THE CURRENT APPLICATION OF THE *MYRIAD* AND *MAYO/ALICE* RULINGS ON PATENT ELIGIBILITY: INCONSISTENT RESULTS AND CONTRADISTINGUISHING BIOTECHNOLOGY PRODUCTS♦

INTRODUCTION

Since the discovery of DNA molecules by Watson and Crick at the turn of the twentieth century, knowledge of biology has significantly increased to the point that it is possible to completely sequence the DNA of some species of bacteria, yeast, and plants.[1] Now that it is clear that mutation in certain genes can result in a higher risk of certain diseases, biotechnology is primarily focused on detecting genes, detecting whether a specific gene is prone to mutation, and coming up with different methods to prevent, as well as treat, genetic diseases. For example, the future of biotechnology was demonstrated in a recent study that found a genetic link to erectile dysfunction.[2]

In addition to the basic curiosity of human nature, the main contributor to the fast-paced discovery of new organisms and molecules, as well as to the invention of new organisms and biotechnology methods, is patent law.[3] Patent law ensures that new discoveries and inventions are shared by attributing ownership to those who first discovered or invented them, thereby incentivizing individuals to explore and create.[4] However, not everything is patentable; the judicial branch recognized that some discoveries and inventions that recite or heavily rely on abstract ideas, natural phenomena, laws of nature, and products of nature cannot be patented.[5] Prior to 2012, genes were patent-eligible upon discovery.[6] The entire biotechnology field was taken aback, however, when the United States Supreme Court decided that genes cannot be patented based on the product of nature doctrine. Subsequent cases have further limited the extent to which biology products or methods can be patented.[7]

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1 *See* Leslie A. Pray, *Discovery of DNA Structure and Function: Watson and Crick*, SCITABLE BY NATURE EDUC. (2008), https://www.nature.com/scitable/topicpage/discovery-of-dna-structure-and-function-watson-397 [https://perma.cc/W54Q-V2WS]; *see also Timeline: Organisms that have had their genomes sequenced,* YG [hereinafter *Timeline*], https://www.yourgenome.org/facts/timeline-organisms-that-have-had-their-genomes-sequenced [https://perma.cc/EY49-ZVVX] (last updated Jan. 19, 2015).

2 Eric Jorgenson et al., *Genetic variation in the SIM1 locus is associated with erectile dysfunction*, 115 PNAS 11018 (2018), https://www.pnas.org/content/pnas/115/43/11018.full.pdf [https://perma.cc/7K7A-QLQF]. This study found that the mutation of SIM1 locus on the sixth chromosome was associated with a twenty-six percent rise in the risk of impotence. *Id.* With this new information, researchers could shift their focus to identifying other key genetic variants that trigger the disease, investigating the precise mechanisms by which they operate, testing better treatments for erectile dysfunction, and coming up with preventative approaches. *Id.*

3 *See* John M. Golden, *Biotechnology, Technology Policy, and Patentability: Natural Products and Invention in the American System*, 50 EMORY L.J. 101, 113 (2001).

4 *Id.* at 104-05.

5 *Id.* at 123-24.

6 Nicholas J. Landau, *The New Patent Policy on Natural Products Is a Game Changer for Universities and Life Sciences Companies*, BRADLEY (Sept. 16, 2014), https://www.bradley.com/insights/publications/2014/09/the-new-patent-policy-on-natural-products-is-a-g__. [https://perma.cc/26V2-TLFT].

7 *Id.*

The United States Patent and Trademark Office (USPTO) attempted to clarify much of the confusion regarding the application of the patent ineligibility analysis framework by circulating memos after each controversial decision and providing examples of biological science patent claims. This Note will argue that even with the USPTO's efforts, courts have applied this framework differently, resulting in inconsistent discrimination against biotechnology products. Additionally, this Note attempts to navigate the current patent eligibility framework and how it has been applied by different courts regarding patent claims of biotechnology products. Part I of this Note covers both a brief and informative scientific overview of DNA, RNA, and cDNA, and a history of gene patents, including the development of a judicial exception to patent ineligibility using the framework provided by *Myriad Genetics*[8] and *Mayo/Alice*.[9] Part II of this Note discusses four cases considering patent claims of biotechnology products and compares how the courts applied the *Myriad Genetics* and *Mayo/Alice* framework to their facts differently. Lastly, Part III sets up a hypothetical patent claim using recent science technology, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), to apply the *Myriad Genetics* and *Mayo/Alice* framework by referring to the cases in Part II. Additionally, Part III will provide suggestions as to what the USPTO can do to clarify the seemingly inconsistent results of the hypothetical patent claim depending on the jurisdiction.

Currently, U.S. courts, as well as the USPTO, patent litigators, and prosecutors, rely on the *Mayo/Alice* two-step analysis of patent eligibility to: (1) determine whether a claim is directed to a patent-ineligible concept; and (2) determine whether its elements contain a concept that is sufficiently inventive to transform the nature of the claim into a patent-eligible application.[10] In theory, the modified product created by using CRISPR genome editing technology with "markedly different characteristics" from those existing in nature and containing an "inventive concept" would be patent-eligible under both the *Myriad Genetics* and *Mayo/Alice* frameworks. However, with the federal courts' expansion of the judicial exception provided in *Myriad Genetics* and *Mayo/Alice*, modified products achieved by using CRISPR would be further scrutinized beyond the original intention of the *Mayo* and *Myriad Genetics* courts. Therefore, whether the method patent claims are

[8] Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 594 (2013).
[9] Mayo Collaborative Servs. v. Prometheus Laboratories, Inc., 566 U.S. 66 (2012); *see* Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 573 U.S. 208 (2014).
[10] Judith Kim & Scott Schaller, *After* Alice*: the two-step rule*, LSIPR NEWSL. (LSIPR, London, U.K.), Jan. 15, 2013, https://www.sternekessler.com/sites/default/files/2017-11/LSIPR_Jan15_AfterALice.pdf [https://perma.cc/TQW4-MBCA].

validated would depend on the jurisdiction where the patent claims are litigated. In order to solve this inconsistency, the USPTO should provide a set of examples or guidance on what the "conventional, routine, and well-understood" process is that would subject a claim to the law of nature concept, barring it from the subject matter eligibility provision in section 101 of the Patent Act.[11] In doing so, the USPTO should include process patent claims, specifically regarding patents that administer a certain dosage of drug to different individuals for maximum drug effect and that use a "conventional, routine, and well-understood" process. Even in the recently published October 2019 Examples 43 – 46,[12] the USPTO does not explain what "conventional, routine, and well-understood" means in process patents.

I. BACKGROUND

A. *Scientific Background: DNA, RNA, and cDNA*

A deoxyribonucleic acid (DNA) molecule consists of two strands of long polymer chains that are made of four types of nucleotides attached to backbone chains: cytosine, guanine, adenine, and thymine.[13] The two strands are twisted in a spiral ladder shape, creating a "double helix" chain of nucleotides.[14] In eukaryotic cells, which are present in a wide variety of species including animals, plants, fungi, and protists, DNA is organized into long structures that form chromosomes. DNA stores biological information, and a large part of DNA (more than ninety-eight percent for humans) is non-coding, meaning that these sections do not serve as patterns for protein sequences.[15] The two percent of DNA that code for the production of proteins go through both a transcription and translation process. During transcription, the strands of DNA are split and the coding strand is copied to produce ribonucleic acid (RNA) molecules that contain only a single gene.[16] The RNA molecule is modified further

[11] 35 U.S.C. § 101 (2012), https://www.govinfo.gov/content/pkg/USCODE-2017-title35/pdf/USCODE-2017-title35-partII-chap10-sec101.pdf [https://perma.cc/U276-AJ5K].

[12] U.S. PATENT & TRADEMARK OFFICE, APPENDIX 1 TO THE OCTOBER 2019 UPDATE: SUBJECT MATTER ELIGIBILITY LIFE SCIENCES & DATA PROCESSING EXAMPLES 2-41 (2019), https://www.uspto.gov/sites/default/files/documents/peg_oct_2019_app1.pdf [https://perma.cc/DBQ4-UUXE].

[13] *Structure and Function of DNA*, LUMEN: MICROBIOLOGY, https://courses.lumenlearning.com/microbiology/chapter/structure-and-function-of-dna/ [https://perma.cc/DAL5-T84A].

[14] *Id.*

[15] *18.4E: Noncoding DNA*, LIBRETEXTS: BIOLOGY (Nov. 20, 2019) [hereinafter *Noncoding DNA*], https://batch.libretexts.org/print/Letter/url=https://bio.libretexts.org/Bookshelves/Introductory_and_General_Biology/Book%3A_General_Biology_(Boundless)/18%3A_Evolution_and_the_Origin_of_Species/18.4%3A_Evolution_of_Genomes/18.4E%3A_Noncoding_DNA.pdf [https://perma.cc/4YBT-ZTU2].

[16] *Id.*

to form messenger RNA (mRNA).[17] The resulting mRNA is fundamentally different from its DNA template because it consists of only exons, the part of DNA that codes for genes, rather than introns.[18] Subsequently, mRNA undergoes translation to form amino acids, which are the basic building blocks of proteins.[19]

A mutation in the genetic code often results in coding for defective or nonfunctional proteins. Some mutations are harmless, but others can cause or increase the risk of disease.[20] In order to diagnose genetic disorders, one must have knowledge of the normal sequence, as well as the mutations.[21] Genes consist of coding strands and non-coding strands; both strands have non-coding regions, introns and, interspersed between coding regions, exons. It is therefore difficult to identify the coding strand for a particular protein.[22] In order to locate a particular gene sequence, scientists created complementary DNA (cDNA), a completely man-made molecule that differs from the DNA and RNA molecules existing in nature.[23] The process of manufacturing cDNA is as follows: Scientists reverse-transcribe a strand of mRNA and create a DNA string that is an identical copy of a non-coding DNA strand's coding region.[24] There are three important ways in which cDNA differs from mRNA: First, cDNA is complementary to mRNA, using thymine nucleotides rather than uracil; second, the sugar backbones of the RNA and DNA strands differ; and third, cDNA is missing introns, which means that it is not subject to cellular regulation, is not part of a chromosome, and contains a tail region that is not present in DNA.[25]

Although cDNA lacks introns, it can attach itself to DNA within a nucleus of a cell.[26] Scientists use cDNA as a probe for identifying mutated DNA. Scientists look at the various points of attachment, find the

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17 Suzanne Clancy, *RNA Splicing: Introns, Exons, and Spliceosome*, SCITABLE BY NATURE EDUC. (2008), https://www.nature.com/scitable/topicpage/rna-splicing-introns-exons-and-spliceosome-12375/ [https://perma.cc/GP6L-6R2A].

18 *Id.*

19 *Id.*

20 *DNA Sequencing Fact Sheet*, NAT'L HUM. GENOME RES. INST. [hereinafter *DNA Sequencing*], http://www.genome.gov/10001177 [https://perma.cc/96AH-PFJE] (last updated Dec. 18, 2015).

21 *Id.*

22 Archive of *About the Human Genome Project*, HUM. GENOME PROJECT INFO. ARCHIVE 1990-2003, https://web.ornl.gov/sci/techresources/Human_Genome/project/index.shtml [https://perma.cc/8GLU-JP38] (last modified Mar. 26, 2019). The U.S. Human Genome Project was a thirteen-year endeavor to "*identify* all the approximately 20,000-25,000 genes in human DNA" and "*determine* the sequences of the 3 billion chemical base pairs that make up human DNA." *Id.*

23 Matthew Ellis, *cDNA vs Genomic DNA: The Relationship and Differences in Genomic DNA and Complimentary DNA*, BIOCHAIN, https://www.biochain.com/general/cdna-vs-genomic-dna/ [https://perma.cc/TNR6-TB4L].

24 *Id.*

25 One of the primary distinctions between mRNA and cDNA is that the latter is a purely human-made product that is created from mRNA, which lacks introns, the non-coding DNA part. *Id.*

26 *Id.*

endpoints of each gene, and then extract the newly discovered gene with the help of specific and well-known enzymes.[27] This genetic research is particularly useful in five areas: (1) producing drugs from therapeutic proteins or gene transfer into cells; (2) conducting genetic tests for diagnosis or screening; (3) for use as research tools; (4) for nonmedical uses, such as identification, forensics, and ancestry-tracing; and (5) controlling which genes are turned on or off in a cell or tissue.[28]

Microarray-based testing allows for the marking of DNA, RNA, and protein in a single experiment and permits simultaneous analysis of thousands of gene sequences.[29] The widespread use of such tests would enable scientists to access greater amounts of information for better diagnosis and treatment. However, in order to perform these tests, researchers first need to obtain multiple licenses from gene patent owners. Since every human gene sequence is subject to patent protection, the exclusive rights of gene patent owners have presented and continue to create substantial barriers to the further development of microarray-based testing.[30]

B. *The Subject Matter of Patentability*

In 1790, Congress passed the Patent Act, titled "An Act to promote the progress of useful Arts."[31] In 1952, the legislature amended the Patent Act by enacting section 101, which defines patentable subject matter and designates who may obtain a patent as "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."[32] This language indicates that the invention must be a "process, machine, manufacture, or composition of matter" to be patentable subject matter.[33] After satisfying the subject matter requirement, the invention must also be "new" under section 102's definition of novelty.[34] In other words, the

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[27] *See* Golden, *supra* note 3.

[28] Robert Cook-Deegan, *Gene Patents*, *in* FROM BIRTH TO DEATH AND BENCH TO CLINIC: THE HASTINGS CENTER BIOETHICS BRIEFING BOOK FOR JOURNALISTS, POLICYMAKERS, AND CAMPAIGNS 69 (Mary Crowley ed., 2008), https://www.thehastingscenter.org/wp-content/uploads/Gene-Patents-BB15.pdf [https://perma.cc/R92L-AVM3].

[29] Simone Mocellin et al., *DNA Array-Based Gene Profiling: From Surgical Specimen to the Molecular Portrait of Cancer*, 241 ANNALS SURGERY 16, 17 (2005), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1356842/pdf/20050100s00004p16.pdf [https://perma.cc/L5C8-8M23].

[30] Notably, before *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 594 (2013), the human gene was patentable.

[31] Patent Act of 1790, ch. 7, 1 Stat. 109 (repealed 1793), https://fraser.stlouisfed.org/files/docs/historical/congressional/patent-act-1790.pdf [https://perma.cc/28VK-228V].

[32] 35 U.S.C. § 101 (2012).

[33] *Id.*

[34] *Id.* § 102, https://www.govinfo.gov/content/pkg/USCODE-2017-title35/pdf/USCODE-2017-title35-partII-chap10-sec102.pdf [https://perma.cc/E8L2-NHQU].

invention must be distinguishable from the prior and current knowledge and work of others, what has already been patented in the United States and abroad, and what has been disclosed in print at the time of invention. Lastly, the invention must also be "useful" and "nonobvious" under the non-obviousness requirement of section 103.[35]

Congress wrote section 101 to encompass a broader range of innovation than the 1790 Patent Act.[36] Under the scope of this broad language of what counts as patentable subject matter, many scientists who isolated and purified natural substances were able to obtain U.S. patent protection.[37] However, exceptions to patentability exist, including abstract ideas, laws of nature, natural phenomena and, more recently, products of nature.[38]

Many scholars point to *Ex parte Latimer* as making the first reference to the "product of nature" doctrine.[39] At the time *Latimer* was litigated, the Patent Act of 1870 was still in effect, which provided that a patent could be granted for "any new and useful art, machine, manufacture, or composition of matter, or any new and useful improvement on any art, machine, manufacture, or composition of

[35] *Id.* § 103, https://www.govinfo.gov/content/pkg/USCODE-2017-title35/pdf/USCODE-2017-title35-partII-chap10-sec103.pdf [https://perma.cc/GG26-3F96] (precluding patent protection "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains").

[36] Eric A. Stone et al., *What is Patentable? Making Sense of Section 101*, FED. LAW., Oct./Nov. 2013, at 24, http://www.fedbar.org/Resources_1/Federal-Lawyer-Magazine/2013/October November/Features/What-Is-Patentable-Making-Sense-of-Section-101.aspx?FT=.pdf [https://perma.cc/3SQB-6ZAA].

[37] Landau, *supra* note 6 ("An early example of a patent for a purified natural substance is U.S. Patent 141,072 issued to Louis Pasteur in 1873, which claimed beer yeast 'free from organic germs of disease.' Likewise, Jokichi Takamine was the first to purify adrenaline, for which he was granted U.S. Patent 730,176. Felix Hoffman received U.S. Patent 644,077 in 1898 for purified acetyl salicylic acid, the active ingredient in aspirin. Perhaps the best example of a patent for a purified natural substance is Selman Waksman's U.S. Patent 2,449,866 for the landmark antibiotic streptomycin." (internal footnote omitted)).

[38] An abstract idea cannot be patented. *See* Le Roy v. Tatham, 55 U.S. 156, 175 (1853) ("A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right. Nor can an exclusive right exist to a new power, should one be discovered in addition to those already known."); *see also* Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980) ("The laws of nature, physical phenomena, and abstract ideas have been held not patentable." (internal citations omitted)); *see also* Diamond v. Diehr, 450 U.S. 175, 185 (1981) ("Excluded from such patent protection are laws of nature, natural phenomena, and abstract ideas." (internal citations omitted)). The product of nature is a relatively new doctrine and is not explicitly stated as one of the exceptions in the Patent Act. *See* Golden, *supra* note 3.

[39] *See, e.g.*, Laura W. Smalley, *Will Nanotechnology Products be Impacted by the Federal Courts' "Product of Nature" Exception to Subject-Matter Eligibility Under 35 U.S.C. 101?*, 13 J. MARSHALL REV. INTELL. PROP. L. 397, 407 (2014), https://repository.jmls.edu/cgi/viewcontent.cgi?article=1326&context=ripl [https://perma.cc/SQZ5-4PEH]; *see also Ex parte* Latimer, 1889 Dec. Comm'r Pat. 123.

matter, not known or used by others . . . ."[40] In *Latimer*, the applicant had applied for a patent for isolating fibrous material from pine needles, but the patent examiner had rejected his claim because the physical characteristics of the final product were indistinguishable from any other fiber.[41] The Commissioner of Patent affirmed the examiner's decision, finding that the final product was not something "new or different from the fiber in its natural state."[42] As a result, the product of nature doctrine was formulated to preclude patent protection for "[a] product whose physical characteristics are indistinguishable from those of its naturally-occurring counterpart," regardless of any novelty in the process of making the product and the usefulness of the final product.[43]

The product of nature doctrine was used as a supplementary measure to the novelty requirement rather than as an exception to the patent subject matter requirement.[44] In the 1958 case *Merck & Co. v. Olin Mathieson Chemical Corp.*, Merck sued Olin Mathieson for infringing its patent on a vitamin B12-active composition derived from the fermentation of any of several strains of fungi.[45] The defendant, however, argued that the patent was invalid because an identical B12 compound already existed naturally in cattle livers.[46] In 1947, Merck researchers had been able to isolate an identical pure crystalline substance from both the fermentation products of fungi and the livers of cattle.[47] Merck's patent claims were therefore not based on the pure crystalline substance it had isolated, but instead on compositions with a lower level of vitamin activity than that of the pure substance.[48]

In reviewing the product of nature defense as concerning the novelty requirement, the Fourth Circuit stated:

> (1) [T]hat a patent may not be granted upon an old product though it be derived from a new source by a new and patentable process, and (2) that every step in the purification of a product is not a patentable advance, except, perhaps, as to the process, if the new product differs from the old "merely in degree, and not in kind."[49]

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40 Patent Act of 1870, ch. 230, 16 Stat. 198 (1870), https://www.loc.gov/law/help/statutes-at-large/41st-congress/session-2/c41s2ch230.pdf [https://perma.cc/7TB4-9CNR].
41 *Ex parte Latimer*, 1889 Dec. Comm'r Pat. at 124.
42 *Id.* at 126
43 John M. Conley & Roberte Makowski, *Back to the Future: Rethinking the Product of Nature Doctrine as a Barrier to Biotechnology Patents* (*Part I*), 85 J. PAT. & TRADEMARK OFF. SOC'Y 301, 322 (2003).
44 *Id.*
45 Merck & Co., Inc. v. Olin Mathieson Chem. Corp., 253 F.2d 156 (4th Cir. 1958).
46 *Id.* at 162.
47 *Id.* at 160.
48 *Id.*
49 *Id.* at 162.

The Fourth Circuit validated Merck's product patent claim and, referring to the first point, emphasized that "until the patentees produced them, there were no such B(12) active compositions. No one had produced even a comparable product. The active substance was unidentified and unknown."[50] Regarding the second point, the court found that Merck's final product was more than just differing "merely in degree" and described it as having "great and perfected utility," as opposed to the "complete uselessness" of the naturally occurring compound.[51]

Referring to the product of nature doctrine, the Supreme Court invalidated the product patent claim in *Funk Brothers Seed Co. v. Kalo Inoculant Co.*[52] Prior to *Funk Brothers Seed Co.*, Bond had discovered strains of rhizobia, nitrogen-fixing bacteria, that contained mutually non-inhibitive qualities.[53] Bond had used these newly discovered strains to mix a new culture of rhizobia.[54] The mixed culture was able to inoculate the seeds of plants that only reacted with certain species of rhizobia.[55] The Supreme Court held the product claim invalid, stating that ". . . it certainly was not the product of invention. There is no way in which [the Court] could call it such unless [it] borrowed invention from the discovery of the natural principle itself."[56]

The question of whether genetically engineered organisms can be patented arose in *Diamond v. Chakrabarty*.[57] In *Chakrabarty*, microbiologist Ananda Chakrabarty appealed the patent examiner's decision that genetically engineered bacteria that were capable of breaking down specific components of crude oil could not be patented because "(1) . . . micro-organisms are 'products of nature,' and (2) that as living things they are not patentable subject matter under 35 U.S.C. § 101."[58] The Supreme Court reversed the patent examiner's decision, holding instead that the living subject matter of Chakrabarty's product claim was valid, and therefore patentable, because "the patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. His discovery is not nature's handiwork, but his own; accordingly it is patentable subject matter under § 101."[59]

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50 *Id.* at 162-63.
51 *Id.* at 164.
52 Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127 (1948).
53 *Id.* at 130.
54 *Id.*
55 *Id.* at 130.
56 *Id.* at 132.
57 Diamond v. Chakrabarty, 447 U.S. 303 (1980).
58 *Id.* at 306.
59 *Id.* at 310.

C. *The History of Gene Patents*

Six months after *Chakrabarty*, the first patent on a recombinant DNA method, which used cells to produce useful proteins and turned them into valuable drugs, was granted to Stanford University and the University of California.[60] From then on, genes, when claimed in their isolated and purified form, were considered patent-eligible and resulted in roughly 47,000 genetic patents granted in the United States.[61] However, accompanying these biotechnical improvements were questions of patentability arising under the product of nature doctrine.[62] In 1987, the USPTO published an official memorandum to address these growing concerns. It stated that "[t]he Patent and Trademark Office now consider[ed] nonnaturally occurring non-human multicellular living organisms, including animals, to be patentable subject matter within the scope of 35 U.S.C. 101."[63] Even though the memorandum permitted the examination of claims directed to multicellular living organisms, it explicitly provided that "[a] claim directed to or including within its scope a human being w[ould] not be considered to be patentable subject matter under 35 U.S.C. 101."[64]

Discussion of the limitation on "directed to . . . human being" appeared once again in 2011, this time arising within the context of section 33 of the Leahy-Smith America Invents Act (AIA), which states that "[n]otwithstanding any other provision of law, no patent may issue on a claim directed to or encompassing a human organism."[65] According to its legislative history, this section "has no bearing on stem cell research

60 Landau, *supra* note 6.

61 *Id.*

62 *New Patent Legislation Sets Dangerous Precedent and Stifles Research*, BIOTECHNOLOGY INNOVATION ORG. (Sept. 2, 2003) [hereinafter *New Patent Legislation*], https://www.bio.org/sites/default/files/CFS_Sept.2003.pdf [https://perma.cc/NQ4L-G793].

63 Donald J. Quigg, *Animals – Patentability*, OFF. GAZ. PAT. & TRADEMARK OFFICE, Apr. 21, 1987, at 8, 8, https://babel.hathitrust.org/cgi/imgsrv/download/pdf?id=wu.89050369487;orient=0;size=100;seq=536;attachment=0 [https://perma.cc/RVF9-K82Y].

64 *Id.* ("The grant of a limited, but exclusive property right in a human being is prohibited by the Constitution. Accordingly, it is suggested that any claim directed to a non-plant multicellular organism which would include a human being within its scope include the limitation 'non-human' to avoid this ground of rejection.").

65 Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 33(a), 125 Stat. 284, 340 (2011), https://www.uspto.gov/sites/default/files/aia_implementation/20110916-pub-l112-29.pdf [https://perma.cc/9V7K-VDSA]; *see New Patent Legislation, supra* note 62. This congressional prohibition on the patenting of claims directed to or encompassing human organisms is also addressed in an official press release, published by the USPTO on April 1, 1998, responding to the then-current negative media coverage surrounding "the existence of a patent application directed to human/non-human chimera." Press Release, U.S. Patent & Trademark Office, Facts on Patenting Life Forms Having a Relationship to Humans (Apr. 1, 1998), https://www.uspto.gov/about-us/news-updates/facts-patenting-life-forms-having-relationship-humans [https://perma.cc/4DRD-ZKL2]. Specifically, the USPTO took the position "that inventions directed to human/non-human chimera could, under certain circumstances, not be patentable because, among other things, they would fail to meet the public policy and morality aspects of the utility requirement." *Id.*

or patenting genes, it only affects patenting human organisms, human embryos, human fetuses or human beings."[66] Section 33 of the AIA merely codified the existing USPTO policy, and following its passage courts still applied the product of nature exception to determine whether certain biotechnology products constituted patentable subject matter.

Until recently, genes were considered a patent subject matter under section 101 without any doubt.[67] For instance, in 2000, Q. Todd Dickinson, the former Under Secretary of Commerce for Intellectual Property and Director of the USPTO, stated that "[g]enes and other genomic inventions remain patentable . . . so long as they meet the statutory criteria of utility, novelty and non-obviousness. Genes and genomic inventions that were patentable last week continue to be patentable this week, under the same set of rules."[68] Moreover, Rebecca Eisenberg, the Robert and Barbara Luciano Professor of Law at the University of Michigan and a specialist in patent law and the regulation of biopharmaceutical innovation, approved of gene patents as products of human inventions:

> [T]he prohibition against patenting products of nature only prevents the patenting of DNA sequences in a naturally occurring form that requires no human intervention . . . . Patents have thus issued on "isolated and purified" DNA sequences, separate from the chromosomes in which they occur in nature, or on DNA sequences that have been spliced into recombinant vectors or introduced into recombinant cells of a sort that do not exist in nature.[69]

D. Mayo*,* Myriad Genetics *and* Alice*: The Current Framework for Patent Eligibility*

In 2012, the Supreme Court addressed whether a patent related to the improved use of drugs to treat autoimmune disease was unpatentable

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66 157 CONG. REC. E1178 (daily ed. June 23, 2011) (statement of Rep. Smith), https://www.uspto.gov/sites/default/files/aia_implementation/20110623-smith_rmrks_e1177.pdf [https://perma.cc/5MYH-SFHP].

67 Before the USPTO's enactment of a new policy, a gene, when discovered in its isolated and purified form, was considered patentable so long as the gene never before existed in pure form. *See* Landau, *supra* note 6. Thus, under the previous framework, an estimated 47,000 genetic patents claiming something about DNA or RNA, and an additional 3,000 to 5,000 patents on human genes, issued in the United States. Zach Fitzner, *New bipartisan patent bill raises ethical and practical questions*, EARTH.COM (June 25, 2019), https://www.earth.com/news/new-patent-bill-ethical-questions/ [https://perma.cc/V9KQ-2A3S].

68 Press Release, U.S. Patent & Trademark Office, US Patent Policy Unaffected by US/UK Statement on Human Gene Sequence Data (Mar. 16, 2000), https://www.uspto.gov/about-us/news-updates/us-patent-policy-unaffected-usuk-statement-human-gene-sequence-data [https://perma.cc/VA6M-KFML].

69 Rebecca S. Eisenberg, *Re-Examining the Role of Patents in Appropriating the Value of DNA Sequences*, 49 EMORY L.J. 783, 785-86 (2002) (internal footnote omitted), https://repository.law.umich.edu/cgi/viewcontent.cgi?article=2214&context=articles [https://perma.cc/F6MJ-UUAS].

because it fell under the laws of nature exception in *Mayo Collaborative Servs. v. Prometheus Labs., Inc*.[70] At the time the patent was filed, medical personnel were aware that human bodies produced certain toxic metabolites in response to thiopurine treatment and were reluctant to recommend such treatment to their patients.[71] Inventors discovered concentrations of metabolites in a significant number of patients that correlated with toxic side effects and therapeutic effectiveness.[72] Applying this discovery, the inventors came up with a method to optimize thiopurine treatment by adjusting the dosage to maintain the resulting metabolites within a particular concentration window.[73] However, the patent on this method merely improved an old method of treating patients with thiopurines.

The issue was whether an improvement of an old method was patent-eligible under section 101, where only the new and useful element of the improved method was a discovery. The Court determined that the relationship between concentrations of thiopurine metabolites and toxicity constituted a "law of nature" because such a relationship was a consequence of the body's metabolizing thiopurine drugs.[74] The Court reasoned that thiopurine metabolism was a natural process because it occurred in the human body.[75] Because the relationship was a consequence of a natural process, the Court concluded the relationship was a "law of nature."[76]

After determining that the patent at issue claimed a law of nature, the Court examined whether the patent contained an "inventive concept."[77] The Court defined "inventive concept" as an "element[] or a combination of elements . . . sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself."[78] If the patent was found to contain an inventive concept, the patent would satisfy subject-matter eligibility requirements despite claiming a law of nature. The Court explained that "if a law of nature is not patentable, then neither is a process reciting a law of nature, unless that process has additional features . . . ."[79] The Court concluded that, since the administering of the thiopurine drugs and subsequent measuring of resulting metabolites involved "well-understood, routine, [and]

70 Mayo Collaborative Servs. v. Prometheus Laboratories, Inc., 566 U.S. 66 (2012).
71 *Id.* at 73.
72 *Id*.
73 *Id*.
74 *Id*. at 77-78.
75 *Id*.
76 *Id*. at 92.
77 *Id*. at 77.
78 *Id*. at 72-73.
79 *Id*. at 77.

conventional activity," there was no inventive concept in the claimed application of the natural laws.[80] Therefore, the Court held that because "the patent claims at issue here effectively claim[ed] the underlying laws of nature themselves[,] [t]he claims [were] consequently invalid."[81]

In its landmark decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, the Supreme Court held that isolated, naturally-occurring DNA is not patent-eligible under the product of nature exception in section 101 of the Patent Act.[82] Breast cancer disproportionately affects the female population: According to the statistics, about thirteen percent of women in the U.S. will be diagnosed with breast cancer in their lifetime; approximately three percent will die from breast cancer.[83] Treatment for cancer is a lucrative business—not including the individual burden of disease and other indirect costs, the direct cost of treating cancer was $124.6 billion in 2010; $16.5 billion, the largest share, was for the treatment of female breast cancer.[84] Breast Cancer 1 (BRCA1) and Breast Cancer 2 (BRCA2) are genes that repair damaged DNA, and a mutation in one of these genes may cause the cells to develop genetic alterations that could potentially lead to cancer.[85] Mutations in BRCA1 or BRCA2 account for five to ten percent of all breast cancer diagnoses and about fifteen percent of all ovarian cancer diagnoses.[86] Women with mutations in these genes can take steps to reduce the risk of death through enhanced screening, medications, and preventive surgery to remove their breasts and/or ovaries.[87]

Myriad Genetics discovered the location and sequence of the BRCA1 and BRCA2 genes.[88] Myriad then developed a medical test to detect mutations in these genes to assess the likelihood of a patient's

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80 *Id.* at 73.

81 *Id*. at 92.

82 Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 594 (2013).

83 AM. CANCER SOC'Y, BREAST CANCER FACTS & FIGURES 2019-2020, at 3 (2019), https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf [https://perma.cc/7FXX-VP7Y] ("Approximately 1 in 8 women (13%) will be diagnosed with invasive breast cancer in their lifetime and 1 in 39 women (3%) will dies from breast cancer . . . ." (internal footnote omitted)).

84 Lara Cartwright-Smith, *Patenting Genes: What Does* Association for Molecular Pathology v. Myriad Genetics *Mean for Genetic Testing and Research?*, 129 PUB. HEALTH REP. 289 (2014), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3982540/pdf/phr12900289a.pdf [https://perma.cc/YHV8-8LT4].

85 *BRCA Mutations: Cancer Risk and Genetic Testing*, NAT'L CANCER INST. [hereinafter *BRCA Mutations*], http://www.cancer.gov/cancertopics/factsheet/Risk/BRCA [https://perma.cc/WAS3-FA9M].

86 *Id*.

87 Susan M. Domchek et al., *Association of Risk-Reducing Surgery in BRCA1 or BRCA2 Mutation Carriers with Cancer Risk and Mortality*, 304 JAMA 967 (2010).

88 Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 576 (2013).

developing breast and/or ovarian cancer.[89] The test involved two processes:

> The first process involved separating segments of DNA containing the sequences of nucleotides (which comprise the "ladder rungs" in the double helix of DNA) typically found in the BRCA1 and BRCA2 gene sequences. The second process involved creating a copy of the original natural DNA sequence that contains only exons (i.e., nucleotides that code for amino acids, the building blocks of proteins), called cDNA.[90]

Through its discovery and development of a medical test, Myriad obtained several patents, which afforded Myriad the exclusive right to control the use of the test for twenty years. The patents included the method for isolating the BRCA1 and BRCA2 genes and the creation of cDNA.[91] With these patents, "Myriad was the only company that could administer the [BRCA1 and BRCA2] tests, for which it charged $3,000-$4,000, yielding a profit of $57 million through June 2013."[92] When scientists at other institutions began offering BRCA testing, Myriad asserted that the testing infringed its patents. One of the scientists, Dr. Harry Ostrer, sued to declare Myriad's patent invalid, and other doctors, patients, and advocacy groups jointly sued Myriad.[93] They argued that patents on gene sequences, DNA molecules, cDNA, and comparisons of gene sequences should be invalid because "[t]hey interfere with diagnosis and treatment, quality assurance, access to health care, and scientific and medical innovation."[94]

The case reached the Supreme Court, where the majority agreed with the petitioners and invalidated the patents on the isolated genes, reasoning that such products were not "with markedly different characteristics from any found in nature."[95] Comparing this case to *Funk*

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89 *Id.*

90 Cartwright-Smith, *supra* note 84 (internal footnote omitted).

91 Megan Krench, *New Supreme Court Decision Rules That cDNA Is Patentable What It Means for Research and Genetic Testing*, SCI. AM.: GUEST BLOG (July 9, 2013), http://blogs.scientificamerican.com/guest-blog/2013/07/09/new-supreme-court-decision-rules-that-cdna-is-patentablewhat-it-means-for-research-and-genetic-testing [https://perma.cc/M6CF-FQA6].

92 Cartwright-Smith, *supra* note 84 (internal footnote omitted); *see* Krench, *supra* note 91; *see also* Andrew Pollack, *After Patent Ruling, Availability of Gene Tests Could Broaden*, N.Y. TIMES (June 13, 2013), http://www.nytimes.com/2013/06/14/business/after-dna-patent-ruling-availability-of-genetic-tests-could-broaden.html?hp&_r=0 [https://perma.cc/9BMG-EGKB].

93 *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office,* 669 F. Supp. 2d 365, 385-92 (S.D.N.Y. 2009).

94 Brief of Amici Curiae American Medical Ass'n et al. in Support of Petitioners at 37, Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576 (2013) (No. 12-398), https://www.aclu.org/sites/default/files/field_document/2013.01.31_-_american_medical_association_et_al._amicus.pdf [https://perma.cc/MN5G-4WPG].

95 Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 590 (2013) (internal citation omitted). Notably, "[t]he [Federal] District Court granted summary judgment to [Dr. Ostrer and the other plaintiffs], concluding that Myriad's patents were invalided because they covered

Brothers Seed Co., the Court explained that isolating DNA from the human genome did not significantly change the composition of the DNA. Because Myriad did not create or alter genetic information in BRCA1 and BRCA2, the isolated DNA was not patentable because it was a product of nature.[96] Nevertheless, the Court ruled on behalf of Myriad, holding that "cDNA is not a 'product of nature,' so it is patent eligible under § 101."[97] Since the creation of cDNA requires scientists to isolate the exons and introns within a gene and put together only the exons, the Court explained that cDNA is not naturally occurring and that "the lab technician unquestionably creates something new when introns are removed from a DNA sequence to make cDNA."[98]

After the Court rendered its decision in *Myriad Genetics*, the product of nature doctrine was applied to the following patent categories: (1) chemicals derived from natural sources (e.g., antibiotics, fats, oils, petroleum derivatives, resins, toxins, etc.); (2) foods; (3) metals and metallic compounds that exist in nature; (4) minerals; (5) natural materials (e.g., rocks and soil); (6) nucleic acids; (7) organisms (e.g., bacteria, plants, and multicellular animals); (8) proteins and peptides; and (9) other substances found in or derived from nature.[99]

Although the patent claim at issue in *Alice Corp. Pty. Ltd. v. CLS Bank International* was not related to biotechnology, it is central to the understanding of the Supreme Court's current framework for determining the patentability of a claim.[100] In *Alice Corp.*, the patent claim at issue was about a method of mitigating "settlement risk," the risk that only one party to an agreed-upon financial exchange will satisfy its obligation.[101] The patents in suit claimed "(1) a method for exchanging financial obligations, (2) a computer system configured to carry out the method for exchanging obligations, and (3) a computer-readable medium containing program code for performing the method of exchanging obligations."[102] The Court affirmed the lower court's decision invalidating Alice Corp.'s patent claims because they were tied to a patent-ineligible abstract idea. Referring to both *Mayo* and *Myriad Genetics*, the Court first posed the question of whether the patent claim at issue was "directed to a patent-

products of nature." *Id.* at 576. However, the Court of Appeals subsequently reversed the district court's decision, holding instead that the composition claims to isolated DNA molecules, including cDNAs, may be patented. *See Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office,* 689 F.3d 1303, 1323 (Fed. Cir. 2012).

96 *Myriad Genetics, Inc.*, 569 U.S. at 591.

97 *Id*. at 577.

98 *Id*. (internal citation omitted).

99 Landau, *supra* note 6.

100 Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 573 U.S. 208, 217 (2014).

101 *Id.* at 212.

102 *Id.* at 214.

ineligible concept," such as laws of nature, natural phenomena, and abstract ideas.[103] If the answer to this question was no, then the patent claim would be considered eligible. However, if the question was answered in the affirmative, then a second question would be raised. The Court needed to determine whether the claimed elements, considered both individually and as an order combination, transform the nature of the claim into a patent-eligible application.[104] Citing *Mayo*, the Court noted that "'[s]imply appending conventional steps, specified at a high level of generality,' to a method already 'well known in the art' is not '*enough*' to supply the 'inventive concept' needed to make this transformation."[105] The Court applied a two-step analysis to determine that the patent claims, which were directed to an abstract idea, failed to transform that abstract idea into a patent-eligible invention because the method claims merely required generic computer implementation.[106]

II. THE INCONSISTENCY OF COURTS' APPLICATION OF THE *MYRIAD GENETICS* AND *MAYO/ALICE* FRAMEWORK ON RECENT BIOTECHNOLOGY INNOVATIONS

Despite the Supreme Court's holdings in *Mayo, Myriad Genetics*, and *Alice Corp.*, many lower courts have since rejected patent claims related to biotechnology because such claims are "directed to" a patent-ineligible concept. For example, in *In re Roslin Institute (Edinburgh)*, the Federal Circuit ruled that cloned animals are unpatentable subject matter using the product of nature doctrine.[107] *Roslin* concerned the patentability of Dolly, a sheep cloned from an adult sheep's somatic cell. The Federal Circuit held that "the natural organism itself . . . was unpatentable because its 'qualities [were] the work of nature' unaltered by the hand of man."[108] The issue in *Roslin* was not whether the method of cloning was unpatentable, but rather whether the products of cloning method was unpatentable.[109] Relying on *Myriad Genetics*, the court reasoned that Dolly was an "exact genetic replica" of her donor parent because the isolated DNA used to clone Dolly was neither created nor altered.[110] Because the *Roslin* decision was published before *Alice Corp.*, which held that claims directed to patent-ineligible concepts could nevertheless

103 *Id.* at 218.
104 *Id.* at 221.
105 *Id.* at 209 (citing Mayo Collaborative Servs. v. Prometheus Laboratories, Inc., 566 U.S. 66, 67-68, 72, 77 (2012)).
106 *Id.* at 226.
107 *In re* Roslin Inst. (Edinburgh), 750 F.3d 1333, 1339 (Fed. Cir. 2014) (internal citation omitted).
108 *Id.* at 1336.
109 *Id.*
110 *Id.* at 1337.

be patentable if they contain some inventive concept, it stopped at the first step of the *Mayo/Alice* analysis.

Notably, all the cases concerning product patent and method patent claims decided after *Roslin* refer to *Myriad Genetics* and the *Mayo/Alice* framework, respectively, to evaluate patentability. However, they have applied the framework differently, thereby producing inconsistent results in the patentability of biotechnology overall. The cases discussed in this section are: *BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation v. Ambry Genetics Corporation*,[111] *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*,[112] *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals International Ltd.*,[113] and *Roche Molecular Systems, Inc. v. Cepheid*.[114] *Ambry Genetics* and *Vanda Pharmaceuticals* concern method patent claims, where the former was found unpatentable while the latter was found patentable. *Ariosa Diagnostics* is about a product patent claim, which was found unpatentable. The *Roche Molecular Systems* decision, published in October 2018, concerns both product and method patent claims, both of which were found unpatentable.

In *Ambry Genetics*, the Federal Circuit decided whether a pair of DNA primers, which are "short, synthetic, single-stranded DNA molecule[s] that bind[] specifically to . . . intended target nucleotide sequence[s]" and are used for amplification of the BRCA genes, was patent ineligible.[115] After the Supreme Court's decision in *Myriad Genetics*, Ambry Genetics announced its plan to sell BRCA testing services.[116] In response, Myriad sued Ambry, alleging infringement of several of Myriad's remaining valid patent claims.[117] In *Myriad Genetics*, the Supreme Court had not yet rendered a decision on the patentability of the DNA primers at issue in *Ambry Genetics*. Following the explanation of products of nature in *Myriad Genetics*, the Federal Circuit invalidated the DNA primer patent claims.[118] The court held that primers "contain the identical sequence of the BRCA sequence directly opposite to the strand to which they are designed to bind[; thus,] [t]hey are structurally identical to the ends of DNA strands found in nature."[119] Moreover, citing *Myriad Genetics*, the court stated that "DNA structure with a function similar to that found in nature can only be patent eligible as a composition

111 BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig. v. Ambry Genetics Corp., 774 F.3d 755 (Fed. Cir. 2014).
112 Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371 (Fed. Cir. 2015).
113 Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd., 887 F.3d 1117 (Fed. Cir. 2018).
114 Roche Molecular Sys., Inc. v. Cepheid, 905 F.3d 1363 (Fed. Cir. 2018).
115 *Ambry Genetics Corp.*, 774 F.3d at 758.
116 *Id.*
117 *Id.* at 757.
118 *Id.*
119 *Id.* at 760.

of matter if it has a unique structure, different from anything found in nature."[120]

In stating that DNA primers and BRCA sequences are structurally identical, the *Ambry Genetics* court only looked at the linear order of nucleotides rather than the structures of the claimed patent primers.[121] While primers and naturally occurring DNA may share the same sequences, their three-dimensional shapes differ.[122] Many have looked at the *Ambry Genetics* ruling as limiting patent eligibility beyond what the *Myriad Genetics* Court held. In his note, Philip Merksamer explained that the *Myriad Genetics* Court limited its holding to purified and isolated DNA, leaving room for new DNA-based applications.[123] However, according to Merksamer, the *Ambry Genetics* holding further limited the subject matter of patent eligibility to only patents of molecular diagnostics—meaning that DNA-based products are not patentable unless they have different sequences from those existing in nature.[124]

In *Ariosa Diagnostics*, the Federal Circuit held that a patent claim for amplifying and detecting the paternally inherited cell-free fetal DNA (cffDNA) was patent-ineligible because such a method was a well-understood, routine, or conventional activity when the application for the patent was filed.[125] In 1997, Dr. Lo and Dr. Wainscoat discovered trace amounts of fragmented fetal DNA circulating in maternal blood.[126] They applied this discovery of cffDNA using well-understood DNA manipulation techniques to create a non-invasive prenatal test.[127] Sequenom had exclusively licensed the '540 patent on the non-invasive prenatal test, and Ariosa, Natera, and Diagnostics Center each developed non-invasive prenatal tests without a license to the '540 patent.[128] In 2011, each company filed a declaratory judgment action against Sequenom, asserting that they were not infringing the '540 patent because the patent applied to laws of nature. Sequenom argued that "a method applying or using a natural phenomenon in a manner that does not

120 *Id.* at 761 (internal citation omitted).
121 *Id.*
122 Alistair H. Kidd & Karin Kidd-Ljunggren, *A revised secondary structure model for the 3'-end of hepatitis B virus pregenomic RNA*, 24 NUCLEIC ACIDS RES. 3295, 3299 (1996), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC146111/pdf/243295.pdf [https://perma.cc/Q3HB-23JE].
123 Philip Merksamer, Ariosa Diagnostics v. Sequenom: *Metastasis of* Mayo *and* Myriad *and the Evisceration of Patent Eligibility for Molecular Diagnostics*, 31 BERKELEY TECH. L.J. 495, 519 (2016), https://scholarship.law.berkeley.edu/cgi/viewcontent.cgi?article=2115&context=btlj [https://perma.cc/H5L4-DS24].
124 *Id.*
125 Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1373 (Fed. Cir. 2015) (internal citation omitted).
126 *Id.*
127 *Id.*
128 *Id.*

preclude alternative methods in the same field is non-preemptive, and, by definition, patent-eligible under Section 101."[129]

The *Ariosa Diagnostics* court invalidated the '540 patent, asserting that the claims were "generally directed to detecting the presence of a naturally occurring thing or a natural phenomenon."[130] The court's holding consequently broadened the *Mayo/Alice* law of nature analysis. The court concluded that amplified cffDNA is a natural phenomenon and sought to apply *Mayo/Alice*'s second step in determining whether the patent at issue had an "inventive concept" beyond the natural phenomenon.[131] Therefore, the court determined that the patent lacked an inventive concept because the amplification and detection elements of the claim were well-understood, routine, and conventional in 1997, when scientists generally understood how to amplify and detect DNA.[132]

The *Ariosa Diagnostics* court expanded the law of nature limitation in *Mayo* and, as a result, many have criticized its holding. Professor Christopher Holman has argued that the adoption of the reasoning applied in *Ariosa Diagnostics* would produce absurd consequences.[133] For example, a method to detect human-made toxins in drinking water would be patent-eligible, but a method to detect naturally occurring pathogens would fall within a judicial exception and require additional scrutiny to determine patent eligibility.[134] Additionally, the court did not consider the amplified cffDNA to be a human-made composition with a new use not found in nature.[135] Amplified cffDNA provides clinically useful information on fetal characteristics, whereas naturally occurring cffDNA, without any human manipulation, does not.[136] Only after naturally occurring cffDNA has been transformed into a new substance, through a process such as amplification, does it become useful for fetal testing.[137] Additionally, in *Mayo*, many already knew about thiopurine drugs and the measuring of metabolites, while in *Ariosa Diagnostics*, no one was amplifying and detecting cffDNA at the time of the '540 patent because no one knew cffDNA existed.[138]

Leading up to *Vanda Pharmaceuticals*, Vanda owned the '610 patent, a method patent on treating schizophrenia patients with

129 *Id.* at 1378.
130 *Id.* at 1376.
131 *Id.* at 1377.
132 *Id.*
133 Merksamer, *supra* note 123, at 522-23.
134 *See id.* at 523 n.204.
135 *Id.* at 523.
136 *Id.*
137 *Id.*
138 *Id.* at 524.

iloperidone.[139] The correct dosage of iloperidone depended on the patient's genotype, and the cytochrome π450 2D6 (CYP2D6) gene encoded an enzyme known to metabolize iloperidone.[140] The use of the '610 patent showed "that treatment of a patient, who has lower CYP2D6 activity than a normal person, with a drug [such as iloperidone,] that is pre-disposed to cause QT prolongation and is metabolized by the CYP2D6 enzyme, can be accomplish[ed] more safely by administering a lower dose of the drug . . . ."[141] For patients who had lower than average CYP2D6 activity, the '610 patent provided examples of dose reductions for poor metabolizers compared to the dosage given to individuals with normal CYP2D6 activity.[142] The '610 patent claim provided the following method for treating a schizophrenic patient using iloperidone:

> [(1)] determining whether the patient is a CYP2D6 poor metabolizer by: [(a)] obtaining or having obtained a biological sample from the patient; and [(b)] performing or having performed a genotyping assay on the biological sample to determine if the patient has a CYP2D6 poor metabolizer genotype; and [(2)] if the patient has a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount of 12 mg/day or less, and [(3)] if the patient does not have a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount that is greater than 12 mg/day, up to 24 mg/day, [(4)] wherein a risk of QTc prolongation for a patient having a CYP2D6 poor metabolizer genotype is lower following the internal administration of 12 mg/day or less than it would be if the iloperidone were administered in an amount of greater than 12 mg/day, up to 24 mg/day.[143]

West-Ward argued that the '610 patent claim was ineligible under section 101 because the claim was directed at laws of nature and natural phenomena, which are known as judicially exclusive subject matter, and are very similar to *Mayo* and *Myriad Genetics*.[144] However, the Federal Circuit, applying the *Mayo/Alice* two-step analysis, held that the '610 patent claim was not directed at patent-ineligible subject matter because it recited "specific steps: (1) determining the patient's CYP2D6 metabolizer genotype . . . and (2) administering specific dose ranges of iloperidone depending on the patient's CYP2D6 genotype."[145] The court thus distinguished this case from *Mayo*: Because the claims in *Mayo* were directed to a diagnostic method based on the "relationships between [the]

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139 Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd., 887 F.3d 1117, 1120-21 (Fed. Cir. 2018).
140 *Id.* at 1121.
141 *Id.* (internal citation omitted).
142 *Id.*
143 *Id.* (internal citation omitted).
144 *Id.* at 1133.
145 *Id.* at 1134 (internal citation omitted).

concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm,"[146] it resulted entirely from a natural process and the patent claim merely constituted a description of that relation. In contrast, the '610 patent claims were directed to a method of using iloperidone to treat schizophrenia. The '610 patent therefore went beyond providing a law of nature by applying the relationships between iloperidone, CYP2D6 metabolism, and QTc prolongation;[147] rather, the '610 patent claim stated specific steps based on the patients' genotypes and postulated a method that could provide "a new way of using an existing drug" that was safer for patients because it reduced the risk of QTc prolongation.[148]

The *Vanda Pharmaceuticals* decision confused many because the '610 patent claim in *Vanda Pharmaceuticals* was very similar to the patent claim in *Mayo*, which was held patent-ineligible. Specifically, both patent claims concerned the administration of certain concentrations of a drug after evaluating a patient's ability to metabolize it. To address the apparent inconsistency, the USPTO circulated a memo on June 7, 2018, explaining the outcome of *Vanda Pharmaceuticals*.[149] In using the *Alice*/*Mayo* framework, the USPTO stated that the *Vanda Pharmaceuticals* patent claims were eligible under the first step of the *Alice*/*Mayo* framework because the claims were "directed to a method of using iloperidone to treat schizophrenia, rather than being directed to a judicial exception."[150] The USPTO stressed the importance of evaluating the claims as a whole, explaining that, in limiting the scope of '610 patent claim in *Vanda Pharmaceuticals* as mere use of the natural relationship between the patient's genotype and the risk of QTc prolongation, the claim would be directed to a law of nature.[151] Moreover, the USPTO agreed with the *Vanda Pharmaceuticals* court that "[m]ethod of treatment claims (which apply [to] natural relationships as opposed to being 'directed to' them) were identified by the Supreme Court as not being implicated by its decisions in *Mayo* and *Myriad Genetics* because they 'confine their reach to particular applications.'"[152] In other words, while the *Vanda Pharmaceuticals* patent claims were an application of a

146 *Id.* (internal citation omitted).
147 *Id.* at 1135.
148 *Id.*
149 Memorandum from Robert W. Bahr, Deputy Comm'r for Patent Examination Policy, U.S. Patent & Trademark Office, on Recent Subject Matter Eligibility Decision: *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals* to Patent Examining Corps (June 7, 2018), https://www.uspto.gov/sites/default/files/documents/memo-vanda-20180607.PDF [https://perma.cc/3H5N-RCZV].
150 *Id.*
151 *Id.*
152 *Id.* (emphasis omitted) (internal citation omitted).

natural relationship to come up with a method of treatment, the *Mayo* patent claims were not a method of treatment because the step of administering a drug to a patient was performed to gather data about natural relationships—which is "directed to" a law of nature.

In *Roche Molecular Systems*, the patent claim at issue was the '723 patent entitled "Detection of a Genetic Locus Encoding Resistance to Rifampin in Microbacterial Cultures and in Clinical Specimens."[153] The '723 patent was directed at methods for detecting the pathogenic bacterium Mycobacterium tuberculosis (MTB) by identifying MTB, which was resistant to the antibiotic "rifampin," and synthetic DNA molecules, called "primers," that were used to detect the MTB.[154] The MTB infection was a primary cause of tuberculosis, and before the '723 patent existed, the general method of MTB detection in a tuberculosis patient was the use of sputum examination by the acid-fast bacilli smear.[155] However, this sputum examination was limited because it could not indicate whether the MTB from a patient was resistant to antibiotics, thereby making it impossible to treat patients infected with MTB strains that were resistant to rifampin, which was the first-line anti-tuberculosis drug.[156] In order to improve the method of treating tuberculosis patients, scientists searched for a more efficient way to detect MTB. They discovered that rifampin has a unique site of action on a particular gene that encodes the β subunit of bacterial RNA polymerase (the *rpoB* gene).[157] The *rpoB* gene's DNA sequences were known to be highly conserved, meaning there was little variation from one bacterial species to another, making the gene a prime candidate for studying rifampin resistance in MTB.[158]

The inventors of the '723 patent sequenced the *rpoB* genes and, after comparing the sequenced genes across different species, they discovered that the *rpoB* gene in MTB contained eleven "position-specific 'signature nucleotides'" that were only present in MTB but not in other bacteria.[159] Based on these eleven MTB-specific signature nucleotides, the Roche inventors came up with a diagnostic test that could "(1) identify whether or not a biological sample contains MTB, and (2) if MTB is present, predict whether that MTB is a strain that is resistant to rifampin treatment."[160] The diagnostic test of the '723 patent involved extracting a DNA sample from the patient and amplifying that sample through the

153 Roche Molecular Sys., Inc. v. Cepheid, 905 F.3d 1363, 1365 (Fed. Cir. 2018).
154 *Id.* at 1365.
155 *Id.*
156 *Id.*
157 *Id.* at 1366.
158 *Id.*
159 *Id.*
160 *Id.*

application of a polymerase chain reaction (PCR), which uses a short, single-stranded nucleotide sequence, a primer, that has the ability to hybridize to at least one of the eleven position-specific signature nucleotides in the MTB *rpoB* gene.[161] The '723 patent provided two types of claims:

> (1) composition-of-matter claims for the primers used in the PCR, which could hybridize to the *rpoB* gene of MTB at a site that includes at least one of the eleven signature nucleotides ("the primer claims"); and (2) process claims for methods for detecting MTB that include amplifying target sequences by PCR and detecting amplification products, which, if present, indicate the presence of MTB ("the method claims").[162]

Regarding the primer claim, the *Roche Molecular Systems* court distinguished the primer at issue here from the primer in *Ambry Genetics*. In *Ambry Genetics*, the Federal Circuit held that, because the claimed primers had sequences that were identical to naturally occurring DNA strands and did not perform a significantly new function, they were not patent-eligible.[163] Roche contended that its primers were more similar to cDNA than the isolated DNA at issue in *Myriad Genetics* because its primers were expressed in terms of chemical composition and relied on chemical changes resulting from isolating sections of DNA, which were not identical to naturally existing DNA.[164] Specifically, Roche argued that its claimed primers required both a 3-prime end and a 3-hydroxyl group, which provided a free end to which the next nucleotide could be attached and was necessary for all primers. In contrast, the complete, naturally occurring bacterial MTB DNA molecule was circular and contained neither of those elements.[165] Roche stated that the primers in *Ambry Genetics* had the sequence of human DNA, which is linear and has a 3-prime end and 3-prime hydroxyl group, thus making the primers and the DNA structurally identical.[166] Notwithstanding Roche's arguments regarding the patentability of the primer, the court held that "no reasonable juror could conclude that there was a structural difference between the claimed primers and the corresponding naturally occurring

161 *Id.*
162 *Id.*
163 BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig. v. Ambry Genetics Corp., 774 F.3d 755, 765 (Fed. Cir. 2014).
164 Roche Molecular Sys., Inc. v. Cepheid, No. 14-cv-03228-EDL, 2017 U.S. Dist. LEXIS 113280, at *34-35 (N.D. Cal. Jan. 17, 2017).
165 *Id.* at *35.
166 *Id.*

segment of the *rpoB* gene to make the primers patentable under *Myriad Genetics* and *In Re BRCA1-*."[167]

On the issue of the method patent, the court utilized the *Mayo*/*Alice* two-step analysis. Applying the first step, the court determined that the discovery that the *rpoB* gene of MTB had signature nucleotides and the application of that discovery using the well-known technique of PCR to amplify and detect the presence of MTB and rifampin-resistant MTB was directed to a law of nature—a patent-ineligible concept.[168] Appling the second step, the court determined that the method claims were not directed to any change to the previously-known PCR process itself because the underlying PCR laboratory process was admittedly well-known and routinely used by 1994. Furthermore, the court found that Roche's method claims added no "inventive concept" that would qualify them for patent eligibility.[169] The court distinguished Roche's method claims for using the PCR process, which was well-known and routine at the time, from CellzDirect's method claims for using a process of freezing and thawing hepatocytes twice, also well-known and routine at the time.[170] The patent at issue in *CellzDirect* "recite[d] an improved process for preserving hepatocytes for later use," and the *Roche Molecular Systems* court argued that the claimed process of freezing and thawing twice was not conventional and routine even though the prior art had evolved into something distinct from this process.[171] In responding to Roche's argument that its method of amplifying "specific, identified signature nucleotides" similarly satisfied step two of the *Mayo/Alice* analysis, the court stated that *CellzDirect* was "a brand new process that not only had not been done before, but indeed had been commonly understood as unworkable."[172] Furthermore, the court concluded that "'the use of newly developed, nonpatentable primers to bind to newly identified naturally occurring signature nucleotides[, which were held nonpatentable under *Myriad Genetics*] . . . using the well-known, routine process of PCR in a conventional way does not transform the claimed methods into' patent-eligible subject matter."[173]

In holding that the invention was patent ineligible, the *Roche Molecular Systems* court mixed two separate patent claims (a product patent claim and a method patent claim) and concluded that, because the

167 *Id.*at *37.
168 *Id.* at *51-53.
169 *Id.*
170 *Id.* at *52; *see* Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc., 827 F.3d 1042, 1046 (Fed. Cir. 2016).
171 *Rapid Litig. Mgmt. Ltd.*, 827 F.3d at 1045; *see Roche Molecular Sys., Inc.*, 2017 U.S. Dist. LEXIS 113280, at *64.
172 *Roche Molecular Sys., Inc.*, 2017 U.S. Dist. LEXIS 113280, at *58.
173 *Id.* at *59.

product claim was deemed ineligible, the method claim should also be ineligible.[174] For instance, the *Roche* court found that:

> Roche's attempts to distinguish Genetic Technologies and Ariosa are unpersuasive because the identification of specific naturally-occurring nucleotides or the use of primers developed based on this identification simply does not confer patentability where there is no new, inventive concept added to the well-known underlying method so as to satisfy the step two analysis. This is true even where the invention, when viewed as a whole, could be seen as "revolutionary."[175]

When the USPTO circulated its memo regarding the decision of *Vanda Pharmaceuticals* and stressed the importance of looking at each claim as a whole—rather than limiting the scope of the naturally existing relationship—it surely did not mean that courts should look at each entire case as a whole, consequently merging different patent claims. Additionally, in its effort to distinguish *Roche* from *CellzDirect* at the second step of the *Mayo/Alice* analysis, the *Roche Molecular Systems* court did a poor job at explaining which "conventional, routine and well-understood" process could be changed to become "something more" to be patent-eligible. Moreover, in its analysis of the product claim, the *Roche Molecular Systems* court relied heavily on *Ariosa Diagnostics*, which has already been widely criticized for expanding the scope of judicial exclusion that discriminates against biotechnological products.

In looking at these decisions and the *Mayo*/*Alice* framework analysis performed by the four courts on biotechnological products, there is more confusion as to what aspect of the patent claim directs it to a patent ineligibility concept and what aspect of the patent claim that is already determined to be directed to a patent ineligibility concept transforms it to be patent-eligible.

III. A HYPOTHETICAL CASE ON PRODUCTS DIRECTED TO PATENT-INELIGIBLE CONCEPT THROUGH THE METHOD OF UTILIZING CRISPR GENOME EDITING TECHNOLOGY

In this section, a hypothetical case concerning products created from CRISPR will be used to illustrate that the current application of patent eligibility framework is inconsistent and unfairly puts a burden on biotechnological products. First, a brief background on CRISPR will be discussed before the hypothetical case is introduced. Then, the

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[174] *Id.* at *65.

[175] *Id.* (citing Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1380-81 (Fed. Cir. 2015)).

hypothetical case will be analyzed under the different court rulings from Part II.

A. *Background on CRISPR*

CRISPR (which, as defined above, is an acronym for Clustered Regularly Interspaced Short Palindromic Repeats) was discovered in archaea by Francisco Mojica.[176] CRISPRs serve as part of the bacterial immune system, and they are created when bacteria capture a part of the invading virus's DNA and create DNA segments.[177] These CRISPR arrays work like a memory system for the bacteria: If the same virus attacks again, the bacteria can produce RNA segments from the CRISPR arrays to target the virus's DNA.[178] The bacteria then use Cas9, or another similar enzyme, to cut the DNA apart and disable the virus.[179] After this process was discovered, scientists developed a method to engineer CRISPR to edit the genome.[180]

CRISPR genome editing technology works similarly to the way bacteria's CRISPR works in nature.[181] Scientists transcribe CRISPR sequences to a short RNA sequence, along with a short guide sequence, which changes depending on which gene the scientists want to target.[182] Once the target DNA is found, the Cas9 enzyme is produced by the CRISPR system, which cuts off the DNA at the targeted location, effectively shutting the gene off.[183] Once the DNA is cut, researchers can add or delete genetic material, or replace it with a customized DNA sequence.[184]

With CRISPR genome editing technology, researchers can permanently modify genes in living cells and organisms, and also efficiently treat genetic diseases by correcting mutations at precise locations within the genome.[185] This technology is being used to research

176 Later, it was discovered that CRISPR also exists in bacteria. *Questions and Answers About CRISPR*, BROAD INST. [hereinafter *CRISPR*], https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/questions-and-answers-about-crispr [https://perma.cc/KJ27-YGNS].

177 *Id.*

178 *Id.*

179 *Id.*

180 *Id.*

181 *What are genome editing and CRISPR-Cas9?*, U.S. NAT'L LIBR. MED.: GENETICS HOME REFERENCE [hereinafter *Genome Editing*], https://ghr.nlm.nih.gov/primer/genomicresearch/genomeediting [https://perma.cc/Q2LV-VTFT].

182 *Id.*

183 *Id.*

184 *Id.*

185 There are different CRISPR patents, depending on the protein utilized and how the DNA is cut, and with these different CRISPR patents, there were disputes over ownership. For example, with respect to the CRISPR-Cas9 patent, used to make genetic changes to eukaryotic organisms, there was a dispute over the ownership of the technology between the University of California, Berkeley (UC), and the Broad Institute of MIT and Harvard in Cambridge, Massachusetts. *See* Heidi Ledford,

single-gene disorders, such as cystic fibrosis, hemophilia, and sickle cell diseases.[186] Additionally, CRISPR technology can potentially develop treatment and prevention for more complex diseases, such as cancer, heart disease, mental illness, and human immunodeficiency virus (HIV) infection.[187] More importantly, and related to the product of nature doctrine, CRISPR genome editing allows scientists to quickly create cell and animal models, which might have significantly different characteristics from those that exist freely in nature.[188]

B. *Introduction of the Hypothetical Case*

Researchers have also used CRISPR to create new species. Using CRISPR-Cas9, a team from New York University School of Medicine created a new yeast species by fitting sixteen of its chromosomes into two chromosomes.[189] Another team in China packed all sixteen chromosomes into just one chromosome.[190] These two different species of yeast created by the use of CRISPR technology do not function differently from the yeast species that already exist in nature. In fact, the two-chromosome yeast reproduce at the same rate as the yeast that exist in nature, and the one-chromosome yeast reproduce at a slower rate.[191] However, these genetically modified yeasts can be characterized as different species

Pivotal CRISPR patent battle won by Broad Institute, NATURE (Sept. 10, 2018), https://www.nature.com/articles/d41586-018-06656-y [https://perma.cc/3CZ2-686E]. On September 10, 2018, the U.S. Court of Appeals for the Federal Circuit decided that the Broad Institute owned the patent for CRISPR-Cas9, and UC was given two months from the decision date to appeal to the Supreme Court. *Id.* The European Patent Office (EPO) initially announced in early 2017 that it intended to grant the CRISPR-Cpf1 patent to the Broad Institute. Paul Goldsmith, *European Patent Office to grant CRISPR-Cpf1 patent to Broad Institute, MIT, and Harvard University*, BROAD INST. (Feb. 27, 2017), https://www.broadinstitute.org/news/european-patent-office-grant-crispr-cpf1-patent-broad-institute-mit-and-harvard-university [https://perma.cc/F388-WVYC]. However, the EPO then revoked the patent in January 2018 because the European patent filing omitted one of the inventors who had previously been included in the U.S. filing. Kelly Servick, *Broad Institute takes a hit in European CRISPR patent struggle*, SCI. (Jan. 18, 2018, 3:30 PM), http://www.sciencemag.org/news/2018/01/broad-institute-takes-hit-european-crispr-patent-struggle [https://perma.cc/VYY7-2J3U]. In 2018, Benson Hill was granted a patent related to CRISPR 3.0 Cms1 genome editing nucleases, which are primarily used to enhance crop performance. *Benson Hill Biosystems granted patent for novel genome editing system*, NEWS MED. (Feb. 20, 2018), https://www.news-medical.net/news/20180220/Benson-Hill-Biosystems-granted-patent-for-novel-genome-editing-system.aspx [https://perma.cc/HPC3-8P3F].

186 CRISPR can be used to correct the genetic errors that cause disease, eliminate the microbes that cause disease, resurrect species, create new, healthier foods, and reduce or eradicate malaria-carrying mosquitoes, the planet's most dangerous pest. Victor Tangermann, *A CRISPR Future: Five Ways Gene Editing Will Transform Our World*, FUTURISM (Jan. 30, 2018), https://futurism.com/crispr-genetic-engineering-change-world/ [https://perma.cc/7XNV-5PJN].

187 *Id.*

188 *Id.*

189 Ewen Callaway, *Entire yeast genome squeezed into one lone chromosome*, NATURE RES. (Aug. 1, 2018), https://www.nature.com/articles/d41586-018-05857-9 [https://perma.cc/E76F-E8WH].

190 *Id.*

191 *Id.*

because they are unable to successfully "breed" either with each other or with the yeast that exists in nature.[192] There is a potential application of this study to real-world situations. For example, researchers can genetically modify strains of the new species of yeast that can break agricultural byproducts into biofuels and release these species into nature without being concerned about the more considerable impact such new species will have on the ecosystem.[193]

C. *Patent Eligibility of the Man-Made Yeast Species Created by Using CRISPR*

Anyone who "invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof" may acquire a patent.[194] First, the claim at issue must be directed to a process, machine, manufacture, or composition of matter to be eligible for a patent. Then, the claim must be evaluated in light of whether it monopolizes the "building blocks of human ingenuity," because a claim directed toward products of nature, laws of nature, natural phenomena, and abstract ideas is not patent-eligible.[195] The Supreme Court has instructed courts to distinguish between claims that seek to protect patent-ineligible subject matter and those that "integrate the building blocks into something more."[196] Therefore, the second step in determining patent eligibility is to determine "whether the claims at issue are directed to . . . patent-ineligible concepts."[197]

A claim is "directed to" a judicial exception if it is "recited in the claim, i.e., the claim sets forth or describes the exception."[198] An example of a claim that is "directed to" a judicial exception would be "[a] machine comprising elements that operate in accordance with F=ma[,]" because this claim recites the law of nature that force equals mass times acceleration.[199] If the claim at issue is determined to be directed to a patent-ineligible concept, then the next step would be to "examine the elements of the claim to determine whether it contains an ' "inventive concept" ' sufficient to 'transform' the claimed abstract idea into a patent-eligible application."[200] If the elements of a claim involve "well-

192 *Id.*
193 *Id.*
194 35 U.S.C. § 101 (2012).
195 Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 573 U.S. 208, 216 (2014).
196 *Id.* at 217.
197 *Id.*
198 U.S. PATENT & TRADEMARK OFFICE, 2014 INTERIM GUIDANCE ON PATENT SUBJECT MATTER ELIGIBILITY (2014), https://www.uspto.gov/sites/default/files/documents/training%20-%202014%20interim%20guidance.pdf [https://perma.cc/3JP4-YC6G].
199 *Id.*
200 *Alice Corp. Pty. Ltd.*, 573 U.S. at 221 (quoting Mayo Collaborative Servs. v. Prometheus Laboratories, Inc., 566 U.S. 66, 72 (2012)).

understood, routine, [or] conventional activity previously engaged in by researchers in the field," they do not constitute an "inventive concept."[201] The second step of the *Mayo/Alice* test is satisfied when the claim limitations involve something more than "well-understood, routine, conventional activity previously engaged by those in the field."[202]

1. Step One of the *Mayo/Alice* Test on Products Created with CRISPR: Is It Directed to Products of Nature, Laws of Nature, Natural Phenomena, and Abstract Ideas?

Assuming that these man-made yeasts have significant potential utility, they would satisfy the threshold test of patent protection eligibility, which asks whether they are directed to a process, machine, manufacture, or composition of matter. The one- and two-chromosome yeasts would fall under the composition of matter. Then, the first step of the *Mayo/Alice* test should be applied to determine whether the claims for these man-made yeasts are directed to products of nature, laws of nature, natural phenomena, and abstract ideas. In this type of claim for patent eligibility, it seems like the product of nature, natural phenomena, and the law of nature exceptions would apply, but the abstract ideas exception would not.[203]

In looking at the latter exception, the patent eligibility of these new types of yeast species rests on whether they have "'markedly different characteristics from any found in nature[.]'"[204] According to footnote eight of *Myriad Genetics*, "[t]he possibility that an unusual and rare phenomenon *might* randomly create a molecule similar to one created synthetically through human ingenuity does not render a composition of matter nonpatentable."[205] Thus, even if some unforeseen mutation in natural yeast resulted in a similar chromosomal composition to those found in the one- and two-chromosome yeasts created through CRISPR, the man-made yeasts would not be barred from patentability. The question remains, then, whether the one- and two-chromosome yeasts significantly changed the composition of naturally existing yeast to overcome the product of nature bar to the patent subject matter in section 101.

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201 *Mayo Collaborative Servs.*, 566 U.S. at 79.

202 *Id.*

203 *See* U.S. PATENT & TRADEMARK OFFICE, *supra* note 198, at 12 ("These are the labels commonly used by the courts, but there is no bright line between the exceptions. For example, courts have labelled mathematical formulas as both abstract ideas and laws of nature, and have labelled 'products of nature' as natural phenomena and laws of nature.").

204 Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 590-91 (2013) (quoting Diamond v. Chakrabarty, 447 U.S. 303, 310 (1980)).

205 *Id.* at 576 n.8.

To create the two-chromosome yeast, the New York University team used CRISPR to remove genetic material at the end and middle of chromosomes (known as telomere and centromeres) and relied on yeast's natural DNA-repair mechanism to produce a strain with just two chromosomes.[206] As for the one-chromosome yeast, the team in China used CRISPR to remove fifteen centromeres and thirty telomeres, in addition to nineteen long, repeated sequences.[207] By removing the telomeres and centromeres of sixteen chromosomes of yeast, both teams shuffled the remaining parts of the sixteen chromosomes, connecting them to create two elongated chromosomes and one even longer chromosome.

There is no evidence that this method of changing yeast's DNA sequence to create a new species has ever been done before. However, the combination of chromosomes after the removal of telomeres and centromeres could be seen as similar to the method used to create cDNA. The *Myriad Genetics* Court ruled that cDNA is not a product of nature because the creation of cDNA requires the isolation of exons and introns within a gene so that only the exons can be put together.[208] Similarly, the method for creating the one- and two-chromosome yeasts could be characterized as the removal of telomeres and centromeres (introns) to put together the rest of the gene-coding part of chromosomes (exons), which is not naturally occurring.

Additionally, example five in the USPTO's December 2014 Nature-Based Products guidelines illustrates that a patent claim on a naturally occurring product that is unchanged from its natural state without markedly different characteristics is not patent-eligible, but changes in biological function between a claimed product and its natural counterpart.[209] Example five analyzes genetically modified bacterium, comparing stable energy-generating plasmids, which provide hydrocarbon degradative pathways and exist within certain bacteria in nature,[210] with Pseudomonas bacteria, which are naturally occurring, contain one stable energy-generating plasmid, and are capable of degrading a single type of hydrocarbon.[211] There are no known Pseudomonas bacteria in nature that contain more than one stable energy-

206 Callaway, *supra* note 189.
207 *Id.*
208 *Ass'n for Molecular Pathology*, 569 U.S. at 594-95.
209 *Subject matter eligibility*, USPTO, https://www.uspto.gov/patent/laws-and-regulations/examination-policy/subject-matter-eligibility [https://perma.cc/J8P4-2Y8W]; *see* U.S. PATENT & TRADEMARK OFFICE, EXAMPLES: ABSTRACT IDEAS (2016), https://www.uspto.gov/sites/default/files/documents/101_examples_1to36.pdf [https://perma.cc/4HX3-A8YN].
210 U.S. PATENT & TRADEMARK OFFICE, *supra* note 209, at 7.
211 *Id.*

generating plasmid.[212] If an applicant presents genetically modified Pseudomonas bacterium that include more plasmids than are found in a single naturally occurring Pseudomonas bacterium, the plasmids themselves, without significantly different characteristics from those existing in nature, are patent-ineligible.[213] However, the modified bacterium with multiple plasmids would be patent-eligible, as it has a different functional characteristic from naturally occurring Pseudomonas bacteria because it can degrade at least two different hydrocarbons.[214] Additionally, this modified bacterium also has a different structural characteristic, because it has more plasmids than those existing in nature.

Similar to the Pseudomonas bacteria example provided in the USPTO's guidelines, the one- and two-chromosome yeasts have different functional characteristics from naturally occurring yeast (assuming that these yeasts have significant potential utility and do not disrupt the ecosystem with some unforeseen consequences as a result of their breeding with naturally existing yeast). Furthermore, they also contain different structural characteristics, because the chromosomal compositions of the one- and two-chromosome yeasts are different from yeasts that naturally exist in nature. Even following *In re Roslin Institute (Edinburgh),* the one- and two-chromosome yeasts would not fall under the product of nature exception to patent eligibility because these yeasts are not an "exact genetic replica" of the naturally existing yeasts.[215]

The next question is whether the method of creating these man-made yeasts falls under the law of nature exception. The *Mayo* Court ruled that an improvement on an old method was not patent-eligible under section 101 when the only new and useful element of the improved method was a discovery. In *Ariosa Diagnostics*, the court invalidated the patent at issue because the claims "[were] generally directed to detecting presence of a naturally occurring thing or a natural phenomenon . . . ."[216] The method of creating the one- and two-chromosome yeasts involves using CRISPR to remove the parts of yeast's chromosomes that do not code for any genes and relying on its natural DNA-repair mechanism to connect the rest of its chromosomes. The *Ariosa Diagnostics* court expanded the law of nature exception established in *Mayo*, holding that a method that was "well-understood, routine, or conventional activity . . . when the application for the '540 patent was filed" was patent ineligible.[217] Thus, because the CRISPR products utilize the natural

212 *Id.*
213 *Id.*
214 *Id.*
215 *In re* Roslin Inst. (Edinburgh), 750 F.3d 1333, 1337 (Fed. Cir. 2014).
216 Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1376 (Fed. Cir. 2015).
217 *Id.* at 1375.

phenomenon of yeast's DNA-repair mechanism to connect the chromosomes, the *Ariosa Diagnostics* and *Roche Molecular Systems* courts would rule that mechanism is directed to a judicially exclusive patent concept.[218]

Moreover, the *Roche Molecular Systems* court's inadequate explanation as to what "conventional, routine, and well-known" process at the time is subject to law of nature or natural phenomenon makes it unclear whether the CRISPR method itself would be the "conventional, routine, and well-known" process. If that were the case, it would bar the entire patent-eligible product from patent eligibility simply because its creators heavily depended on CRISPR in making it. However, as the *Vanda Pharmaceuticals* court and the USPTO memo on that decision pointed out, the claim should be looked at as a whole—so although a part of the CRISPR yeast product claim is directed to natural phenomenon, it would be characterized as a brand new organism when considered as a whole, similar to the bacteria in *Chakrabarty*.[219] Thus, under *Vanda Pharmaceutical**s***, the CRISPR yeast product would not be directed to a patent-ineligible concept, so there would be no need to analyze this claim under the second *Mayo/Alice* step.

2. Step Two of the *Mayo/Alice* Test on Products Created with CRISPR: Does It Contain Inventive Concept to Transform It into a Patent-Eligible Product?

Assuming that this hypothetical product is under the jurisdiction of *Ariosa Diagnostics* and *Roche Molecular Systems*, the yeasts produced with CRISPR technology will need to go through the second step of the *Mayo/Alice* test. In *Ariosa Diagnostics*, the court concluded that amplified cffDNA is a natural phenomenon and sought to apply *Mayo*'s second step to determine whether the patent at issue had an "inventive concept" beyond the natural phenomenon.[220] The court held that the patent lacked an inventive concept since the amplification and detection elements of the claim were well-understood, routine, and conventional in 1997, a period when scientists generally understood how to amplify and detect DNA.[221] In *Roche Molecular Systems*, the court determined that the method claims were not directed to any change to the previously-known PCR process itself because the underlying PCR laboratory process was admittedly well-known and routinely used by 1994; furthermore, Roche Molecular Systems' method claims added no "inventive concept"

218 *See* discussion *infra* Part II.
219 *See* discussion *infra* Part II.
220 *Ariosa Diagnostics, Inc.*, 788 F.3d at 1376.
221 *Id.* at 1376-77.

to become patent-eligible.[222] Additionally, the *Roche Molecular Systems* court concluded that "'the use of newly developed, nonpatentable primers to bind to newly identified naturally occurring signature nucleotides[, which are not patentable under *Myriad Genetics*,] using the well-known, routine process of PCR in a conventional way does not transform the claimed methods into'" something more.[223]

Following the *Roche Molecular Systems* court's line of reasoning—that, because PCR was a conventional and well-known process at the time, heavy reliance on PCR in the creation of a method for detecting MTB genes that are resistant to antibiotics lacks the "inventive concept" to move forward—the yeasts made by relying heavily on CRISPR, which could be viewed as a conventional and well-known process, would not pass the second prong of the *Mayo/Alice* analysis. Thus, somewhat counterintuitively, the yeasts themselves would be patent-eligible, but the method of creating them would not be. This outcome would lead to chaos, as different institutions could use the same methods to create the same yeasts, which would be patent-eligible, without infringing the product patent of the yeasts.

D. *Suggestions for the USPTO*

As shown from the hypothetical patent claim above, following *Vanda Pharmaceuticals*, the one- and two- chromosome yeast would satisfy the first step of the *Mayo/Alice* test, making both the product and method patentable without requiring further analysis under the second step. However, following *Ariosa Diagnostics* and *Roche Molecular Systems*, the one- and two- chromosome yeasts would need to be analyzed under the second step of the *Mayo/Alice* test, which asks whether the product/method contains a sufficiently inventive concept to transform it to a patent-eligible product. Because the second step lacks USPTO guidance as to the proper evaluation of what qualifies as an inventive concept, courts rely on common law to make this determination, which has resulted in inconsistent outcomes. Thus, under *Roche Molecular Systems*, the one- and two- chromosome yeast would be patent-eligible as products, while their method would not be patent-eligible.

However, pursuant to the latest updated version of Patent Examining Procedure published in January 2018, the USPTO advises that, for a process claim, "the general rule is that the claim is not subject to the markedly different analysis for nature-based products used in the process. This is because the analysis of a process claim should focus on

222 Roche Molecular Sys., Inc. v. Cepheid, 905 F.3d 1363, 1372 (Fed. Cir. 2018).

223 *Id.* at 1368 (quoting Roche Molecular Sys., Inc. v. Cepheid, No. 14-cv-03228-EDL, 2017 U.S. Dist. LEXIS 113280, at *58-59 (N.D. Cal. Jan. 17, 2017), *aff'd*, 905 F.3d 1363 (Fed. Cir. 2018)).

the active steps of the process rather than the products used in those steps."[224] Therefore, the USPTO uses *CellzDirect* as an example to show that, because the patent in that case was process- rather than product-based, the *CellzDirect* court did not subject the claim to a "markedly different characteristics analysis for the nature-based products (the hepatocytes) used in the process."[225] On the one hand, the USPTO does not hypothesize as to what would have happened if CellzDirect had instead focused its claim on the preparation and production of multi-cryopreserved hepatocytes. On the other hand, the USPTO provides that,

> [I]n the limited situation where a process claim reciting a nature-based product is drafted in such a way that there is no difference in substance from a product claim, the claim is subject to the markedly different analysis for the recited nature-based product . . . . For example, consider a claim that recites, in its entirety, "a method of providing an apple." Under the broadest reasonable interpretation, this claim is focused on the apple fruit itself, which is a nature-based product. Similarly, claims to detecting naturally occurring cell-free fetal DNA (cffDNA) in maternal blood were held to be directed to the cffDNA, because the "existence and location of cffDNA is a natural phenomenon [and thus] identifying its presence was merely claiming the natural phenomena itself."[226]

By using an apple as its example, the USPTO again bypasses the subtle difference in the three-dimensional shapes of biochemical products that are slightly different from naturally-existing chemicals.

In the October 2019 Life Sciences and Data Processing Examples 43–46, the USPTO attempts to explain what qualify as patent eligible method patent claims in administering drug dosages.[227] Example 43 concerns Nephritic Autoimmune Syndrome Type 3 (NAS-3), an autoimmune disease that is associated with causing cell lysis and inflammation that eventually lead to kidney failure.[228] One of the conventional first-line treatments for NAS-3 is glucocorticoids, a class of steroids; however, not every individual respond well to glucocorticoids.[229] Researchers found that a certain ratio between levels of two proteins, known as C11 and C13, indicates a particular patient response to glucocorticoids. Based on this, they came up with a way to

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224 U.S. Dep't of Commerce, Patent & Trademark Office, MPEP § 2106.04(c) (9th ed. Rev. 08.2017, Jan. 2018) [hereinafter MPEP], https://www.uspto.gov/web/offices/pac/mpep/mpep-2100.pdf [https://perma.cc/D5F5-4D3Q].

225 *Id.* (citing Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc., 827 F.3d 1042, 1049 (Fed. Cir. 2016)).

226 *Id.* (citing *Rapid Litig. Mgmt. Ltd.*, 827 F.3d at 1048) (discussing the court's holding in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*).

227 U.S. PATENT & TRADEMARK OFFICE, *supra* note 12.

228 *Id.* at 2.

229 *Id.*

calculate the ratio of C11 and C13 levels measured in a blood sample from a patient diagnosed with NAS-3 to determine whether the patient had a non-responder phenotype and administer a treatment based on that determination.[230] The USPTO provides that the administration of "a treatment to the patient having a non-responder phenotype" is similar to the claims at issue in *Mayo*, as it explains mathematical concepts rather than "requiring any particular application of the recited calculation, and is best the equivalent of merely adding the words 'apply it' to the judicial exception."[231] This statement simply restates the holding of the *Mayo* case and does not clarify when administering a treatment would meet a patent-eligible standard.[232]

The conventional second line treatment of NAS-3 is therapy with non-steroidal agents such as rapamycin, which is a naturally-occurring chemical isolated from bacteria.[233] Regarding the method claim on this treatment method, the USPTO provides that it is patent eligible because, although this claim "recites an additional nature-based product limitation (the rapamycin in the administration step), analysis of the claim as a whole indicates that [it] remains focused on a process of determining how much C11 and C13 is present in the blood sample and then treating a patient [accordingly]."[234] The only difference between this claim and the previous claim depends on the two naturally-existing substances: rapamycin and glucocorticoids. However, the calculation of how much rapamycin to administer was deemed patent eligible while the calculation of how much glucocorticoids to administer was deemed patent ineligible. The USPTO seems to focus on the first-line treatment rather than the second-line treatment, but it again fails to explain whether and how the second-line of treatment might fall under the limitation of well-understood, routine, and conventional activity to make it subject to patent ineligible concept.

Therefore, the USPTO should provide a set of examples or guidance on what the "conventional, routine, and well-understood" process is to be subject to the law of nature concept, barring it from the subject matter eligibility requirement in section 101. Moreover, in publishing a set of examples, the USPTO should include more process patent claims, specifically regarding patents that administer certain dosages of drugs for different individuals for maximum drug effect and that also use "conventional, routine, and well-understood" processes. In those examples, the USPTO should attempt to define what would be considered

230 *Id.*
231 *Id.* at 4.
232 *Id.*
233 *Id.* at 2.
234 *Id.* at 7.

a "conventional, routine, and well-understood" process by limiting the scope of what each adjective could convey. A possible definition could be as follows: conventional—a specific process has been used for the last ten years; routine—in producing a new, innovative biotechnological product, a specific process is often used (maybe more than fifty percent of the time) in this specific field; and well-understood—there is nothing new about the process, and most people in the field understand this process to be unpatentable.

CONCLUSION

By applying the *Myriad Genetics* and *Mayo/Alice* framework on patent eligibility to hypothetical engineered strands of yeast, this Note showed that biotechnology products are discriminated against under the inconsistent outcomes of that framework. In order to further prove that the current application of the framework is confusing and inconsistent, this Note used a hypothetical case of possible product and method claims resulting from the use of CRISPR. Depending on the jurisdiction of where the patent claims are litigated, the result of whether the method patent claims are validated or not would be different. To solve this inconsistency, this Note proposes that USPTO should provide a set of examples or guidance on what the "conventional, routine, and well-understood" process is to be subject to the law of nature concept, barring it from the subject matter eligibility requirement of section 101.

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