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Gene Patenting—The Supreme Court Finally Speaks

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Are human genes patentable? On June 13, the Supreme Court gave its long-awaited answer —a unanimous "no." The case, *Association for Molecular Pathology v. Myriad Genetics*,[1] has generated enormous interest among medical institutions, industry organizations, patient advocacy groups, and scientists. "Life's instructions," James Watson asserted in one of 49 *amicus curiae* (friend of the court) briefs, "ought not be controlled by legal monopolies created at the whim of Congress or the courts." For some, the gene patents were a symbol of a shrinking commons and an over-reaching patent system that traded too much monopolistic power for too little innovation. For others, the challenge to Myriad's gene patents amounted to an attack on the intellectual property protections that fuel private investment in biomedical discovery.

While ethical and policy arguments were a major feature of the debate surrounding the case, the decision focused squarely on the definitions of two codes: the genetic code and the patent code. All nine Justices on the Court agreed that the segments of DNA that make up human genes are not patentable subject matter under section 101 of the Patent Act because they are products of nature.[2] However, the Court held, molecules reverse-transcribed from messenger RNA to eliminate intron sequences——so-called complementary DNA, or cDNA—are patentable. The decisive sentence of Justice Thomas's ruling crisply stated, "A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring."

The decision joins a suite of recent Supreme Court cases that are reshaping patent law, with important implications for innovation in the life sciences. Here we review the *Myriad Genetics* case and the Court's reasoning, and discuss the implications for health care and the biotechnology industry. Patient advocates and industry groups alike can find something to celebrate in the Court's decision: while it will open up competition in the genetic testing arena and drive down prices, it leaves undisturbed most of the intellectual property rights on which the biotechnology industry depends.

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The Battle over Patenting Breast Cancer Genes

The human genes at issue in the *Myriad Genetics* case are *BRCA1* and *BRCA2*. Through federally funded research dating back to the 1980s, Mary-Claire King and others identified a region of chromosome 17 that must contain a gene mutated in families with many cases of breast cancer. [3] That gene became known as *BRCA1*, and it turned out to also predispose to ovarian cancer.

King's 1990 report of genetic linkage for a "breast cancer gene" set off an intense race to clone and sequence it. A team led by Mark Skolnick of the University of Utah won that race;[4] Skolnick was also a cofounder of Myriad Genetics. In 1994, Michael Stratton and others mapped another locus in chromosome 13,[5] which precipitated another furious race to identify and clone what became known as *BRCA2*. That race ended in a near-tie,[6] with the Stratton group publishing in *Nature*[7] just a day after Myriad filed a patent application,[8,9,10] having "gotten wind" of the Stratton work.[11]

At the time, Myriad successfully sought patent protection for an array of inventions: methods of analyzing genetic mutations, cDNA, and, most controversially, isolated DNA sequences (Table 1). Their patent applications on *BRCA1* and *BRCA2* were broken into separate patents, covering different aspects of the work. These patents undergirded Myriad's commercialization of its BRACAnalysis test for predisposition to breast cancer, which it first made available in 1996. Myriad filed subsequent patents and acquired rights to other *BRCA* patents by out-of-court settlements, and now states that it has 24 patents containing over 500 claims relating to this field.[12]

The American Civil Liberties Union (ACLU) and Public Patent Foundation, representing more than 20 plaintiffs, filed suit against Myriad in May 2009 in federal court for the southern district of New York. The litigation arose in large part because, in the intervening decade, a steady drumbeat of criticism had grown against Myriad's business practices and patents on genes in general. Objections raised by public health advocates included Myriad's restriction on certain uses of its genes in the context of research, its refusal to allow independent confirmatory testing of ambiguous initial results,[13] and the high price of Myriad's genetic test (up to $4,000).[14] Advances in sequencing technology had made it possible for patients to have dozens of genes sequenced for less than what Myriad charged for *BRCA1* and *BRCA2* testing.[15] Fueling advocates' arguments were surveys showing gene patents reduced access to testing[16,17] and research finding that legal restrictions on gene sequences reduced product development by up to 20–30% compared with diagnostic products arising from freely available sequences.[18]

Inventors must satisfy several statutory criteria in the Patent Act to obtain patent protection, but the *Myriad* case focused on just one: whether the claimed inventions met the basic definition of patentable subject matter. That is, did they constitute "inventions" at all? The Patent Act defines the scope of patentable subject matter as "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof."[2] The Supreme Court has previously established that "Anything under the sun that is made by man" is patent eligible,[19] but has read into the patent statute an important implicit caveat that laws of nature, natural phenomena, and abstract ideas belong in the public domain.

Judge Robert Sweet's March 2010 summary judgment order in the *Myriad* case invoked longstanding Supreme Court doctrines to conclude that this caveat excluded DNA from patentability.[20] He invalidated all 15 claims challenged in 7 of Myriad's patents. The next year, a divided panel of the Court of Appeals for the Federal Circuit (CAFC) tempered the district court's holding. The three-judge panel unanimously affirmed Judge Sweet's

determination that Myriad could not patent its method of testing for cancer risk by comparing a patient's isolated *BRCA1* and *BRCA2* sequences to the wild-type sequences. By contrast, the panel upheld Myriad's method claim for using *BRCA1/2* in screening potential cancer therapeutics and held that cDNA could be patented.

Most controversially, the CAFC split 2-1 on whether "isolated" DNA molecules corresponding to sequences found in cells were patentable.[21] The two judges in the majority reached their conclusion that isolated DNA is patent eligible in different ways. Judge Lourie reasoned that the act of severing covalent bonds in the process of isolating the DNA created a new molecule, while Judge Moore argued that not only fragmentation but also the demonstrable utility of isolated DNA sequences compared to native DNA was the basis for patent eligibility.[22] Judge Bryson wrote a vigorous dissent arguing that the manmade molecules claimed were not patent eligible because they were not "markedly different" from their natural counterparts.

The Supreme Court reviewed the CAFC's decision in 2011, but sent the case back to the CAFC for reconsideration in light of a newly issued Supreme Court decision invalidating a patent on a method of diagnostic testing.[23] The CAFC did not substantively change its decision in 2012, reiterating the same logic and coming to the same 2-1 split.[24] On November 30, 2012, the Supreme Court agreed to hear arguments on one question only: are human genes patentable?

Supreme Court Decision

To answer this question, the Supreme Court returned to the opaque and oft-contested boundary line between human inventions and discoveries of naturally occurring phenomena. Writing for a unanimous Court, Justice Clarence Thomas cited the Court's long history of drawing a distinction between compositions of matter that are manmade and those that are naturally occurring (Table 2). The relevant doctrine, however, has been "vague and malleable," in the words of Justice Felix Frankfurter.[25] Cases have lacked clarity and consistency over the last hundred years, with the criterion that inventions must involve the application of human ingenuity seemingly established in different ways.

In considering patents on DNA sequences, Justice Thomas struck a balance between the longstanding principle that discoveries of natural phenomena are not patentable and the competing notion that "all inventions at some level … apply laws of nature, natural phenomena, or abstract ideas" by drawing a line between genomic DNA and cDNA. The isolated DNA sequences were not the proper subject of patents, he wrote, because they were not "markedly different" from the sequences found in nature. Indeed, they derived their diagnostic utility from having the identical sequence. Justice Thomas distinguished Myriad's claims from those at issue in the landmark 1980 case of *Diamond v. Chakrabarty*, which ushered in the modern explosion in biotechnology patents. In that case, a bacterium was genetically engineered to contain four naturally occurring plasmids, each of which was useful in breaking down oil. The inventor inserted the plasmids into the microbe's own DNA, giving rise to an organism not found in nature. No similar transformation of a product of nature was present in Myriad's claims covering the isolated DNA sequences.

The cDNA claims, the Court held, were another matter. Because cDNA is reverse engineered by scientists from mRNA to include only the protein-coding exons, it is different from any naturally occurring genetic material. It thus falls on the invention side of the line between discovery and invention.

The parties challenging the cDNA patent claims argued that cDNA is a product of nature because it represents the naturally determined stretch of nucleotides that codes for the

mRNA. Its information is what matters, they asserted, and that is the same as naturally occurring DNA. However, the Court focused on the human ingenuity involved in reverse transcribing the sequence as a separate nucleotide array. The fact that some DNA sequences mimicking cDNA may occur by chance in nature was deemed insufficient to undercut its patentability.

Myriad represents the third in a series of decisions since 2010 in which the Supreme Court has redefined the boundaries of its three main exclusions from patentability—laws of nature, natural phenomena, and abstract ideas. In each of these categories, the Court has ultimately demonstrated a more restrictive stance on patent eligibility than the US Patent and Trademark Office or the CAFC.

The first case, *Bilski v. Kappos*, involved an abstract idea. In striking down a patent on an investment strategy, the Court announced that it supported a "high enough bar" on patenting abstract ideas that would not "put a chill on creative endeavors and dynamic change."[26] The patent was invalidated because it "would preempt use of this approach in all fields," over a vigorous dissent from Justice John Paul Stevens, who agreed with the outcome but wanted to set down an even more formal rule excluding business methods from patent eligibility.

Next in 2012 came *Mayo v Prometheus*, in which the Court unanimously invalidated patent claims on a method of adjusting dosage of thiopurine anti-inflammatory drugs based on evaluating metabolite levels.[23] In that decision, the Court expressed concern "that patent law not inhibit further discovery by improperly tying up the future use of laws of nature," which in that case was the correlation between dosages of a drug and its physiological effects.[27]

Myriad extends this judicial anxiety to the context of DNA molecule claims. In concluding that "groundbreaking, innovative, or even brilliant" discoveries of such natural phenomena are not patentable, the Court stressed the social cost: it "would 'tie up' the use of such tools and thereby inhibit future innovation premised upon them."

Implications for Health Care and Innovation

Advocacy groups have heralded the *Myriad* decision as a huge win for patients. "VICTORY!," the ACLU declared, "Our genes belong to us!"[28] The invalidation of genomic DNA claims—and the appellate court's earlier refusal to allow patents on methods of detecting *BRCA1/2* mutations—permits other companies to market their own genetic tests. Indeed, within days of the *Myriad* ruling, at least five competitors had announced that they would enter the market.[29,30]

It is possible that Myriad might respond to this new competition with further infringement litigation. Myriad's patent claims covering other methods and other "synthetic" DNA sequences such as primers and probes have not been challenged, and the Supreme Court specifically noted that they might indeed cover patentable subject matter. With the prospects for such infringement claims uncertain, however, Myriad may instead seek to capitalize on an important competitive advantage it will continue to have in the market. Having spent nearly two decades amassing a vast, proprietary library of *BRCA* gene variations while holding its monopoly on testing, Myriad is uniquely well positioned to be able to interpret rare mutations.[31]

Ultimately, the end of Myriad's monopoly should improve access to genetic testing and rapid turnaround of results by driving down price—DNATraits, for example, will charge less than $1,000—and expanding capacity for analyzing samples. When the case was brought, for example, one crucial concern was whether the claims in question blocked whole genome sequence (WGS) analysis. Myriad argued that its patents on "isolated" DNA

involved sequestering *BRCA* sequences from others in the genome and that WGS would not infringe such patents. The ACLU pointed out, however, that the plain meaning of the claims would indeed cover molecules created in doing WGS. Given the outcome of the case (and in light of Myriad's own oral arguments before the Court), institutions offering WGS should no longer fear lawsuits from parties holding patents on isolated DNA.[31] One countervailing concern from patients' perspective, however, is quality control. As genetic and pharmacogenomic tests become available from a wider diversity of laboratories, greater regulatory attention to ensure consistency and maintenance of high standards may be required.

While the *Myriad* decision places in jeopardy thousands of patent claims, its effects on biotechnology companies and innovation will probably be modest. A recent analysis estimated that as many as 3,535 unexpired patents on naturally occurring, human gene sequences may be affected,[32] although the applicability of the decision will depend on the specifics of each individual patent claim. Further, because nothing about the Supreme Court's reasoning would prevent its holding from being applied to non-human genes, several thousand patent claims relating to other organisms may also be affected, with implications for a range of applications outside human medicine. However, the same study showed that patent claims on merely "isolated" DNA were already on the decline. Since 2005, companies have sought to patent naturally occurring gene sequences much less frequently than they did in the past, perhaps because the Patent Office raised the bar for meeting another requirement for patenting an invention—showing that it has practical utility. Some companies also found it more difficult than expected to profit from these DNA sequences and abandoned their patents.[32,33,34]

Claims on DNA that has been engineered, in contrast, have been on the rise—in both frequency and scientific importance[32]—and will continue to enjoy protection following *Myriad*.[31] Synthetic DNA patents include those on vectors and engineered molecules that could be useful as therapeutics themselves (for example, in gene transfer) or in the process of making therapeutic proteins for so-called "biologic" drugs. Since these technologies remain squarely within the bounds of patentability outlined by the Supreme Court, the effects on innovation emerging from these areas should be minimal.

Finally, *Myriad* is important as an expression of strident judicial opposition to patents on methods of making medical diagnoses. Myriad's challenged method claims for detecting genetic sequence alterations were struck down unanimously by the CAFC, and the Supreme Court declined to take up the question on appeal. It will therefore be impossible for companies to mimic Myriad's business model of identifying a gene sequence and attempting to control the production of diagnostics from it. Whether this will reduce private investment in genetic diagnostics and necessitate supplemental public research funding remains to be seen.

Conclusion

The *Myriad* decision will be an important symbol for those who seek to foster scientific discovery by protecting and expanding the public domain. It also has symbolic resonance with the ideal that our common humanity cannot be owned. The Universal Declaration on the Human Genome and Human Rights declares the human genome to be "the heritage of humanity" and that "the human genome in its natural state shall not give rise to financial gains."[35] The Supreme Court quietly came to a similar conclusion, though with attention to preserving the incentives important for biomedical innovation.

It is interesting that although the Supreme Court decision concerns *human* genes, humanness had no bearing on the decision. Nor does the law allow courts to consider whether patenting human genes—or anything else—should be disallowed on grounds of morality. There is a disconnect, then, between the reasons the Supreme Court articulated for its decision and the rich set of ethical and policy concerns that have animated much of the public interest in the case.

Those powerful ideas may or may not have swayed the Court as it considered a vague and open-ended legal doctrine. If the questions raised during oral argument are any indication, however, the justices were primarily interested in innovation—both in preserving patent incentives for investing in research and the blocking effects that patent rights can have on upstream discovery. Viewed in this light, the decision represents a careful balancing act.

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Table 1

Types of Patents Issued to Myriad Genetics Relating to *BRCA* Genes

Covered Claims	Type of Patent	Clinical Utility	Current Status
Isolated DNA sequences, *BRCA1* and *BRCA2*	Composition of matter	Used in both of the above methods	Invalidated
Exon-only strands of *BRCA1* and *BRCA2* nucleotides [cDNA]	Composition of matter	Used in both of the above methods	Upheld
Method of (1) growing a transformed eukaryotic host cell containing a *BRCA1* gene in the presence of a compound that might be a cancer therapeutic and (2) comparing growth rates of cancer cells in the presence and absence of the compound	Method	Screening the effectiveness of potential cancer therapeutics	Upheld
Method of comparing a patient's isolated DNA sequence to the "wild type" *BRCA1* and *BRCA2* sequences	Method	Detecting whether a patient (or tumor sample) has mutations associated with breast or ovarian cancer	Invalidated

Table 2

Major Supreme Court Decisions Defining the Boundary between “Inventions” and “Products of Nature”

Case	Claimed Invention	Decision
American Wood-Paper Co. v. Fibre Disintegrating Co. (1874)	Refined cellulose caused by decomposition of the original substance	Not patentable, because the product is well-known to exist in nature and is in a “nearly pure” state
Cochrane v. Badische Anilin & Soda Fabrik (1884)	Artificial version of natural red dye alizarine produced by manipulating original	Not patentable, because being produced in a novel way does not make it a new composition of matter
American Fruit Growers v. Brogdex Co. (1931)	Fruit with skin treated with mold-resistant borax	Not patentable, because the mere addition of borax does not lead to the creation of a product that has a “new or distinctive form, quality, or property”
Funk Brothers Seed Co. v. Kalo Inoculant Co. (1948)	Mixture of several naturally-occurring species of bacteria	Not patentable, because aggregation of species does not produce any new bacteria or enlargement of the activity of the individual strains, and is hence only a discovery of the handiwork of nature
Diamond v. Chakrabarty (1980)	Microbe with specially-inserted DNA plasmid	Patentable, because the bacterium is not found in nature
Association for Molecular Pathology v. Myriad Genetics (2013)	Isolated BRCA1 and BRCA2 DNA sequences cDNA	Not patentable, because merely isolating a naturally occurring DNA sequence does not constitute an inventive step Patentable, because cDNA is not found in nature

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