⁷¹ worries of limited cumulative research,¹⁷² and issues of quality healthcare access.¹⁷³ Altogether, there was good reason for public concern and for the Court to rule in favor of *Molecular Pathology*.

But while the *Myriad* holding was undoubtedly a win for proponents of bodily autonomy and cumulative innovation, the ACLU's fear of stalled research has still materialized after a pro-plaintiff holding. Of course, as uncovered in Part II.B, *Myriad* has not led to judicial litigation over the patent eligibility of pharmaceuticals derived from natural products. This may be because companies can still patent aspects of natural therapeutics, like the method of providing the discovered natural product to patients with a certain disease.¹⁷⁴ In the context of Mambalgin-1, for example, Mr. Mathers could have claimed the isolated peptide's ability to treat spinal discomfort in multiple sclerosis patients or some other knowledgeable application of the product.¹⁷⁵ While method patents may not be as desirable as active ingredient patents,¹⁷⁶ they still represent one way to elicit commercial exclusivity for some component of a natural therapeutic discovery.

Therefore, this Note does not suggest that *Myriad* should be reversed. Instead, for policymakers who are concerned about insufficient incentives for research on natural therapeutics like Mambalgin-1, this Note offers a toolkit of solutions *outside* the patent system. Congress has shown continuing interest in

170. See *The Legacy of Henrietta Lacks*, JOHNS HOPKINS MED., <https://perma.cc/62J9-XZJF> (archived May 14, 2023); *Science*, N.Y. TIMES BEST SELLERS (June 2013), <https://perma.cc/K5A9-QUH6>.

171. See Brief of Canavan Found. et al. as Amici Curiae Supporting Petitioner, Ass'n for Molecular Pathology v. Myriad Genetics, Inc. 569 U.S. 576 (2013) (No. 12-398), 2013 U.S. S. Ct. Briefs LEXIS 646.

172. See Brief for Am. Med. Ass'n et al. as Amici Curiae Supporting Petitioner, Myriad, 569 U.S. 576 (2013) (No. 12-398), 2013 U.S. S. Ct. Briefs LEXIS 603.

173. See Brief for Nat'l Women's Health Network et al. as Amici Curiae Supporting Petitioner, Myriad, 569 U.S. 576 (2013) (No. 12-398), 2013 U.S. S. Ct. Briefs LEXIS 653.

174. At the conclusion of the *Myriad* opinion, Justice Thomas clearly noted what was not implicated: "method claims" and "patents on new *applications* of knowledge . . ." *Myriad*, 569 U.S. at 595-96. The court noted that "Myriad was in an excellent position to claim applications of knowledge" of the BRCA1 and BRCA2 genes, language adopted from the Federal Circuit Court of Appeals. *Id.* at 596. The Federal Circuit further explained that their main concern was claims which "effectively preempt any attempt to sequence the BRCA genes . . ." Ass'n for Molecular Pathology v. USPTO, 689 F.3d 1303, 1349 (Fed. Cir. 2012) (Bryson, J., concurring in part and dissenting in part). Claims of knowledge application and the methods derived from that knowledge do not preempt cumulative use of products of nature. *Id.*

175. See *Myriad*, 569 U.S. at 596; Ass'n Molecular Pathology, 689 F.3d at 1349.

176. Patents for methods are easier to invalidate than patents for active ingredients. See C. Scott Hemphill & Bhaven Sampat, *Drug Patents at the Supreme Court*, 339 SCIENCE 1386, 1386 (2013).

improving the landscape of Section 101 jurisprudence, but these patent eligibility concerns need not be addressed by amending the Patent Act. Instead, this Note offers alternative suggestions for how Congress can address insufficient incentives and create new ones to ensure that promising therapeutics are developed, particularly for pervasive chronic illnesses that greatly disrupt society. This non-patent policy toolkit includes increasing the period of regulatory exclusivity for therapeutics derived from nature, expanding funding opportunities available through the National Center for Complementary and Integrated Health, and addressing insufficient tax credits for therapeutic development.¹⁷⁷

A. Increase Regulatory Exclusivity Periods for Natural Therapeutics that Treat Chronic Illness

Congress has already sanctioned a “separate system of regulatory exclusivity for many products requiring FDA approval before marketing,”¹⁷⁸ which includes therapeutics. Current commercial protections include:

The Hatch-Waxman Act [which] provides five years of exclusivity for any drug with a new active ingredient and three years for other drugs that require new clinical trials, the Biologics Price Competition and Innovation Act [which] provides twelve years of exclusivity for new biologics, and the Orphan Drug Act [which] provides seven years of exclusivity for new drugs that treat rare diseases. An additional six months of exclusivity is available for drugs or biologics that undergo certain pediatric studies.¹⁷⁹

“In the end, the best way for Congress to promote the development of unpatentable drugs is through the FDA, by requiring the agency to withhold regulatory approval from generics for long enough to replicate the protection normally provided by patents.”¹⁸⁰ Yet these periods of exclusivity are shorter than what patents for pharmaceuticals provide,¹⁸¹ which was the first concern raised by Mathers when asked whether alternative commercial exclusivity options were considered for Mambalgin-1 development.¹⁸² He explained that potential investors did not find the available commercial exclusivity periods satisfactory. He noted that the available options simply were not long enough to warrant taking

177. This Note builds off research identifying categories of incentives beyond patents that can be used to spur innovation in the natural biotech field. See Lisa Larrimore Ouellette, *Patentable Subject Matter and Nonpatent Innovation Incentives*, 5 U.C. IRVINE L. REV. 1115, 1116 (2015).

178. *Id.* at 1130.

179. *Id.*

180. Roin, *supra* note 158, at 564.

181. Patented pharmaceuticals do not receive twenty years of exclusivity like most other patented inventions. This is because clinical trial time eats into the twenty-year patent period. The period of actual market exclusivity for patented pharmaceuticals, therefore, averages about thirteen to fourteen years. See Erika Lietzan & Kristina M.L. Acri née Lybecker, *Distorted Drug Patents*, 95 WASH. L. REV. 1317, 1363 (2020).

182. Mathers Interview, *supra* note 16.

the risk inherent in therapeutic development, but suggested that a longer period of exclusivity might have triggered investment in Mambalgin-1 as a commercial therapy.¹⁸³

You can [provide non-patent incentives] through providing commercial exclusivity, right? So, you know, we do that through other mechanisms. So for orphan and rare diseases, for example . . . you are provided seven years of exclusivity . . . regardless of a patent . . . that's a way to incentivize innovation outside of the patent system. The problem is, typically, those exclusivity periods typically are not . . . long enough payoff periods for investment . . . with that high failure rate.¹⁸⁴

Mathers and his team needed something more.

Benjamin Roin's research provides additional support for Mathers's sentiments. He has explained that "there is compelling evidence that the current periods of FDA-administered exclusivity are inadequate because pharmaceutical companies continue to screen drugs with weak patent protection out of their pipelines."¹⁸⁵

Given the chronic illness epidemic in our country, the government has a vested interest in ensuring all potential therapies able to curb painful symptoms and mitigate other features of illness are developed, including those derived from products of nature. To facilitate this innovation, Congress should consider designating a commercial exclusivity exception for natural therapeutics that treat chronic illnesses, with a persuasive period of fourteen years. This length of time would match the average amount of commercial exclusivity provided to patented pharmaceuticals and ensure that lack of patentability does not affect investment for promising therapeutics. Fourteen years also falls within the range that Roin argues will spur innovation to the same extent as patent protection.¹⁸⁶

B. Sufficiently Fund Grants and Direct Funding Opportunities at the National Center for Complimentary and Integrated Health

The National Institutes of Health is the government agency tasked with biomedical and public health research.¹⁸⁷ As stewards of this research, they not only undertake their own innovation, but allot competitive grants to scientists and biotech companies pursuing cutting-edge biomedical work.¹⁸⁸ The NIH also hires

183. *Id.*

184. *Id.*

185. Roin, *supra* note 158, at 566–67 (footnote omitted).

186. *Id.* at 567.

187. *About NIH*, NAT'L INSTS. OF HEALTH, <https://perma.cc/9JPK-BUY6> (archived May 14, 2023).

188. "The NIH invests about \$41.7 billion annually in medical research for the American people." *Budget*, NAT'L INSTS. HEALTH, <https://perma.cc/F5GX-53A3> (archived November 15, 2015). The "NCCIH has funded approximately 1,970 scientific research and training grants, which have contributed to more than 11,000 peer reviewed scientific publications."

and supports postdoctoral fellows to pursue health research and awards prizes to cutting-edge inventions.¹⁸⁹ These efforts are influenced by the separate institutes and centers that the NIH oversees, including the National Center for Complementary and Integrated Health (NCCIH).¹⁹⁰

One of the NCCIH's primary goals is to catalyze "advances in natural products research . . . and support[] clinical studies of the use of natural products for symptom management, well-being, and health promotion."¹⁹¹ They explicitly state a broad interest "in studying the biological activities of natural products, including studies in preclinical models for a wide variety of potential clinical indications," "pain management via improved understanding of chronic pain[,] . . . developing new, nonaddictive pain treatments," and better understanding "basic biological mechanisms of action of natural products."¹⁹²

The NCCIH offers natural product clinical trial resources and grants specifically for early- and late-stage natural product therapy development.¹⁹³ They even recently held a workshop titled "Natural Products and Pain: The Search for Novel Non-Opioid Analgesics" as a mechanism to support natural product pain management research, discuss specific research barriers in this area, and share opportunities, such as grants, prizes, and clinical trial support that are available through the NCCIH.¹⁹⁴ Importantly, the NCCIH devotes "approximately 40 percent of its budget to research related to pain and pain management."¹⁹⁵ Additionally, the NCCIH has supported successful research and clinical trials that have led to positive products.¹⁹⁶

Biotech companies can and should highlight the government supports present at the NCCIH when pitching potential therapeutic projects to interested investors. However, in 2021, the federal government decreased the NCCIH's

NAT'L INSTS. OF HEALTH, *Congressional Justification FY 2021, NATIONAL CENTER FOR COMPLEMENTARY AND INTEGRATIVE HEALTH* (2021), <https://perma.cc/Y7BF-9DQ4>. [hereinafter *Justification 2021*].

189. NAT'L INST. OF HEALTH, Executive Summary 5 (2022), <https://perma.cc/Z85G-ZZMV>.

190. See *Institutes Centers, and Offices*, NAT'L INSTS. OF HEALTH, <https://perma.cc/C7BX-7PHQ> (archived June 16, 2022).

191. *Natural Products Research—Information for Researchers*, NAT'L CTR. FOR COMPLEMENTARY AND INTEGRATIVE HEALTH, <https://perma.cc/W8YL-GYDA> (archived May 14, 2023).

192. *Id.*

193. *Id.*

194. Chen & Hopp, *supra* note 10.

195. *Justification 2021*, *supra* note 188.

196. For example, the NCCIH funded the Trial to Assess Chelation Therapy (TACT), which began in 2002. This clinical trial "sought to determine the safety and efficacy of EDTA (ethylene diamine tetra-acetic acid)" in people with coronary artery disease. *Justification 2021*, *supra* note 188. The results of the study show that EDTA is an effective therapy that can reduce cardiovascular events and the likelihood of heart disease. *Id.* See *Clinical Trials*, U.S. NAT'L LIBR. OF MED., <https://perma.cc/5QZR-8LWE> (archived May 14, 2023), for all other completed clinical trials funded by the NCCIH.

budget by \$13.7 million.¹⁹⁷ Going into the next fiscal year and every year thereafter, Congress should reinstate a budget that exceeds the 2020 budget of \$151.9 million and places value on the benefits of natural medicines. Additional funding can increase the amount of Research Project Grants that the NCCIH awards each year to promising innovations ready for clinical stage trials of natural product therapeutics.¹⁹⁸

Additionally, the “NCCIH is also leading an effort to establish an Intramural Pain Research Center,” given its commitment to developing a non-narcotic pain killer.¹⁹⁹ This center will “invest in pragmatic clinical trials of nonpharmacologic approaches for pain management.”²⁰⁰ It is still under development, but its efforts will include supporting new natural therapies that can reduce pain. Congress should support and fund the Intramural Pain Research Center. If it had been around in 2010, it might have led to the commercialization of Mambalgin-1 as a natural pain therapy.

Benjamin Roin supports additional government funding being allocated to clinical trials. He notes that “potential benefits from government financing of clinical research are substantial, [but] funding for government-sponsored clinical trials is chronically in short supply, and recent spending cuts [for natural product research] reflect Congress’s unwillingness to commit necessary resources to important clinical research.”²⁰¹ Further investment in NCCIH support of clinical trials through grants and direct funding is encouraged, particularly given their success with supporting trials.²⁰²

C. Create Federal Tax Credits for Clinical Trials of Natural Therapeutics That Treat Chronic Illness

Given the pervasiveness of chronic illness in society and its contribution to

197. Justification 2021, *supra* note 188.

198. In 2021, the NCCIH awarded 183 Research Project Grants for promising clinical trials, but this was a decrease from the number of grants awarded in 2020. *Id.*

199. *Id.*

200. *Id.*

201. Roin, *supra* note 158, at 562 (citing Claiborne Johnston, John D. Rootenberg, Shereen Katrak, Wade S. Smith, & Jacob S. Elkins, *Effect of a US National Institutes of Health Programme of Clinical Trials on Public Health and Costs*, 367 LANCET 1319, 1324 (2006); Jennifer Couzin, *Tight Budget Takes a Toll on U.S.-Funded Clinical Trials*, 315 SCIENCE 1202, 1202-03 (2007); Mike Mitka, *Scientists Warn NIH Funding Squeeze Hampering Biomedical Research*, 297 JAMA 1867, 1867 (2007); Charlie Schmidt, *Cooperative Groups Say NCI Trials Funding Inadequate; Some Turn to Industry*, 99 J. NAT’L CANCER INST. 830, 830-32 (2007); Nancy S. Sung et al., *Central Challenges Facing the National Clinical Research Enterprise*, 289 JAMA 1278, 1284 (2003); and Joseph Loscalzo, *The NIH Budget and the Future of Biomedical Research*, 354 NEW ENG. J. MED. 1665, 1665-66 (2006)).

202. Justification 2021, *supra* note 188 (highlighting successful NCCIH trials, such as the AREDS trial, the TACT trial, and the Cystine trial).

“[i]ncreased medical expenses, lost income, lost productivity, compensation payments, and legal charges,”²⁰³ the government has a financial interest in the development of therapeutics. Ouellette notes that “R&D tax incentives are another significant source of support for biomedical research.”²⁰⁴ She further explains that:

The largest general R&D incentives in the current federal Tax Code are section 174, which allows companies to deduct research expenses immediately rather than over a period of future years, and section 41, which provides a tax credit for companies that increase their R&D spending. Together, these provisions are estimated to cost U.S. taxpayers \$11 billion in 2014 for all technologies, with the portion going to pharmaceutical R&D likely around \$2 billion.²⁰⁵

Importantly, pharmaceutical companies can also claim the federal tax credit for twenty-five percent of the cost of clinical trials for rare diseases.²⁰⁶ This government policy should extend to clinical trials for chronic illnesses, which would capture products of nature targeted at the diseases that so greatly impact our country’s community health, productivity, and economic stability.

CONCLUSION

Myriad was filed, litigated, and held under the banner of cancer care and bodily autonomy. But the results of this decision are far more nuanced than initially presented. *Myriad* has had dangerous implications for health and scientific research, but in ways beyond the ACLU’s concern over private control of human genes.

Since 2013, *Myriad* has not made much of an impact in the federal court system and there are still some medications derived from natural products being brought through the FDA approval process. However, there are claims of natural therapeutics being rejected by the USPTO, as illustrated by the identified PTAB cases and comments submitted to the USPTO by biotech companies. Yet these results do not capture the unpursued therapeutics that never reached the patent or FDA regulatory stage because of *Myriad* frustrations. Mambalgin-1 is evidence that a specific, promising innovation was not pursued specifically because of *Myriad*. Given the substantial uncertainty about whether *Myriad* has had any effect at all, this story represents thorough and moving evidence that *Myriad* has impacted social and medical gains.

203. See *Chronic Pain*, JOHNS HOPKINS MED., <https://perma.cc/GZ5J-S58U> (archived May 14, 2023).

204. Ouellette, *supra* note 177, at 1132.

205. *Id.*

206. *Research Tax Credit, Domestic Production Activities Deduction & Orphan Drug Credit*, BDO U.S. (Jan. 4, 2018), <https://perma.cc/97P2-YC3A> (“[F]or tax years beginning after December 31, 2017, the law reduces the ODC rate to 25%, down from 50%,” a difference in the tax credit since Ouellette published her work on alternative non-patent incentives).

This, of course, does not mean that *Myriad* should be reversed. It was decided to ensure greater access to genetic testing and to facilitate cumulative innovation. But policymakers should be aware that *Myriad* has its downsides and non-patent incentives should be pursued to ensure that socially valuable natural therapeutics are researched and developed. Alas, if Chicken Little were a fully informed member of the biotech community, he would exclaim that “the sky has not yet fallen, but let us ensure that non-patentable therapeutics derived from nature are supported by other incentive mechanisms!”