Making the Case Against Gene Patents

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On June 13, 2013, the Supreme Court issued a unanimous decision in Association for Molecular Pathology v. Myriad Genetics, *holding that a naturally occurring DNA segment that has merely been "isolated" is not patent eligible, and effectively overturning a longstanding policy that had allowed for patents to be issued on thousands of human genes. Drawing largely on the expert testimony and arguments presented during the court proceedings, this paper provides an overview of the discovery and patenting of the BRCA1 and BRCA2 genes at issue in the case, the impacts of gene patents on biomedical research and innovation and clinical practice, and the legal analysis presented by the plaintiffs throughout the case for how patents issued on genes violate the Patent Act and the U.S. Constitution. Finally, it discusses how the Court's decision in this case marked an extraordinary victory not only for the plaintiffs directly involved, but more generally for women, patients, researchers, civil liberties, and the future of medicine.*

1. Making the Case Against Gene Patents

On June 13, 2013, the Supreme Court issued a unanimous decision in *Association for Molecular Pathology v. Myriad Genetics*, holding that human genes

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cannot be patented. Finding that "a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated," the Court put an end to the U.S. Patent and Trademark Office's (USPTO) fundamentally misguided and longstanding gene patenting policy that had allowed for thousands of patents to be issued on naturally occurring "isolated" DNA sequences.

The Court's decision in the case (hereinafter, *AMP*) marked an extraordinary victory not only for the twenty plaintiffs directly involved, but more generally for women, patients, researchers, civil liberties, and the future of medicine. At issue in the case were patents that had been granted on two genes (BRCA1 and BRCA2) that have been associated with hereditary forms of breast and ovarian cancer. Myriad Genetics, a private corporation based in Utah, had successfully applied for and obtained a suite of patents on these genes which provided the company with exclusive rights over, and an effective monopoly on, clinical diagnostic testing or any other use or application of the genes.

When *AMP* was initially filed in federal court in 2009, few predicted a victory for the plaintiffs. The USPTO had been issuing patents on genes for more than twenty years, the biotechnology industry had grown up around this practice, and the patent bar viewed gene patenting as status quo. Many factors contributed to the twists and turns in this case and its ultimate outcome. Key to its success was the involvement of a diverse and highly committed group of plaintiffs, experts, and supporters brought together by the American Civil Liberties Union (ACLU) and the core legal and policy issues at stake that united them. The community's success in integrating legal precedent governing patent eligibility with the implications of gene patents for public health and biomedicine resulted in a compelling set of arguments that ultimately prevailed despite what appeared to many interested onlookers at the offset to be insurmountable challenges.

Drawing largely on the expert testimony and arguments presented during the court proceedings, this article provides an overview of the core policy and legal arguments against the patenting of isolated DNA that were at stake in *AMP*. First, it presents a brief history and description of gene patenting, the discovery and patenting of the BRCA1 and BRCA2 genes, and the specific patent claims that were challenged in the litigation. Next, it provides a detailed overview of the detrimental impacts that gene patents have had on science and innovation. It then outlines the legal analysis articulated by the plaintiffs throughout *AMP* for how patents issued on genes violate the Patent Act and the U.S. Constitution. Finally, it traces the court rulings in the case and discusses the implications of the Supreme Court's decision, including how the invalidation of these patent claims will serve to benefit patients, biomedical research and precision medicine.

2. The Patenting of Human Genes

The first gene patent (Patent No. 4,363,877) was issued to the University of California in 1982 related to a gene for human chorionic somatotropin, a growth hormone that promotes breast development during pregnancy (Huang and Murray 2009). Throughout the 1980's, scientists continued to obtain patents on genes whose function they had identified (Williams-Jones 2002, pp. 125–6). By the 1990's, the scope of patent applications had widened, as applicants sought patents on gene segments whose utility was unknown. For example, the National Institutes of Health (NIH) announced in 1991 its applications on 350 gene segments discovered during the Human Genome Project. NIH stated that its applications were intended to protect the government's rights and to prevent preemptive patenting. Ultimately, however, these patents were rejected by the Patent Office (Schmidt 2000). In October 1992, the Secretary of the U.S. Department of Health and Human Services reversed the NIH policy of seeking patents. The trend to seek patents on gene sequences, however, was by then firmly established. In October 1996 the USPTO announced that it had a backlog of patents covering over 500,000 gene sequences (Abate 2000, p. A8).

2.1. The USPTO's Justification

The USPTO grants patents pursuant to the Patent Act, enacted by Congress and codified at title 35 of the U.S. Code. The Patent Act lays out a number of criteria for patents, including standards for novelty, utility, non-obviousness, written description, and subject matter eligibility. Section 101 of the Patent Act sets forth the basic definition of "inventions patentable" and states: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of the title."

In 1999 and 2000, the USPTO undertook a process of revising its examination guidelines for determining whether patent applications met the "utility" requirement—a criterion that is separate from the subject matter eligibility analysis under Section 101 (USPTO [1999] 2000). This revision was sparked by a widespread concern that patents were being issued on very small segments of genetic material where the utility was unknown. While the USPTO directed its inquiry to the utility question, several commenters took issue with the more fundamental question of whether human genes should be patent eligible subject matter at all under Section 101. For example, members of the National Advisory Council for Human Genome Research of the NIH argued that allowing patents on genes, including utilities not demonstrated in the patent, would stifle scientific discovery and commercial application (National Advisory Council for Human Genome Research 2000). The National Breast Cancer Coalition wrote that "scientists

should have free access to the raw fundamental data on the human genome," because such "unencumbered access would benefit the public by providing the greatest opportunity for scientific advancements against diseases" (Nat'l Breast Cancer Coalition 2000, p. 77). Others opposed gene patents on the basis that genes are discoveries rather than inventions and therefore not eligible for patent protection, or that genes are a fundamental aspect of humanity (American College of Medical Genetics 2000; Association for Molecular Pathology 2000; Scherer 2000). Some suggested that the scope of DNA patent claims be limited to specific uses and not include claims over the DNA itself. Still others suggested that the USPTO should seek guidance from Congress on the matter.

Despite significant opposition to DNA patenting, the USPTO solidified its policy to issue gene patents through the publication of its revised utility examination guidelines in 2001, stating that an "isolated and purified DNA molecule that has the same sequence as a naturally occurring gene," including a gene excised from a natural chromosome, is patentable subject matter (USPTO 2001, p. 1092). The USPTO's justification? "[A]n excised gene is eligible for a patent as a composition of matter or as an article of manufacture because that DNA molecule does not occur in that isolated form in nature" (USPTO 2001, p. 1093). The USPTO saw no reason to distinguish genes from other chemicals and further argued that when chemicals (including DNA) are patented, "progress is promoted because the original inventor has the possibility to recoup research costs, because others are motivated to invent around the original patent, and because a new chemical is made available as a basis for future research" (USPTO 2001, pp. 1094–5). The USPTO did require that at least "one specific, substantial, and credible utility" be demonstrated before a DNA molecule could be patented, thus responding to concerns that small DNA fragments, including expressed sequence tags (ESTs),[3] were being patented where the utility had not yet been ascertained or substantiated.

Thus, by 2001, the USPTO had established in no uncertain terms that it would grant patents on segments of naturally occurring DNA that had simply been isolated from a human cell so long as one utility—such as a correlation with a disease—had been established. In 2005, scholars estimated that this policy had resulted in explicit claims over 4,382 of the 23,688 protein-coding human genes—18.5% of human genes (Jensen 2005). These claims were contained in 4270 patents owned by 1156 different assignees, with roughly 63% assigned to private firms (Jensen 2005). At least 3000 of the patented genes were controlled by a single entity, while the remaining genes involved multiple assignees.

3. Expressed sequence tags are small stretches of DNA within a coding region of a gene. They can be used to identify full-length genes as well as for gene mapping.

2.2. BRCA1 and BRCA2 Patents

In the 1930s and 1940s, scientists began documenting unusually high rates of breast cancer in certain families, leading them to suspect that cancer susceptibility may be hereditary (Davies and White 1995, p. 81). However, it was not until decades later that scientists had acquired sufficient tools and knowledge about the human genome to allow them to begin to systematically search for a gene or genes that might be linked to this hereditary risk (Davies 1995, p. 88). By the late 1980's, researchers around the world were looking for the genetic basis of breast and ovarian cancer (Williams-Jones 2002, p. 131). In 1990, a team led by Mary-Claire King announced that they had identified the long arm of chromosome 17 as the site of a gene associated with increased risk for breast cancer, dubbed BRCA1. In August 1994, Mark Skolnick and researchers at Myriad Genetics, University of Utah, NIH, and McGill University sequenced that gene. Skolnick's research was backed by $5 million in federal funding, as well as funding from Eli Lilly (Williams-Jones 2002, p. 131).

Myriad first filed patents on BRCA1 in the U.S. in 1995, and by 1998, patents with broad claims over the gene itself had been issued. NIH filed a competing application, which it ultimately withdrew after two of its researchers were named on the Myriad patent. OncorMed, another company doing research on BRCA1, did obtain a competing patent (Patent No. 5,654,155; Murray 1999) for a non-mutated BRCA1 allele describing a DNA sequence more likely to be found in the population than the wildtype sequence described in the Myriad patent. Myriad and OncorMed subsequently filed suit against each other, cases that were settled when Myriad acquired OncorMed's patents (Williams-Jones 2002, pp. 132–3).

Myriad first filed applications relating to BRCA2 in 1996, which were approved in 1998. These patents were accompanied by additional controversy, because Myriad's application had been filed the day before the BRCA2 sequence was to be published in *Nature* by the UK consortium led by Michael Stratton at the Institute for Cancer Research and the Sanger Centre (Williams-Jones 2002, p. 133). Although both the Myriad Genetics and Stratton groups claimed priority in isolating the BRCA2 gene, a citation network analysis demonstrated that the scientific community tends to believe that the Stratton group was first to map and sequence it.[4]

4. Declaration of Shobita Parthasarathy. 2009, ¶¶12–13. *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp. 2d 181 (2009).

3. What Was Patented?

The term "gene patent" has been used to refer to a wide range of different patent claims. A single gene can have multiple patents. And a single patent can have dozens of claims. The most controversial claims fall in two categories: composition of matter claims to "isolated DNA," and claims to methods for identifying a sequence or the existence of a mutation. The controversy around gene patenting has centered primarily on composition claims on isolated, but otherwise unaltered, human genomic DNA, because these claims have the effect of covering any and all uses of the isolated DNA molecule.

In the Myriad litigation, nine of the challenged claims were *composition of matter* claims on "isolated" BRCA1 and BRCA2 DNA.[5] These claims covered DNA coding for the BRCA1 and BRCA2 proteins, DNA with the wild-type nucleotide sequence, DNA with as few as 15 of the nucleotides of the BRCA1 gene, DNA coding for naturally occurring mutated forms of the BRCA2 protein, and DNA molecules with specified, naturally occurring mutations. For example, one of the challenged claims to isolated DNA was as follows: "An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO. 2" (where SEQ ID NO. 2 lays out the wild-type sequence). Because virtually any use of the gene requires that it be isolated—namely, excised from the cell, as defined by the USPTO and in the patents—the claim has the effect of covering *any and all uses* of the BRCA1 gene—i.e., DNA coding for a BRCA1 polypeptide. In addition, many different DNA sequences, or combinations of nucleotides, can code for the same polypeptide. As such, with this claim and others, Myriad has patented not just one version of the BRCA1 gene that it may have initially sequenced, but *every possible version* of the gene that exists in the US population.

Five of the claims challenged in *AMP* were *method* claims, where the purported method involves comparing or analyzing two genetic sequences for the purpose of determining whether a mutation exists.[6] For example, claim 1 of Patent '857 stated: "A method for identifying a mutant BRCA2 nucleotide sequence in a suspected mutant BRCA2 allele which comprises comparing the nucleotide sequence of the suspected mutant BRCA2 allele

5. The claims included: claims 1, 2, 5, 6, and 7 of Patent 5,747,282; claims 1, 6, 7 of Patent 5,837,492; claim 1 of Patent 5,693,473.

6. The claims included: claim 1 of Patent 5,709,999; claim 1 of Patent 5,710,001; claim 1 of Patent 5,753,441; claims 1 and 2 of Patent 6,033,857. There was also a sixth method claim that was challenged, claim 20 of Patent '282, involving comparing the rate of growth of a host cell in the presence of a possible cancer therapeutic to the rate of growth of the cell in the absence of the possible cancer therapeutic.

with the wild-type BRCA2 nucleotide sequence, wherein a difference between the suspected mutant and the wild-type sequence identifies a mutant BRCA2 nucleotide sequence." With this claim, Myriad patented any process by which one genetic sequence—such as that of a patient—is compared with the normal, or wild-type sequence. No tools or steps are specified; a person could violate the claim simply by mentally comparing two given sequences.

4. The Impacts of Gene Patents on Innovation, Clinical Practice, and Patient Care, and Research

4.1. Patents and Progress

> *The Congress shall have the power…To promote the Progress of Science and the useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.* (United States Constitution, Article I, Section 8, Clause 8)

The Constitution made clear that patent protection should serve to further scientific advancement. Also implicit in this clause is the notion that, without patent protection, such progress might not occur. Individuals might not want to disclose or pursue such inventions, for example, because of concerns that others might copy their ideas and reap the benefits (the so-called free rider problem). By rewarding an inventor with an exclusive right to market or use his or her innovation for a period of time (e.g., 20 years), the patent system helps stimulate innovation by providing inventors and their investors with the assurance that they will benefit from their invention.

While it may be true that the patent system serves to foster progress overall, it is not the case that strong patent protection in a given arena *necessarily* stimulates innovation. Joseph E. Stiglitz, Nobel Prize-winning economist and former Chief Economist of the World Bank, explains that there are two fundamental inefficiencies with the patent system that can work to impede innovation. First, the system of rewarding an inventor with an exclusive right to use his or her innovation results in *restricting the use of knowledge*.[7] There are always social costs associated with this restriction, since knowledge is a "public good"— one that is non-excludable and non-rivalrous in consumption (everyone potentially can benefit from it, and there is no extra cost associated with an additional person gaining those benefits). Second, the patent system grants temporary *monopoly power,*

7. Declaration of Joseph E. Stiglitz. 2009, ¶11, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F. Supp. 2d 181 (2009).

which can lead to inequities as well as major distortions of resource allocations.[8] The social costs of these distortions and inefficiencies can outweigh the benefits of disclosure, especially in cases where patents granted are overly broad or improperly awarded on basic knowledge or natural laws or phenomena.

Gene patenting is a classic—if not extreme—example where social costs clearly outweigh benefits. First, the problem of *restricting knowledge* is especially pronounced when patents are issued on isolated DNA. Sir John Sulston, a Nobel Prize winning scientist who played a central role in the human genome project, describes genes as "the most fundamental information about humanity."[9] Our DNA embodies a linear genetic code consisting of four nucleic acids – adenine (A), thymine (T), cytosine (C), and guanine (G)—that gets copied more or less faithfully from one generation to the next.[10] The ordering of this sequence encodes for the generation of our proteins and the development and functioning of our cells. Because DNA, unlike other chemicals, is first and foremost an informational molecule, patents on DNA are essentially patents on information. This is true regardless of whether the DNA is in a so-called "isolated" state or not. As Sulston explains, "'Isolating and purifying' a gene is simply copying it into another format. It's like taking a hardback book written by someone else, publishing it in paperback and then claiming authorship because the binding is different."[11]

The social costs of granting *monopoly power* on genes are also high. A gene patent holder is given exclusive rights over all uses of that gene. This may include preventing individuals from having their gene tested (regardless of method), preventing scientists from developing diagnostic tests or therapeutics involving that gene, controlling access to information about that gene, eliminating all competition for any commercial applications, and laying claims to future discoveries that others make about that gene, such as the finding of additional disease-relevant mutations.

At the same time, the public gets little, if anything, in return for the granting of a patent on a gene. The disclosure of information—in this case, the publishing of the sequence of the gene—is something that occurs frequently in the public domain and that likely would occur in short order regardless of whatever incentive is provided by the patent.[12] There

8. Declaration of Joseph E. Stiglitz. 2009, ¶11, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F. Supp. 2d 181 (2009).

9. Declaration of John E. Sulston. 2009, ¶10, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

10. Declaration of Joseph E. Stiglitz. 2009, ¶13, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F. Supp. 2d 181 (2009).

11. Declaration of John E. Sulston. 2009, ¶26, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

12. Declaration of Fiona E. Murray. 2010, ¶¶7–20, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2010).

is in fact considerable evidence that patent protection is not necessary for encouraging gene discoveries or the advent of genetic tests, and in fact, may even serve to stifle data sharing, research and development in biomedicine. As described below, gene patents have served to undermine clinical diagnostic testing and patient care and impede research and data sharing.

4.2. Impacts of Gene Patents on Clinical Diagnostic Testing

> *The Committee…found no cases in which possession of exclusive rights was necessary for the development of a genetic test…Furthermore, exclusive rights do not result in faster test development…The Committee {also} found that patents on genes and associations threaten the development of new and promising testing technologies.* (Secretary's Advisory Committee on Genetics, Health and Society, April 2010)

Gene patent proponents argue that patent protection is necessary to ensure the development of molecular diagnostic tests. However, most of the new clinical DNA tests that have been developed each year have not concerned patented genes. Moreover, genetic tests were on the market for BRCA-related breast cancer, as well as hearing loss, Spinocerebellar ataxia (SCA), Long QT Syndrome, Canavan disease, and hemochromatosis *before* patents were awarded and the relevant patent holder started to offer testing.[13] Rather than allowing broad availability of testing, patent holders in these instances used their exclusive rights to shut down or prevent clinical laboratories from offering testing.

Several laboratories in the United States were offering BRCA testing at the time that Myriad was awarded its patents. One by one, Myriad worked to shut down testing at each of these sites. OncorMed, a medium-sized start-up biotechnology company, had been highly involved in BRCA gene discovery research, and developed its testing services based on its own patents and licenses related to the BRCA genes. In 1998, after a series

13. In the case of hemochromatosis, a survey found that, while awareness of the patent appeared to inhibit the adoption by clinical laboratories, patents were not necessary for rapid introduction of the test (Declaration of Mildred Cho. 2009, ¶¶20–21, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009)). Laboratories began immediately offering clinical genetic tests for hemochromatosis after the discovery of the gene in August 1996. The mean time from publication to adoption was 14 months, and 60% reported introducing the test before the first patent was issued in January 1998 (Declaration of Mildred Cho. 2009, ¶21, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009)).

of lawsuits that settled out of court, Myriad bought OncorMed's patents and testing services for an undisclosed sum.[14]

Arupa Ganguly, a professor in the Department of Genetics at the Hospital of the University of Pennsylvania and the Director of the University of Pennsylvania Genetic Diagnostic Laboratory (GDL) offered comprehensive screening of the BRCA1 and BRCA2 genes for both research and clinical purposes. Starting in May 1998, Dr. Ganguly, her colleague Dr. Haig Kazazian, and the University of Pennsylvania general counsel received a series of letters from Myriad Genetics and their lawyers that asserted that Myriad's BRCA patents covered, among other things, "composition of matter covering the BRCA1 gene [and] any fragments of the BRCA1 gene" and "the BRCA1 gene sequence, mutations in the BRCA1 gene, [...] and methods for detecting alterations in the BRCA1 sequence." The letters stated that their testing activities were infringing their patents and demanded that they "cease all infringing activity."[15] Dr. Ganguly had also been providing BRCA testing at relatively low cost for a research project sponsored by the National Cancer Institute (NCI) that involved 8 cancer centers across the United States. Myriad sent a letter to NCI that made clear that a license was required for any third-party laboratory to offer such testing. Georgetown University, one of the 8 centers participating in the study, received a letter from Myriad in 1999, demanding that Georgetown no longer send genetic samples, because such activity, in their opinion, infringed Myriad's BRCA patents. As a result of these letters, Dr. Ganguly felt she had no choice but to cease all BRCA1 and BRCA2 testing, whether for research or clinical purposes, and to entirely abandon this area of research.

Cease and desist letters were sent by Myriad to other laboratories and university researchers. A survey of U.S. laboratory directors conducted in 2003 revealed that nine labs reported that they had stopped performing tests for BRCA1 and BRCA2 (Cho et al. 2003). Dr. Harry Ostrer, who was then Director of both the Human Genetics Program and Molecular Genetics Laboratory at the NYU Langone Medical Center, received a letter from Myriad in 1998 stating, "I understand that you are either currently providing diagnostic testing services for BRCA1 or are interested in initiating such a service." The letter made clear that such testing would violate Myriad's patents on the BRCA genes and offered Dr. Ostrer an extremely limited license to do single mutation tests and mutation panels of up to only 4 mutations for patients of Ashkenazi Jewish descent. Dr. Ostrer

14. Declaration of Shobita Parthasarathy. 2009, ¶¶22, 24, 27, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

15. Declaration of Arupa Ganguly. 2009, ¶¶2–7, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

chose not to enter into the licensing arrangement because it would not have allowed him to do full BRCA1/2 genetic testing.

Myriad is not the only patent holder that used its exclusive rights over genes to stop laboratories from offering genetic testing. Similar actions were taken by patent holders in regards to genetic tests associated with hearing loss, Alzheimer's disease,[16] Long QT Syndrome,[17] Canavan disease,[18] asthma, and Hemochromatosis.[19] A scientific survey of laboratory directors in the United States revealed that 25% had stopped performing a clinical test that they had developed and were offering because of a gene patent or license, and that 53% had decided not to develop or perform a test for clinical or research purposes because of a patent.[20]

Different labs may utilize different methodologies for performing genetic tests, and interpretation of the results of those tests can be subjective. Where

16. Athena Diagnostics has intermittently used its exclusive rights to various hearing loss and Alzheimer's disease genes to stop laboratories from offering testing. (Secretary's Advisory Committee on Genetics, Health, and Society [SACGHS] 2010, p. 21).

17. Patent enforcement with regards to Long QT Syndrome (LQTS) meant that no genetic test was made available at all for some period of time (SACGHS 2010, pp. 3–4). LQTS is a disorder of the heart's electrical system characterized by irregular heart rhythms that accounts for a small but significant fraction of sudden death in young children. The genetics of the disorder are complex: 9 molecular subtypes have been identified involving mutations along 12 genes. Genetic testing is critical for determining the subtype and, respectively, the most appropriate therapy for the disorder. For example, beta blockers are effective therapy for some subtypes, but can actually trigger arrhythmias in patients with other subtypes. DNA Sciences held an exclusive license for genetic testing for several genes associated with LQTS, but rather than developing a test, the company used patent enforcement to prevent another company, GeneDX, from offering a test. As a result, no testing for LQTS was offered for a 2-year period. At least one patient died during this time at the age of 10 because her LQTS went undiagnosed.

18. Miami Children's Hospital enforced its patent on the Canavan disease gene, resulting in laboratories stopping testing or paying a royalty fee to continue performing testing (SACGHS 2010, H-6).

19. A study of the impacts of patenting and licensing on genetic testing for hemochromatosis, a common condition affecting 1 in 200 to 1 in 300 people of Northern European descent and with a carrier frequency of up to 1 in 10, found that 26% of labs had not developed and were not performing the test, and 4% had stopped performing the test, with 30 out of 36 of those labs citing patents as a reason (SACGHS 2010, E-12-E-13).

20. Declaration of Mildred Cho. 2009, ¶¶11–15, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009). Gene patents may have especially discouraging effects on the development of genetic tests for rare hereditary disorders. As the President of Gene Dx explains, a company focused on the development of genetic tests for rare hereditary disorders. The company president explained, "[G]ene patents have a severe negative impact on the development, and thus the availability, of genetic testing for rare disorders […] I can assure the committee that any gene on which there is patent protection falls to the very bottom of my quite extensive list of genetic tests in which my company is interested" (SACGHS 2010, p. 30).

only one lab runs a genetic test, that lab may be less likely to identify errors in its testing method or analysis. Proficiency testing and sample exchange programs are other aspects of quality control that are jeopardized.[21] Moreover, where a test is developed by a single patent holder, a lack of competition means that there is little incentive for that entity to invest in updating a genetic test or ensuring its accuracy or that it reflects the best available science.

Myriad's monopoly on BRCA testing in the United States allowed it to dictate how these genes should be tested and whether and how new information should be incorporated into its testing system. In 2001, researchers at the Institut Curie in France announced that they had found large cancer-causing rearrangements in the BRCA1 gene that were not included as part of Myriad's test offerings. Myriad initially refused to acknowledge that its test was incomplete. At least one lab inquired with Myriad as to whether they could perform testing for these large rearrangements, but Myriad refused.[22] A 2006 study found that approximately 12% of women from high risk families with breast cancer had likely received false negative test results from Myriad as a result of its failure to test for these additional rearrangements (Walsh et al. 2006). It was only after several years and significant pressure from the scientific community that the company added methods to detect these structural mutations. But rather than incorporating the test into its existing system, Myriad chose to market the test as a separate test ("BRCA Analysis Rearrangement Testing" or BART), at an additional cost of $700 for most patients. Myriad maintained this separate testing regime even after the National Comprehensive Cancer Network issued guidelines recommending that all patients who are advised to obtain genetic testing, and who are not yet aware of a familial mutation, receive large rearrangement testing (Nat'l Comprehensive Cancer Network 2012). Several lab directors have stated that they would reflexively conduct large rearrangement testing in cases where a negative result is received through full sequencing.[23] Some have also stated they would use newer testing methods (such as microarray analysis) that are expected to result in improved testing quality and efficiency.

21. Declaration of David Ledbetter. 2009, ¶23, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

22. Declaration of Ellen Matloff. 2009, ¶¶6–7, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

23. Declaration of David Ledbetter. 2009, ¶¶17–8, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009); Declaration of Wendy Chung. 2009, ¶18. *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, "Declaration of Wendy Chung," 702 F.Supp.2d 181 (2009); Declaration of Harry Ostrer. 2009, ¶9, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

4.3. Impacts of Gene Patents on Patient Care

> *How do I explain to a patient that someone prevents me from looking at and characterizing a segment of her genome? The patient no longer has the ability to control her own body and the testing that can be done. How do I explain that I am not allowed by law to provide a test based on a part of her genome, a test that both the patient and her physician are asking me to perform, and that is necessary for diagnosis?* (Leonard 2002, p. 1388)

Genetic testing can provide vital information to a patient. Not only might it inform a patient of her risk for a hereditary disease or condition, but more and more, genetic testing can be used to determine appropriate preventive care or treatment options. In the case of BRCA testing, research has shown that a woman who tests positive for a BRCA mutation can reduce her risk of cancer through physical activity and avoiding obesity. Some women opt for prophylactic mastectomy or oophorectomy, major life-altering surgeries that can dramatically reduce their risk of cancer. For women who have been diagnosed with cancer, recent studies have shown that certain forms of chemotherapy may be more effective in targeting BRCA-mutated cells.[24]

Patients faced with these critical decisions need timely, reliable information about their genetic status. Gene patents have interfered with a patient's access to testing in a number of ways. First, because these patents allowed the patent holder to prevent other laboratories from offering testing, patients were in some cases not able to obtain confirmatory testing from another laboratory in the event of either a negative or positive test result (SACGHS 2010, pp. 43–4). Confirmatory testing is an integral part of patient care. In the case of a breast cancer patient's care, BRCA testing could only be performed once and by only one lab in the country, unlike most any other test, such as examining tumors to determine cancer type and imaging to determine the spread of cancer.[25]

Second, testing by only one lab in the country can place artificial, unnecessary limitations on how and when information is shared with patients. Dr. Wendy Chung, a professor at Columbia University, is co-investigator of the Breast Cancer Family Registry, a study funded by the National Cancer Institute that examines genetic and environmental factors influencing cancer susceptibility and clinical outcomes in high risk individuals.[26] As part of

24. Declaration of Susan M. Love. 2009, ¶11, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

25. Declaration of Susan M. Love. 2009, ¶¶12–19, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

26. Declaration of Wendy Chung. 2009, ¶¶9–14, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

this study, Dr. Chung provides genetic counseling for patients in the study and her lab performs sequencing of the BRCA genes. Chung feels she has an ethical responsibility to inform her patients of their BRCA status, but the patents forbade her from doing so. As a result, for those patients who opt to learn their BRCA status (approximately 300 per year; a process that takes 2–3 weeks), Chung was forced to send their samples to Myriad Genetics for testing, even while her own lab could have provided testing on site within 48 hours. This difference in time can be highly significant for a woman who may be making critical decisions regarding her course of treatment or care, for example, where she is scheduled to undergo a lumpectomy and would like to know her BRCA status to determine whether to opt instead for a full mastectomy.

Third, patents on genes have allowed the cost of genetic testing to be at the whim of the patent holder or exclusive provider of the test. As of August 2013, Myriad charged $3,340 for its BRACAnalysis test, and an additional $700 for its large rearrangement test ("Myriad raises price of BRCA testing, again" [Yale 2010]). The cost has proven out of reach for many women who either did not have insurance, whose insurance did not cover the cost of the test, or whose insurance had been unable to enter into a contract with Myriad. Only 130 million of America's 308 million people are covered for Myriad's testing.[27] Myriad operates a program to help cover the cost of testing for some indigent women, but the program only applies to women who have an income that is lower than $12,000 per year, who have already been diagnosed with cancer, and who are uninsured.[28] While access is an issue for many medical services, it is generally the case that competition drives down costs of services. Moreover, in the specific case of BRCA testing, several clinical geneticists stated that, were it not for the threat of patent infringement, they would be in a position to offer testing at a lower rate or on a sliding cost scale.[29]

Fourth, gene patents may have prevented patients from obtaining a more comprehensive assessment of their genetic risk. For example, several multiplex testing technologies have been developed that allow for simultaneous

27. Declaration of William E. Rusconi. 2009, ¶4, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

28. Declaration of Ellen Matloff. 2009, ¶12. *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

29. Declaration of Haig H. Kazazian. 2009,¶8, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009); Declaration of Ellen Matloff. 2009, ¶¶12, 14, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009); Declaration of Harry Ostrer. 2009, ¶8, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009); Declaration of Elsa Reich. 2009, ¶¶6, 8, 13. *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

testing of multiple genetic markers with a single test that would be more efficient than conducting a series of individual tests. These multiplex assays are more efficient than traditional testing methods and are essential for investigating complex diseases such as cancer and autism, where multiple genes are thought to play a causative role. However, the thicket of intellectual property rights that resulted from patent claims on isolated genes prevented labs from reporting out information that relates to areas of arrays where patented genes lie.[30] This means that patients may have remained undiagnosed or been presented with an incomplete analysis of their genetic risk for a given condition. A 2010 study by Dr. Mary-Claire King established that testing of 21 genes associated with breast and ovarian cancer could be conducted accurately and efficiently, providing a more personalized assessment of cancer risk than is currently offered through Myriad's testing of only 2 genes (Walsh et al. 2010). Recently, the University of Washington drew on this study to begin offering the BROCA test, which screens 40 genes for hereditary breast and ovarian cancer risk (University of Washington 2013). BRCA1 and BRCA2 were included in this clinical test only after the Supreme Court ruled to invalidate Myriad's patent claims.

Finally, where only one lab performs a genetic test, a single company dictates the standards of patient care for that testing. This includes not only what test is offered and when and under what circumstances it is updated to reflect new information or improved technology, as discussed above, but also important contextual issues such as the appropriateness of genetic counseling and whether testing will be made available through a physician or directly to the consumer. As Shobita Parthasarathy describes, by shutting down all other major BRCA testing providers in the late 1990s, Myriad came to dictate the standards for patient care in breast cancer genetic testing (Parthasarathy 2007). Other models that existed prior to Myriad's assertion of its patents that had included more comprehensive care, genetic counseling, and an emphasis on research are no longer available to women and were replaced with a single model for breast cancer genetic testing.[31]

30. At least two cases have been reported to date where a laboratory, utilizing multiplex testing methods, was forced to mask test results from patients in order to avoid violating a gene patent. (SACGHS 2010, p. 41). See also Sulston Declaration 2009 ¶38, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009); Ledbetter Declaration 2009 ¶24, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

31. Declaration of Shobita Parthasarathy. 2009, ¶¶29–31, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

4.4. Effects of Gene Patents on Research

> *A strict interpretation of our results suggests that follow-on genetic researchers forego about one in ten research projects {…} through the causal negative impact of a gene patent grant.* (Huang 2009, 1214)

Gene patent proponents have argued that patent protection is necessary for obtaining capital investment for initial gene discovery. However, available evidence shows the opposite: unlike other discoveries such as chemical compounds that have pharmaceutical potential and require lengthy and expensive further development in order to become commercially available, patents on genes do not appear to be necessary to create incentives for initial discoveries or for the development of commercial applications, including diagnostics. A study of gene patents issued in the United States showed that two-thirds were for discoveries funded by the U.S. government (Schissel et al. 1999). The discovery of the BRCA genes arose out of a context of increasing international scientific, medical and public interest in breast cancer. The National Institutes of Health (NIH) contributed approximately one-third of the funding toward the discovery of BRCA1, funded a six-person research team to find the BRCA genes, and provided approximately $2 million in research grants to the University of Utah for this research.[32] In addition to the government, disease advocacy groups often contribute to and drive the discovery of genes.[33]

Staunch defenders of gene patents have also argued that the basic tenet of the patent system to require disclosure of the invention serves to promote follow-on research post initial gene discovery.[34] However, a rigorous probing of this question indicated that rather than promoting research, gene patents have an inhibitory effect on future knowledge production. Specifically, the study, conducted by Fiona Murray and Kenneth Huang at MIT, examined more than 1,000 gene discoveries and found that follow-on genetic researchers forego approximately one in ten research projects because of

32. Declaration of Shobita Parthasarathy. 2009, ¶18, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

33. As the Executive Director of the Claire Altman Heine Foundation, an organization focused on the prevention of spinal muscular atrophy (SMA), explains: "In the case of SMA, the patent holder did not even bear the financial burden of the discovery, rather an advocacy group and patients and families suffering from the disease donated funds and tissue samples to a researcher who then patented her discovery and sold it" (SACGHS 2010, p. 25).

34. For example, the Biotechnology Industry Organization (BIO) has stated that "the patent system inherently operates to disseminate rather than sequester knowledge" (BIO 2013, p. 22. Biotechnology Industry Organization. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.* "Brief for Amicus Curiae the Biotechnology Industry Organization in Support of Respondents," No. 12-398 (2013)).

the causal impact of gene patents.[35] Moreover, this trend was found to be exacerbated in situations when patents are broad in scope, privately owned, or where the patented genes are closely linked to human disease, and especially cancer. In applying these results to the patents held by Myriad, Murray estimated that the patents on BRCA1 and BRCA2 have negatively impacted the accumulation of public knowledge of these genes by between 5 and 10%.[36]

Myriad responded to criticism of the effect of gene patents on research by noting that it does not object to research and that more than 18,000 scientists have researched the *BRCA* genes, publishing more than 5,600 research papers on *BRCA1* and over 3,000 research papers on *BRCA2.* The problem with this argument is that these numbers refer to research papers that include any reference to the genes, whether or not sequencing was actually performed,[37] and tell us nothing about how many papers *would* have been published had the genes not been patented. Moreover, the patents gave Myriad the power to define "research," thereby allowing it to shut down labs that did not meet its criteria.[38]

Surveys have also revealed that many practitioners believe their research has been negatively impacted by patents on genes. In a survey of clinical laboratory directors conducted by Mildred Cho et al., 85% of respondents stated that gene patents have resulted in less sharing of information among researchers. In the same study, 67% of respondents believed that patents

35. The researchers examined the influence of gene patenting on the long-run supply of public knowledge by examining 1279 human gene patent-paper pairs: cases where a gene discovery is both published in an academic journal and patented. In such cases, there is typically a three- to four-year lag between the publication of a paper on a gene sequence and the issuance of a patent disclosing the sequence of that gene. During that lag period, the not-yet patented information is essentially part of the public knowledge stream. Once a patent is granted, the patent owner may legally provide, restrict, or prohibit access to any researcher seeking to build upon the patentee's contribution. The researchers compared the difference in gene patent paper citations in the pre- and post-grant period for those affected by the patent grant to the same difference for unaffected gene paper citations. The results of their study found that the negative impact of patent grant on the future public knowledge production, as measured by the annual rate of forward citations to the paired paper, was 17%. A more stringent interpretation of the results showed a 5% decline in the expected rate of citations. This more stringent interpretation suggests that follow-on genetic researchers forego approximately one in ten research projects because of the causal impact of the gene patent grant. (Declaration of Fiona E. Murray. 2010, ¶¶7–19, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2010).

36. Declaration of Fiona E. Murray. 2010, ¶¶5, 20, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2010).

37. Supplemental Declaration of Ellen Matloff. 2010, ¶¶4–11, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2010).

38. Declaration of Arupa Ganguly. 2009, ¶13, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

have resulted in a decreased ability to do research (Cho et al. 2003). Virtually none (less than 1%) of the respondents believed that patents had resulted in more sharing of information among researchers, and only 3% were of the view that patents had resulted in an increased ability to do research. A second study concluded by the American Society of Human Genetics reported that 46% of respondents believed that gene patents delayed or limited their research (Rabino 2001).

When a single entity holds a monopoly on genes, others are not able to do independent genetic testing for research purposes. University research laboratories are arguably in a better position to investigate the thousands of BRCA variants of unknown significance to determine their association with cancer than is Myriad. As Harry Ostrer stated, "By not being able to do independent BRCA1/2 genetic testing and analysis, the ability to determine the meaning of these unknown variants is stymied and at the whim of Myriad's corporate interests. It may very well not be in the financial interests of Myriad to do further research on variants of unknown significance from smaller or underrepresented population groups, like racial minorities, and thus such research would not happen at all unless another lab—and in particular an academic lab like mine—has the opportunity to do so."[39]

4.5. Effects of Gene Patents on Data Sharing

> *All human genomic sequence information should be freely available and in the public domain in order to encourage research and development and to maximize its benefit to society.* (The Bermuda Principles 1996).

The pace of scientific innovation is fundamentally dependent on the degree to which ideas, knowledge and data can be freely exchanged and are widely disseminated. Many geneticists recognized from the launching of the Human Genome Project in 1990 that a key to its ultimate success was keeping the genome freely available to all. In 1996, a group of 50 leading scientists involved in genetic sequencing met in Bermuda and committed to a group of principles for the sharing of genetic data. These included a commitment to release data within 24 hours of its collection by depositing it into a public database and to not take out patents on it. Even some private companies, such as the pharmaceutical company Merck, agreed with the sentiment that the human genome should remain in the public domain.[40]

39. Declaration of Harry Ostrer. 2009, ¶12, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

40. In 1994, Merck funded a massive drive to generate sequences and place them into the public domain (Declaration of John E. Sulston. 2009, ¶¶22, 29, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009)).

Unfortunately, others, including Myriad, chose to seek and vigorously enforce patents on genetic findings in ways that inhibited data sharing. Since 1995, laboratories from around the world have submitted data to the Breast Cancer Information Core (BIC), an on-line central repository for information regarding mutations and polymorphisms in the BRCA genes. BIC is a critical resource for aiding the international scientific community in identifying deleterious mutations and determining the meaning of variants of uncertain significance (VUS), which are genetic variants whose clinical significance is unknown. The value of the BIC is tied to the amount and quality of data provided by the scientific community. Developing an understanding of a particular VUS requires a large dataset that can best be obtained by pooling data from multiple labs.

According to Elizabeth Swisher, a professor at the University of Washington School of Medicine and member of the BIC steering committee since 2004, for several years, Myriad submitted mutation and variant data to the BIC. Because Myriad controlled clinical testing of the BRCA genes in the United States, and because more testing occurs in the U.S. than any other country, Myriad was the largest contributor of data to the BIC. However, beginning sometime in 2006, Myriad started withholding its data (Pollack 2011). Because of the sheer amount of data that Myriad—and only Myriad—was in a position to collect, once it stopped contributing data, the BIC became a far less useful tool for the international community. As Swisher explains, while researchers do not have a formal obligation to contribute variant data to the BIC, "each laboratory has an incentive to do so in order to benefit from the data contributed by others and to further scientific progress. This incentive evaporates when one laboratory controls most of the data about a gene."[41]

5. The Legal Case against Patents on Human Genes

Despite longstanding and widespread public controversy over the issuance of patents on isolated DNA, the USPTO's policy of granting gene patents was never tested in the courts prior to the *AMP* case. On May 12, 2009, the ACLU, together with Public Patent Foundation filed its case in the Southern District of New York on behalf of twenty plaintiffs, including four national scientific organizations, geneticists, genetic counselors, women's health groups, and patients. The geneticists and medical professional organizations, such as the lead plaintiff Association for Molecular Pathology, brought the case because they and their members had the capability and desire to conduct BRCA genetic testing but could not do so due to the patents.[42] The other

41. Declaration of Elizabeth Swisher. 2009, ¶20, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (2009).

42. Complaint 2010, pp. 3–13, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, "Complaint," 702 F.Supp.2d 181 (2010; Park 2014).

plaintiffs, such as the patients, sought access to genetic testing other than that offered by Myriad. At the time of the filing of the lawsuit, breast cancer patients Lisbeth Ceriani and Patrice Fortune were not able to obtain BRCA testing through Myriad because Myriad had not entered into a contract with their insurance programs.[43] Vicky Thomason, an ovarian cancer survivor, and Kathleen Raker, whose mother and grandmother died of breast cancer, were advised to obtain large rearrangement testing but could not afford the additional price charged by Myriad.[44] Breast cancer survivor Genae Girard's request for confirmatory BRCA testing was thwarted when she learned that Myriad was the only lab in the U.S. to offer testing. And Runi Limary, an Asian-American woman diagnosed with breast cancer in her late 20's, sought further testing and research after she was told that she had a BRCA variant of uncertain significance.[45] The case challenged Myriad's patents on two legal grounds—invalidity under Section 101 of the Patent Act and the U.S. Constitution.

5.1. Patent Ineligibility of Claims to Isolated DNA

> *Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.*[46]

Plaintiffs' main legal challenge to the isolated DNA patents relied on Section 101 of the Patent Act. For decades, Section 101 was viewed by the Patent Office and patent bar as largely irrelevant in analyzing whether a patent is valid. After 1980, patent attorneys relied on the Supreme Court's decision in *Diamond v. Chakrabarty* to argue that patents could be obtained on "anything under the sun made by man" (*Diamond v. Chakrabarty* 1980, p. 309), including genes that had simply been removed from the cell. Plaintiffs scrutinized and looked beyond this simplistic rendition of Section 101.

From its earliest cases, the Supreme Court recognized that section 101 of the Patent Act places inherent limits on patent eligibility. This recognition was driven by a concern that patents could intrude on the "storehouse of

43. Complaint 2010, pp. 10, 12, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, "Complaint," 702 F.Supp.2d 181 (2010).

44. Complaint 2010, pp. 11, 13, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, "Complaint," 702 F.Supp.2d 181 (2010).

45. Complaint 2010, p. 11, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, "Complaint," 702 F.Supp.2d 181 (2010).

46. U.S. Code, Title 35, Part II, Chapter 10, §101.

knowledge of all men" (*Funk Bros. Seed Co. v. Kalo Co.* 1948, p. 130). Thus, while the scope of what is patentable is broad, "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work" (*Mayo* 2012, p. 1293). Accordingly, mere discoveries do not automatically merit a patent even where they are extremely useful, new, or required much effort or resources. "Thus, a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity. Such discoveries are 'manifestations of […] nature, free to all men and reserved exclusively to none" (*Diamond v. Chakrabarty* 1980, p. 309).

Plaintiffs drew on principles laid out by the Supreme Court in precedent going back 150 years, including decisions in *Mayo*, *Diamond*, *Funk Brothers*, and *American Fruit Growers*, to make the legal case for the patent-ineligibility of isolated DNA. Plaintiffs relied on these seminal cases, which lay out the key clues to applying section 101, to argue that compositions of matter are not patent-eligible unless they: (1) have markedly different characteristics from any found in nature; (2) are based on an inventive concept; and (3) do not foreclose use of an underlying product or law of nature.

5.2. Isolated DNA Does Not Have Markedly Different Characteristics from Any Found in Nature

First, Plaintiffs argued that legal precedent forbids patents on a composition of matter unless it has markedly different characteristics from any found in nature. In *Diamond v. Chakrabarty* (1980), the Court recognized the patentability of a genetically engineered bacterium capable of breaking down crude oil. The Court considered whether the claimed product had "a distinctive name, character [and] use" and "markedly different characteristics from any found in nature" (*Diamond v. Chakrabarty* 1980, pp. 309–10). Comparing the unpatentable combination of bacteria in *Funk Brothers* with the genetically-engineered *Chakrabarty* bacterium, the Court concluded that unlike the *Funk* combination, the latter has "markedly different characteristics from any found in nature" and that its "discovery is not nature's handiwork" (*Diamond v. Chakrabarty* 1980, p. 310).

> The combination of species produces no new bacteria, no change in the six species of bacteria, and no enlargement of the range of their utility. Each species has the same effect it always had. The bacteria perform in their natural way. Their use in combination does not improve in any way their natural functioning. They serve the ends nature originally provided and act quite independently of any effort of the patentee.

> Here, by contrast, 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 section 101. (*Funk Bros.* 1948, p. 131 quoted in *Diamond v. Chakrabarty* 1980, p. 310)

The *Diamond v. Chakrabarty* Court contrasted this bacterium to the bacteria at issue in the 1948 case of *Funk Brothers*. There, the patent was on a combination of six strains of bacteria that together allowed plants to more efficiently fix nitrogen from the air without mutually inhibiting each other (*Funk Bros.* 1948). Although the six bacteria strains did not exist together in nature, and although the patent holder had "isolated" and mixed the strains, the Court held that the product was not patent eligible because the patent holder did "not create a state of inhibition or of non-inhibition in the bacteria" (*Funk Bros.* 1948, p. 130). "Discovery of the fact that certain strains of each species of these bacteria can be mixed without harmful effect to the properties of either is a discovery of their qualities of non-inhibition. It is no more than the discovery of some of the handiwork of nature and hence is not patentable" (*Funk Bros.* 1948, p. 131).

The focus on the differences between the natural thing and the subject of the patent was also the mode of analysis in the early case of *American Fruit Growers, Inc. v. Brogdex Co.* There, the Court similarly rejected the patenting of a fruit that had been treated with mold-resistant borax (*American Fruit Growers, Inc. v. Brogdex Co.* 1931). Although the "complete article is not found in nature," and despite the "treatment, labor and manipulation" that produced the fruit, the Court held that it did not become an "article of manufacture" unless it "possesses a new or distinctive form, quality, or property" distinct from nature (*American Fruit Growers, Inc. v. Brogdex Co.* 1931, pp. 11–12).

Based on this precedent, Plaintiffs argued that isolated DNA does not have markedly different characteristics from any found in nature. Just as the fruit and the aggregation of bacteria strains were found to be natural phenomena, so too is isolated DNA. DNA, unlike other chemicals, stores and conveys specific information—as dictated by the order of nucleotides—that serves as the blueprint for all of the proteins, cells, and organs that make up the human body. While chemical molecules like water can be described as H_2O, HOH, or OH_2 because they consist of any two hydrogen atoms and an oxygen atom, DNA is not described according to the sugars and phosphates of its backbone, but by the ordering of its nucleotide sequence. Because this blueprint is the defining characteristic of DNA and remains the same before and after isolation, isolated DNA has neither a distinctive

name, character, nor use from naturally occurring DNA nor markedly different characteristics. Both are DNA, their chemical structures are not markedly different, the protein coded for by each is the same, and their use in storing and transmitting information about a person's heredity is identical. Isolated DNA contains all the genetic information necessary to transmit a trait. It is useful because the sequence—the result of "nature's handiwork"— informs the medical professional about how the gene operates in one's body. If isolated DNA had markedly different characteristics from DNA in the body, or if it were different in name, character, and use, it would be of no diagnostic value to medical professionals.

5.3. Isolated DNA Is Not Based on an Inventive Concept

Second, Plaintiffs argued that Myriad's patents were not based on an inventive concept. Key to the Supreme Court's Section 101 analysis has been whether the thing can truly be considered an invention or a product of nature. "'[T]he relevant distinction' for purposes of §101 is not 'between living and inanimate things, but between products of nature, whether living or not, and human-made inventions'." In *Mayo*, the Court asked, does the patent claim arise from an "'inventive concept', sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself?" (*Mayo* 2012, p. 1294). Does it "add enough" or "simply append conventional steps, specified at a high level of generality, to laws of nature [or] natural phenomena"? (*Mayo* 2012, p. 1300). The Court invalidated Prometheus' patents on methods of ascertaining the efficacy of a drug used to treat autoimmune disorders, concluding that nothing of significance was added to the law of nature—the relationship between certain metabolite levels and drug efficacy in a patient (*Mayo* 2012, p. 1297). The Federal Circuit had upheld the patents because the method included administering the drug to a patient and determining the resulting metabolite levels—both steps that it found created a "transformation" that brought the claim within the realm of human invention (*Prometheus Laboratories v. Mayo Collaborative Servs.* 2009, p. 1346). However, the Supreme Court dismissed the trivial nature of these "transformations" (*Mayo* 2012, p. 1303). The steps of administering a drug and determining metabolite levels were routine, conventional science (*Mayo* 2012, pp. 1297–8). The only addition in the patent claim was the identification by Prometheus of the metabolite levels that indicate drug efficacy (*Mayo* 2012, pp. 1297–8). The claims simply "inform a relevant audience about certain laws of nature."

Plaintiffs relied on *Mayo*'s logic to contend that isolated DNA was not based on an inventive concept. The process of isolation was discovered long before Myriad identified the genes, and was considered routine, conventional

science even at that time. Myriad's claims simply informed the scientific community about the naturally occurring sequence of the BRCA1 and BRCA2 genes. Moreover, while Myriad's patents laid claim to any use of every person's BRCA1 and BRCA2 genes, its patents disclosed the sequences of only a few of the millions of possible sequences that actually exist in the human population as a result of human variability.

5.4. Patents on Isolated DNA Preempt Use of People's Genetic Information—a Product and Law of Nature

Third, Plaintiffs drew on the Supreme Court's decisions in *Mayo*, *Funk Brothers*, and other cases to emphasize that patents are invalid if they preempt all use of a product or law of nature. In *Mayo*, the Court explained that a key aspect of the Section 101 analysis turns on whether the patent preempts use of a law or product of nature. Does the patent "risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries […] relative to the contribution of the inventor?" (*Mayo* 2012, pp. 1294, 1303). Ultimately, the Court was troubled that Prometheus could prevent others, such as Mayo, from using the relationship between metabolite levels and drug efficacy—a law of nature—to further refine testing. The patents "foreclosed more future invention than the underlying discovery could reasonably justify" (*Mayo* 2012, p. 1302). Similarly in *Funk Bros.*, the Court struck down patents that would give the patentee a monopoly on a natural phenomenon. The Court said that qualities of the bacteria, "like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. They are manifestations of laws of nature, free to all men and reserved exclusively to none" (*Funk Bros.* 1948, p. 130)[47]

Plaintiffs reasoned that claims on isolated DNA preempt use of a product of nature. The patent claims themselves define isolated DNA according to naturally occurring biological qualities—namely, that it codes for a naturally occurring polypeptide or has a naturally occurring nucleotide sequence. Because DNA is also a blueprint for the cell, claims on "isolated DNA" preempt a law of nature—a piece of the genetic code. That code is determined by biology; Myriad did not invent the length, composition, or

47. Other cases similarly discuss this concern. In *Bilski v. Kappos* (2010), the Court disapproved of patents because "[a]llowing petitioners to patent risk hedging would preempt use of this approach in all fields, and would effectively grant a monopoly over an abstract idea" (*Bilski v. Kappos* 2010, p. 3231). And in *O'Reilly v. Morse* (1853), the Court stated the patentee's claim on any machinery or process using electric current to mark characters at a distance "shuts the door against inventions of other person […]. " (*O'Reilly v. Morse* 1853, p. 113).

function of the BRCA1 or BRCA2 genes. And because isolation is required to study or use the genes, the claims preempted all scientific access to them. These claims prevented others from isolating the patented gene, and determining its sequence of nucleotides, for every person in the United States. Thus, patents on isolated DNA set up exclusive rights over a segment of each person's genetic code, blocking the law of nature consisting of the DNA sequence and its blueprint for the operation of human cells.

5.5. Complementary DNA (cDNA)

Although Myriad did not assert in the district court or the Federal Circuit that any of the challenged claims was limited to cDNA, the patent-eligibility of cDNA became an issue in the case. The US government raised the issue in its briefing, as did the Federal Circuit.

cDNA, or complementary DNA, consists of the nucleotide bases that make up DNA. cDNA is made in the laboratory when naturally occurring mRNA, using the natural processes of the cell, acts as the template to create the complementary DNA. Because mRNA naturally does not include any regions that do not code for protein, the corresponding cDNA also does not include these regions. Thus, cDNA is identical to the underlying DNA except that the non-coding regions have been removed.

Plaintiffs argued that cDNA, when based on naturally occurring DNA and mRNA, is not patent-eligible under Section 101. Plaintiffs contended that cDNA does not have markedly different characteristics from any found in nature, because its sequence is dictated by naturally occurring DNA and mRNA. Both DNA and cDNA have similar functions: they both encode for the same protein. Plaintiffs also asserted there was no inventive concept with claims on cDNA that are based on naturally occurring DNA and mRNA. Myriad did not invent the process of making cDNA, and the fact that cDNA is made in a laboratory cannot alone satisfy the inventiveness inquiry. Presumably, the fruit at issue in *American Fruit Growers* was not treated while still on the tree, or the bacteria of *Funk Brothers* isolated and aggregated in their natural habitat. Lastly, cDNA is a basic scientific tool that serves as the bases for much genetic research. Many genetic engineering experiments involve producing and tinkering with cDNA. While any resulting genetically modified molecules could be patent-eligible, patenting the underlying cDNA itself preempts this type of innovation.

5.6. The Patent-Ineligibility of Claims on Comparing DNA Sequences

Plaintiffs also argued that a number of claims on generic methods for comparing two genetic sequences are invalid under Section 101. Myriad had asserted these claims when sending cease-and-desist letters to other

laboratories. These claims are significant because they covered comparing genetic sequences regardless of whether one had actually performed the isolation or sequencing of the genes. They thereby interfered with scientific activities beyond direct uses of the isolated DNA.

Over the years, the Supreme Court consistently has applied section 101 to invalidate method claims that seek to monopolize abstract ideas or laws of nature. In *Mayo*, the Court relied on the reasoning of *Bilski* (*Bilski v. Kappos* 2010, pp. 3229–31; *Gottschalk v. Benson*[48]; *Parker v. Flook*[49]; *Diamond v. Diehr* 1981) to invalidate a method claim, concluding that the method monopolized a law of nature (*Mayo* 2012, p. 1297). In these cases, The Court stated that limiting the application of an idea to a particular field, or adding insignificant steps, is insufficient to permit patents on what would otherwise be unpatentable (*Mayo* 2012, p. 1298).

Plaintiffs cited this precedent to assert that the challenged method claims in *AMP* patent an abstract idea and law of nature. Five of these claims involve the comparing or analyzing of two genetic sequences (Patent No. 5,809,999, Claim 1; Patent No. 5,710,001; Patent No. 5,753,441; Patent No. 6,033,857, Claims 1, 2). Claim 1 of Patent '857 states:

> A method for identifying a mutant BRCA2 nucleotide sequence in a suspected mutant BRCA2 allele which comprises comparing the nucleotide sequence of the suspected mutant BRCA2 allele with the wild-type BRCA2 nucleotide sequence, wherein a difference between the suspected mutant and the wild-type sequence identifies a mutant BRCA2 nucleotide sequence.

The idea here—the comparing of one sequence to a reference wild-type sequence to identify differences or mutations—is applied to BRCA2 sequences. But as the Supreme Court has instructed, limiting the application of an idea to a specific situation is insufficient. "*Flook* rejected '[t]he notion that post-solution activity, no matter how conventional or obvious in itself, can transform an unpatentable principle into a patentable process.' [...] *Flook* stands for the proposition that the prohibition against patenting abstract ideas 'cannot be circumvented by attempting to limit the use of the formula to a

48. In *Gottschalk v. Benson*, the Supreme Court invalidated a patent on a method of programming a digital computer, finding that the patent in essence was on a mathematical algorithm (*Gottschalk v. Benson* 1972, pp. 71–2).

49. In *Parker v. Flook* (1978), the Supreme Court invalidated a patent on a method for updating alarm limits during the catalytic chemical conversion of hydrocarbons, often performed in oil refining. The Court concluded that the patent claimed an algorithm, even though the method included steps for adjusting the alarm limit following the application of the algorithm, noting that the addition of post-solution activity could not transform an unpatentable principle into a patentable process (*Parker v. Flook* 1978, pp. 590–95).

particular technological environment' or adding 'insignificant postsolution activity'" (*Bilski v. Kappos* 2010). *Mayo* further clarified that the addition of routine, conventional scientific steps do not create a patent-eligible invention, and trivial transformation cannot trump the law of nature doctrine (*Mayo* 2012).

Plaintiffs pointed to the Supreme Court precedent to establish that the method claims clearly cover a phenomenon of nature—whether two BRCA sequences are different or the same. Most of the method claims cover *any comparison* of two BRCA1/2 sequences for *any purpose*, including comparisons to determine predisposition to other diseases like prostate and pancreatic cancers.[50] Furthermore, claim 2 of Patent '857 covers comparing a BRCA2 sequence from a sample with the wild-type sequence, wherein any alteration indicates a predisposition to breast cancer, and further illustrates how the claim preempts use of a law of nature. The claim does not specify which alterations are covered and makes the scientifically incorrect assumption that any alteration indicates cancer predisposition. Thus, a scientist who wants to identify which alterations in fact indicate a breast cancer predisposition will run afoul of the patent claim as soon as he or she compares two gene sequences and considers the significance of an alteration.

Plaintiffs further contended that the challenged claims could be violated by mental processes or "mere inspection" (*Prometheus Laboratories* 2009, p. 1347; *Mayo* 2010). One can do a side-by-side comparison of two given sequences by visual scan or use a simple program[51], or another algorithm. Nothing in the claims precludes the use of one or more of these methods. Moreover, the claims would cover the "comparing" of the BRCA section of a patient's entire genomic sequence with the reference sequence, even though the geneticist doing the comparing had not performed the underlying sequencing or ever "isolated" the DNA, and even though Myriad did not offer whole genome sequencing. These claims, analyzed in their entirety, are directed at noting differences between two sequences, a mental process analogous to what occurs in the "wherein" clauses of Prometheus' claim (*Mayo* 2012). Moreover, even if the claims included isolating and/or sequencing steps, they would still be vulnerable under *Mayo* because those steps are routine, conventional science and simply "pick out the group of individuals likely interested in applying the law of nature" (*Mayo* 2010, pp. 1297–1298, 1303).

50. *See Gottschalk v. Benson*, 1972, 409 U. S. pp. 63, 67, 72 (observing that "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts" are not patentable because they "wholly preempt" the public's access to the "basic tools of scientific and technological work").

51. *See* Basic Local Alignment Search, http://blast.ncbi.nlm.nih.gov/Blast.cgi.

5.7. The Question of USPTO Deference and Industry Reliance

In bringing the case, Plaintiffs faced a major hurdle: the position of the U.S. Patent and Trademark Office, which approved thousands of patents on isolated DNA and issued guidelines concluding it is patent-eligible (USPTO 2001, p. 1093). This practice resulted in thousands of gene patents, held and relied upon by many different entities. Plaintiffs argued against deferring to the Patent Office by pointing to the law rejecting any such deference, the weak legal basis for the Patent Office's position, and the arguments adopted by the U.S. government in the litigation.

First, as a legal matter, the courts have not deferred to the USPTO's interpretations of the substantive standards set out by the Patent Act (*Arnold P'ship v. Dudas* 2004, p. 1340). Instead, Congress created a presumption of validity for issued patents.[52] Forty percent of patents, once challenged in the courts, have been found invalid, demonstrating that this presumption is often overcome and that the respect afforded to the USPTO is far from absolute.[53]

Skepticism about USPTO patent grants is also warranted in light of its historical practice. In 1984, just as it was beginning to issue patents relating to DNA molecules—such as recombinant DNA vectors—following the *Chakrabarty* decision, it also issued patents that claimed genes directly, without even the superficial limitation of isolation or purification.[54] By granting patents on genes themselves, the USPTO clearly violated the bounds of section 101 and the unanimous consensus that genes are not patentable.

Moreover, Plaintiffs pointed out that the legal reasoning behind the USPTO's position was weak. In issuing its guidelines on gene patents, the USPTO cited two authorities (USPTO 2001, pp. 1092–3). It first pointed to the patent that had been granted to Louis Pasteur on purified yeast. The Pasteur patents, however, were never enforced and were later acknowledged to be invalid under *American Fruit Growers* by Pasquale J. Federico, later the Commissioner of Patents and the principal drafter of the 1952 Patent Act (Federico 1937). Secondly, the USPTO relied on Learned Hand's 1911

52. U.S. Code, Title 35, Part III, Chapter 29, §282. http://www.law.cornell.edu/uscode/text/35/282 (accessed 27 April 2014)

53. Institute for Intellectual Property & Information Law 2011, University of Houston Law Center, Patstats. org, Full Calendar Year 2011 Report, http://www. patstats. org/2011_Full_ Year_Report. html (indicating that 37% of all patents challenged on obviousness grounds were held invalid). See also Paul F. Morgan and Bruce Stoner 2004 (citing USPTO statistics showing that 74% of patents previously issued by the Patent Office later challenged through the reexamination process were either canceled or changed by the USPTO, meaning their original approval was undeserved).

54. For example, Patent No. 4,472,502 dated September 18, 1984, claimed: "A DNA sequence encoding a polypeptide having ability to convert L-malate into L-lactate, said sequence being derived from Lactobacillus and having a length of about 5 kbp or less." This gene was useful because it controls malolactic fermentation, a natural process for wine-making.

Parke-Davis decision and its statement that "even if [the adrenaline] were merely an extracted product without change, there is no rule that such products are not patentable" (*Parke-Davis & Co. v. H. K. Mulford Co.* 1911) The statement was made in dicta, but in any case has clearly been superceded by the Supreme Court's ruling in cases like *Mayo*, *Chakrabarty*, *Funk Brothers*, and *American Fruit Growers*, discussed above.

Indeed, the USPTO was not the only agency with relevant expertise on the issue of whether genes should be patented. The United States, in its amicus brief, rightly noted that the issue of subject matter eligibility of isolated DNA turns on questions that implicate the expertise and responsibilities of a wide array of federal agencies and components, including the USPTO, the National Institutes of Health, the Antitrust Division of the Department of Justice, the Centers for Disease Control and Prevention, the Office of Science and Technology Policy, and the National Economic Council, among others.[55] The USPTO should not dictate the patent-eligibility of genes when other agencies have at least as much insight into whether isolated DNA is markedly different from DNA in the body, whether isolated DNA is truly a human-made invention, and whether patents on isolated DNA would interfere with the storehouse of knowledge.

Finally, Plaintiffs argued that industry reliance alone cannot save otherwise invalid patents. The Supreme Court made clear in its prior findings that the Section 101 threshold is not impacted by the interests of industry or the longstanding existence of certain patents. In *Mayo*, the Court discussed the arguments made by Prometheus and others that industry relied upon and needed these types of patents, patents that had been issued for many years by the USPTO.[56] It found that the Section 101 question must be decided independent of such concerns (*Mayo* 2012, p. 1293). In *Mayo*, as in *Bilski*, the Court's rulings to invalidate the patents affected a large number of other current patents, but this impact did not sway the Court. And the Supreme Court, in recognizing the patent eligibility of the *Chakrabarty* bacterium, reversed the USPTO's policy of refusing to grant patents on living organisms (*Diamond v. Chakrabarty* 1980, p. 318). No deference to the USPTO was warranted in the Court's view.

5.8. Constitutional Arguments

In deciding to bring a challenge to gene patents, the ACLU was particularly motivated by constitutional concerns. Gene patents raise interrelated

55. "Brief for the United States as Amicus Curiae in Support of Neither Party," *Ass'n. for Molecular Pathology v. U. S. Patent and Trademark Office*, 653 F. 3d 1329 (2010).

56. Biotechnology Industry Organization. 2013. "Brief for Amicus Curiae the Biotechnology Industry Organization in Support of Respondents," No. 12-398 (2013).

constitutional issues under the Patent Clause and the First Amendment. The ACLU's investigation into the problems raised by gene patents led to the creation of the ACLU's first policy statement on the proper function of the patent system within our constitutional framework, as well as the first patent lawsuit ever filed by the ACLU. Plaintiffs argued that gene patents violate the constitutional limitations placed on patents by each of these provisions because they do not promote the progress of science and useful arts and instead impede scientific inquiry and create monopolies on information and knowledge.

The legal structure of intellectual property is created by Article I, section 8, clause 8, which covers copyright and patents: Congress has the power "[t]o promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries" (U.S. Constitution, article I, §8, clause 8). Implicit in this provision is the recognition that before monopolies—in the form of patents —can be approved, they must further progress. Supreme Court Justices have recognized this limitation. In *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, Justice Breyer wrote: "[S]ometimes *too much* patent protection can impede rather than 'promote the Progress of Science and useful Arts'" (*Lab. Corp.* 2006, pp. 126–7). Justice Douglas wrote at length about the relationship between the Constitution, the progress of science and patenting:

> It is worth emphasis that every patent case involving validity presents a question which requires reference to a standard written into the Constitution. Article I, s 8, contains a grant to the Congress of the power to permit patents to be issued. But unlike most of the specific powers which Congress is given, that grant is qualified. The Congress does not have free reign, for example, to decide that patents should be easily or freely given. The Congress acts under the restraint imposed by the statement of purpose in Article I, s 8. The purpose is "To promote the Progress of Science and useful Arts." The means for achievement of that end is the grant for a limited time to inventors of the exclusive right to their inventions. (*A. & P. Tea Co.* 1950, p. 154–5)

He stressed: "The standard of patentability is a constitutional standard; and the question of validity of a patent is a question of law" (*A. & P. Tea Co.* 1950, p. 156).

Plaintiffs also invoked the First Amendment as relevant to the constitutional inquiry when examining gene patents. Like other legislative powers conferred by Article I, the power to award copyrights and patents is limited by the First Amendment.

In copyright, where the potential conflict between the First Amendment and intellectual property is more obvious, the Supreme Court has suggested that the First Amendment requires certain doctrines, like the idea/expression distinction, to be incorporated into statute (*Harper & Row Publishers, Inc.* 1985, p. 556; *Eldred* 2003, p. 219; *Salinger* 2009, p. 255; *Maxtone-Graham* 1986, p. 1435; Lee 2013, pp. 9–10). There can be little doubt that patenting of abstract ideas or an entire body of knowledge would violate the First Amendment (*Ashcroft* 2002, p. 253; *Palko* 1937, pp. 326–7; *Reidel* 1971, pp. 355–6; Lee 2013, pp. 28–9). Foundational to the First Amendment is the right to scientific inquiry (Francione 1987, pp. 428–9; Robertson 1977, pp. 1217–18; *Griswold* 1965, p. 1482; *Epperson* 1968, pp. 100–101).

Plaintiffs pointed to these constitutional limitations to oppose the method claims challenged in the case as covering pure thought. None of the method claims specified a particular process for comparing or analyzing gene sequences or testing therapeutics. Instead, they simply instructed that one sequence from a sample should be compared to another, typically the wild-type sequence, without stating how the comparison should be carried out. The only instructive part of these claims is that at the end, the medical professional notes whether these two sequences are the same, different, or different in a way that may be correlated with cancer risk. In other words, Myriad patented a thought, not an inventive process. Plaintiffs argued that because these claims exclude others from considering the significance of differences in the sequences and whether a particular variant is correlated with cancer, or any other disease, they violate both the First Amendment and Article I.

Plaintiffs further asserted that the isolated DNA claims violate Article I and the First Amendment. The doctrine that prevents the patenting of natural phenomena, abstract ideas, and products and laws of nature is partially premised on the observation that it is impossible to invent around those things; as such, patenting them would not advance the useful arts. For a typical downstream invention, such as a carburetor, once the patent is published, others can try to build a better carburetor using different materials or methods. Yet, once a human gene is patented, nobody can invent a new gene that encodes for the protein as it does in the body. And beyond acting as a barrier to an individual's sequence information, these patent claims prohibit the accumulation of knowledge regarding the functioning of a certain gene at a population level. Rather than leading to a greater understanding or a better product, isolated DNA claims exclude others from further work with these genes and thus give entire control over a body of knowledge to the patent holder.

6. Court Rulings

In March 2010, U. S. District Judge Robert Sweet of the Southern District of New York granted plaintiffs' motion and denied Myriad's motion for

summary judgment, concluding that none of the claims survived section 101 (*Ass'n for Molecular Pathology v. US Patent and Trademark Office* 2010, p. 238).[57] He emphasized the informational nature of DNA, and concluded that the challenged composition claims covered products and laws of nature, as isolated DNA embodies the same genetic code as DNA in the body. He further found that the challenged methods covered abstract ideas. Judge Sweet carefully considered the evidence regarding whether these patents impede the progress of science, ultimately stating that these questions could not be resolved on summary judgment (*Ass'n for Molecular Pathology* 2010, p. 220). Because he had invalidated all of the claims under the Patent Act, Judge Sweet dismissed without prejudice the constitutional claims against the USPTO (*Ass'n for Molecular Pathology* 2010, pp. 237–8).

Myriad appealed to the U.S. Court of Appeals for the Federal Circuit. In a significant move, the United States filed an amicus brief at this stage, arguing that isolated DNA is not patent-eligible. The government thus took a position directly opposing its own Patent Office. The Solicitor General stated: "We couldn't write a brief that allowed the patentability of isolated DNA, for to do so would be to make lithium patentable, uranium, coal from the earth, and a whole variety of other substances […]. It was just impossible to do given the Supreme Court's clear guidance " (Katyal 2011).

In July 2011, the Federal Circuit issued a split decision, reversing in part the District Court's opinion. The Federal Circuit unanimously upheld Judge Sweet's ruling as to the majority of the method claims,[58] concluding there was no transformation that could render the claims patent eligible (*Ass'n for Molecular Pathology* 2011, p. 1329). This ruling was not appealed by Myriad, and thus remains binding precedent as to those claims. However, two of the three judges—Judges Lourie and Moore—upheld the patents on "isolated DNA." Judge Lourie focused on what he perceived to be chemically different about isolated DNA, finding that because covalent bonds are broken when DNA is isolated, isolated DNA is a patent-eligible composition (*Ass'n for Molecular Pathology* 2011, pp. 1348–54, 1357). Judge Moore made additional arguments, holding that DNA segments as short as 15 nucleotides are patent-eligible because they can be used as primers and probes in the process of genetic testing (*Ass'n for Molecular Pathology* 2011, pp. 1362–65). She expressed doubt about the patent eligibility of isolated full-length genes but

57. This was Judge Sweet's second ruling in the case. He had previously denied defendants' motions to dismiss, which primarily argued that plaintiffs lacked legal standing to bring the case (*Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office* 2009).

58. The Federal Circuit did uphold one method claim invalidated by Judge Sweet, claim 20 of patent '282.

nonetheless held that the patents were valid because industry had relied on USPTO practice for many years (*Ass'n for Molecular Pathology* 2011, p. 1367). Judge Bryson dissented, noting that "Myriad is claiming the genes themselves, which appear in nature on the chromosomes of living human beings" (*Ass'n for Molecular Pathology* 2011, p. 1375). All three judges agreed that cDNA, or complementary DNA, is patent-eligible under Section 101, although Judge Bryson specifically found that claim 6 of Patent '282, which he considered to be claiming cDNA, was not valid because it also claimed genomic DNA. (*Ass'n for Molecular Pathology* 2011, pp. 1378–79).

Plaintiffs sought review by the Supreme Court. While the petition was pending, the Supreme Court issued a decision in *Mayo v. Prometheus*, where it unanimously invalidated method claims for assessing a patient's reaction to a drug because they covered laws of nature. It then vacated the Federal Circuit's decision and ordered further consideration in light of *Mayo*. However, upon remand, the divided Federal Circuit issued decisions echoing its first rulings, with the majority suggesting that *Mayo* had little impact on *AMP* (*Ass'n for Molecular Pathology* 2012). The plaintiffs filed a second petition with the Supreme Court, and the Court granted the petition to review this question: Are human genes patentable?

On June 13, 2013, a unanimous Supreme Court answered with a resounding "no": A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated. Moreover, "Myriad did not create anything. To be sure, it found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention" (*Ass'n for Molecular Pathology* 2013, p. 2117). The "isolation" of the genes did not create an invention, because what Myriad had patented was the "genetic information encoded in the BRCA1 and BRCA2 genes" (*Ass'n for Molecular Pathology* 2013, p. 2118). "[I]ts claim is concerned primarily with the information contained in the genetic *sequence*, not with the specific chemical composition of a particular molecule" (*Ass'n for Molecular Pathology* 2013, p. 2118). Moreover, "the processes used by Myriad to isolate DNA were well understood by geneticists at the time of Myriad's patents 'were well understood, widely used, and fairly uniform insofar as any scientist engaged in the search for a gene would likely have utilized a similar approach'" [sic] (*Ass'n for Molecular Pathology* 2013, pp. 2119–20).

The Court also ruled that cDNA is not a product of nature, with an important caveat: "except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA. In that situation, a short strand of cDNA may be indistinguishable from natural DNA." (*Ass'n for Molecular Pathology* 2013, 2119). The Court stated that it was not expressing an opinion on whether patents on cDNA satisfy other statutory requirements of patentability, citing to possible grounds of invalidity including

sections 102, 103, and 112 of the Patent Act (*Ass'n for Molecular Pathology* 2013, 2119 n. 9).

The Supreme Court agreed with the Plaintiffs that it owed no deference to the USPTO. The Court noted that Congress had never endorsed the USPTO's view on gene patents, and that the United States as *amicus curiae* not only disagreed with the USPTO's position but also had argued that "the USPTO's practice was not 'a sufficient reason to hold that isolated DNA is patent-eligible'" (*Ass'n for Molecular Pathology* 2013, p. 2119). The Court further rejected Myriad's arguments that the patents should be upheld to avoid disturbing the reliance interests of patent holders (*Ass'n for Molecular Pathology* 2013, p. 2119 n7).

None of the courts ruled on the merits of the Plaintiffs' constitutional arguments. Judge Sweet dismissed the constitutional claims against the USPTO based on the doctrine of constitutional avoidance (*Ass'n for Molecular Pathology* 2010, pp. 237–8). Because he ruled in Plaintiffs' favor in invalidating all of the challenged patent claims, he declined to decide the constitutional questions that were raised. Plaintiffs continued to raise the First Amendment argument against the University of Utah defendants throughout the litigation; however, neither the Federal Circuit nor Supreme Court addressed it. Yet, it is clear that the invalidation of the isolated DNA claims by the Supreme Court and of the screening method claims by the Federal Circuit pursuant to Section 101 was rooted in a fundamental objection to allowing patent claims that would dictate access to genetic information and abstract thought, thereby impeding scientific progress and controlling scientific inquiry.

7. Conclusion: Implications and Lessons Learned

The implications of the Court's decision are vast: for one, as a result of the ruling, Myriad will no longer maintain a legal monopoly over any use of the BRCA1 and BRCA2 genes, nor should it be able to dictate the standard of care and extent of testing for these genes. The impacts of the ruling for breast cancer predisposition testing were demonstrated almost immediately after the decision was issued: within 24 hours, at least 5 labs announced that they would begin offering testing for the BRCA1 and BRCA2 genes (Pollack 2013). Some of the labs promised to offer testing at a lower price than Myriad's. The University of Washington announced that it would take steps to immediately add BRCA1 and BRCA2 to the multi-gene panel offered by its lab in order to provide a more personalized assessment of cancer risk than is currently offered through Myriad's testing program. Currently several labs provide BRCA testing, including two of the largest—LabCorp and Quest Diagnostics.

The Court's decision reaches far beyond Myriad, of course. The decision rightly invalidates all existing claims to naturally occurring DNA sequences and should prevent future claims of this sort to be granted.[59] More broadly, the Court's finding reaffirms the vitality of section 101. Along with *American Fruit Growers*, *Funk Brothers*, and *Chakrabarty*, the ruling reestablishes, consistent with precedent, that something is not a patent eligible composition simply because it is removed from its natural environment or commercially useful, or required intensive work and resources. It clarifies that *Chakrabarty* did not bestow blanket section 101 approval on all compositions related to biotechnology but only on those that are markedly different from their naturally occurring form. And it recognizes that some things, in order to promote the progress of science, must be free to all to use.

Coupled with *Mayo*, *AMP* legally prohibits patents that interfere with using products and laws of nature for basic scientific work and clears away the patent thicket that previously impeded laboratories from engaging in genetic testing. Under the two decisions, patent claims on isolated DNA as well as routine methods for comparing genes or identifying mutations are clearly invalid under Section 101. To hold otherwise would be "to permit patent claims to tie up too much use of laws of nature" (*Mayo* 2012, p. 1302).

While any fair application of the Court's unanimous decisions in these cases would render invalid patent claims that grant exclusive rights to examining a gene or prevent others from developing alternative testing methods, the thousands of patents of this type that were issued by the USPTO in the decades before these decisions were rendered are not automatically invalidated based on the rulings. No doubt there will continue to be litigation in this area as patentees seek to defend existing patent rights and test the limits of what is now patent-eligible with the USPTO.

Indeed, within a few weeks of the Court's decision, Myriad filed suit against two laboratories in an attempt to reassert its monopoly on BRCA testing. Each of the laboratories—Ambry Genetics and Gene by Gene—had begun or planned to offer BRCA-related testing. Myriad asserted that the labs were infringing its patents, citing claims that were not the subject of the *AMP* suit but should clearly be invalid under the Supreme Court's decisions in *Mayo* and *AMP* and the Federal Circuit's ruling in *AMP* on the method claims (American Civil Liberties Union et al. 2013). Other labs

59. Though Plaintiffs disagreed with the Court's ruling on cDNA, that aspect of the decision had little impact on the ultimate goals of the case. One does not need to use cDNA in order to conduct genetic testing, and the Court's decision made clear that the ultimate patentability of cDNA is still an unresolved question.

offering BRCA testing are also involved in the litigation. *In Re: BRCA1– and BRCA2–Based Hereditary Cancer Test Patent Litigation* 2014. It is unclear whether this latest litigation is simply a tactic by Myriad to scare off its competitors, or whether it believes in the validity of the claims it has cited. But what is clear is that the company's actions are a real disservice to patients, who deserve greater options to cancer predisposition testing than the one that Myriad has offered for the past 15 years. Moreover, the company's audacious behavior in attempting to thwart any competitors despite the Court's clear direction in this arena underscores a fundamental problem with the patent system as a whole: the public's interest is often the last interest to be served, if at all.

AMP was the first case to challenge the legality of gene patents. The case raised legal questions about the scope of Section 101 that were ripe for consideration in a new era of precision medicine, and where genetic tests are increasingly relied upon in tailoring medical treatments to individual patients. Progress in this field fundamentally depends upon the development of accurate, affordable molecular diagnostics and requires that the human genome be freely available to all. The case benefitted from the collective experiences of scientists, clinicians and patients over many years. It brought together a large and diverse coalition that together provided strong opposition to a patent policy at odds with the system's mission to promote the progress of science. The case succeeded in bringing to the forefront a more holistic understanding of how improperly issued patents can harm people and innovation by giving voice to the full range of legal and policy arguments against gene patenting. By asserting the public's interest in ending monopolies over genes and genetic information, the case reshaped the law and provided a much-needed check on entrenched patenting practices. Ultimately, the case serves as a model for future patent advocacy and reform in the public interest.

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