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The History of Patenting Genetic Material

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Abstract

The US Supreme Court's recent decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.* declared, for the first time, that isolated human genes cannot be patented. Many have wondered how genes were ever the subjects of patents. The answer lies in a nuanced understanding of both legal and scientific history. Since the early twentieth century, "products of nature" were not eligible to be patented unless they were "isolated and purified" from their surrounding environment. As molecular biology advanced, and the capability to isolate genes both physically and by sequence came to fruition, researchers (and patent offices) began to apply patent-law logic to genes themselves. These patents, along with other biological patents, generated substantial social and political criticism. Myriad Genetics, a company with patents on *BRCA1* and *BRCA2*, two genes critical to assessing early-onset breast and ovarian cancer risk, and with a particularly controversial business approach, became the antagonist in an ultimately successful campaign to overturn gene patents in court. Despite Myriad's defeat, some questions concerning the rights to monopolize genetic information remain. The history leading to that defeat may be relevant to these future issues.

INTRODUCTION

Since the mid-twentieth century, biology has produced a vast and rapid increase in our understanding of the molecular mechanisms of life. During this time, the model for drug development has become one in which basic science is largely funded by governments or charitable foundations, while the application of that science takes place at research-intensive private firms. This burgeoning biological knowledge has created one new industry—biotechnology—and reinvigorated another—pharmaceuticals. These industrial developments could not exist, however, without supporting legal structures. The history of applied molecular biology, therefore, is the history of law applied to biology.

One of the most important of these areas of law has been patent law. To recoup their research and regulatory costs, drug manufacturers have typically relied on one form of legal protection—patent monopolies—that has shielded firms from competition while also allowing them to make substantial profits. And as developments in the science of biology have progressed, the objects of these patents have changed: from small, biologically active molecular compounds to complex proteins and molecules of DNA, including entire genes. This shift has led to unprecedented controversies over intellectual property in biology and, in particular, over patenting genes. That controversy, and the patents that were its subject, have now—at least in the United States—reached a surprising end with the US Supreme Court’s decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.* (10).

This article reviews and analyzes the past, present, and future of biological patenting in the United States, with an emphasis on the patenting of genes. We first provide background on patent law for those not steeped in this difficult and distinctive legal field. We then lay out the history of gene patenting from its precursors in the nineteenth century up until the *Myriad* decisions. We describe the social and political controversies concerning patents on various kinds of biological inventions, from the early 1980s through *Myriad*. Finally, we explain the *Myriad* cases in detail and their immediate context; the last part speculates about the future of gene patents and related issues. We tell what we think is a fascinating story, one chapter of a broader, rapidly developing, and yet unfinished book.

A PRIMER ON PATENT LAW

A patent—or, more specifically, a utility patent—is a legal instrument granting its owner a temporary right to exclude others from making, using, selling, offering to sell, or importing the invention it describes (41). Perhaps counterintuitively, a patent gives its owner no affirmative right to practice the invention it describes; if a single invention is covered by two different patents in the hands of two different owners, both owners are blocked from practicing the invention unless they can come to an agreement (59, 79). In addition, other laws, such as FDA drug regulation, may prevent an inventor from practicing his invention (42). This notion, that patents grant the right to exclude as opposed to use, is not rare in property law. Rather, “the right to exclude others [is] ‘one of the most essential sticks in the bundle of rights that are commonly characterized as property’” (39). And, indeed, patents are property in every sense of the word: patents can be bought, sold, assigned, licensed, mortgaged, securitized, abandoned, devised by will, or simply given away (83).

In many ways, a patent’s right to exclude functions as a government-sanctioned monopoly on a particular invention. There is almost never any requirement that a patent holder license his invention at any price or permit his invention to be used by others; he has the right to be the only game in town (70). In exchange for that monopoly, the inventor must disclose, in a written description in the patent, how to make and use the invention (2). After the patent expires—today,

twenty years from the date it was filed with the US Patent and Trademark Office (PTO)—the public may freely use the invention it describes (99). Scholars of patent law have long described this exchange as a quid pro quo: the inventor discloses his invention to the public in return for limited rights for a limited time to prohibit others from entering the invention's market (102).

Not all inventions may be patented. On the contrary, the patent statute requires that inventors prove that their inventions meet several substantive hurdles, namely novelty, utility, and nonobviousness. Novelty actually encompasses three distinct concepts, one necessary to granting a patent and two forbidding such a grant: true novelty, whether the patent applicant is the first to invent the particular invention; derivation, whether the patent applicant wrongfully derived his invention from another; and the statutory bars, whether the patent runs afoul of several statutory provisions prohibiting the patenting of inventions that have been known, used, or sold in public for more than a year (1). In addition, the patent application itself must fulfill several requirements—most significantly, enablement and written description. Enablement requires that the patent application enable a person having ordinary skill in the patent's field to make and use the invention without undue experimentation. The written description requirement requires the patent applicant to fully describe the extent of his claims—the metes and bounds of the patent (2).

Beyond these requirements, the invention one seeks to patent must be the type of invention that the statute, as interpreted by the courts, finds eligible for patent protection. This patent eligibility or patentable subject matter requirement has long been broadly interpreted by courts, giving rise to the famous 1980 dictum from the US Supreme Court that “anything under the sun that is made by man” is patentable (37). Nonetheless, laws of nature, natural phenomena, abstract ideas, and products of nature have long been deemed ineligible for patent protection, although courts have struggled mightily to give those terms concrete meaning (103).

Like other legal rights, patents do not enforce themselves; patent owners can protect their exclusive rights only by suing (or threatening to sue) those who they believe infringe their patent (4). The costs of enforcing issued patents, however, are considerable. The average patent lawsuit costs each party roughly \$2.8 million through trial, and takes two-and-a-half years to resolve. Where the patent holder has won, the median damage award has been approximately \$5 million (92). In addition, successful patent holders can enjoin infringers from using the patented invention, preventing them from, for example, manufacturing a pharmaceutical product until the infringers can come to an agreement with the patent holder (76). For those accused of patent infringement, the costs of defending patent lawsuits are often too much to bear (76).

At the same time, very few patents survive wholly intact during litigation. A defendant can challenge a patent on the ground that it is invalid—that the patent lacks either novelty or utility, is obvious, or fails to meet the law's written description or enablement requirements. Increasingly, defendants have also argued that the patented invention itself does not constitute patentable subject matter because it encompasses a natural law, product, or phenomena, or is too akin to a mere abstract idea. These invalidity defenses are successful, at least in part, in more than 46% of the cases that ultimately go to trial (76).

The high costs of litigating patent disputes, and the appearance that the majority of issued patents are nonetheless invalid, have recently put the patent system under intense scrutiny (139). At the core of these complaints is that the societal benefit of disclosing inventions in patents is not worth the costs of granting patent holders the tremendous power that comes with excluding others. More subtly, it appears that the benefits of patents vary across technological fields, even though patents are supposedly technologically neutral. In some fields, such as computer software, patents appear to hinder technological progress more than they promote it (25). In other industries, such as pharmaceutical and biotechnology development, patents appear to be vital to innovation.

The high prices that come with such monopoly power have also caused vocal condemnation from consumers and medical providers (134).

Such criticisms are not new. The patent system has come under vociferous attack in centuries past, only to have such accusations undermined by succeeding patent-heavy technological revolutions. In any case, patents are still generally the most powerful innovation incentive tools at policy makers' disposal—as they long have been—and will likely continue to be for the foreseeable future.

THE APPLICATION OF PATENT LAW TO BIOLOGY

More than other fields, biology seems to have special salience in patent law. Inventions related to biology—drugs, medical devices, living tissue, microorganisms, and recombinant proteins, for example—have long captured the public consciousness and concern. To that end, patent law concerning biology appears to have given rise to more doctrinal exceptions, statutory carve-outs, and *sui generis* laws than its sister fields (17). At the same time, industry has long argued that biology-related inventions must have patent protection for their life-saving properties to enter the stream of commerce and of medicine (96). Managing these exceptions, despite patent law's attachment to the principle of technological neutrality, has caused—and still causes—trouble for policy makers and legislators.

At the core of these troubles lies the patentable subject matter doctrine, the prohibition on patents encompassing “natural laws, phenomena, or products” or “abstract ideas” (103). In particular the doctrine's prohibition on patenting “products of nature,” for example, appears directed mainly toward biological inventions. And early cases interpreting the doctrine indeed worry about whether the biology-related inventions of the time—medicinal tonics, plant fibers, and biological extracts—were unpatentable products of nature (15). Thus, for much of the nineteenth century, biology-related inventions were only marginally eligible for patent protection.

But the doctrine has long contained a broad exception for “isolated” or “purified” natural products, stemming from one of the first patent races. At the turn of the twentieth century, researchers began to notice that extracts from the adrenal gland possessed several pharmaceutical properties. In 1900, Japanese chemist Jōkichi Takamine, working for the American pharmaceutical firm Parke-Davis & Co., identified the extracts' active principle, epinephrine or adrenaline. In an effort to protect its research—and to squelch competition—Parke-Davis secured a patent on the chemical compound itself (15). Parke-Davis then immediately sued several of its competitors in New York, who defended on the ground that the patent was invalid, as it encompassed a product of nature. In a famous decision by Judge Learned Hand, one of the most famous American judges of the first half of the twentieth century, the court surprisingly declared that the patent was valid. Because the adrenaline claimed in the patent was isolated and purified from its natural surroundings, it was not a product of nature; it was “for every practical purpose a new thing commercially and therapeutically” (89, p. 103). The true effect of Judge Hand's decision in *Parke-Davis* is difficult to measure, but the legal fiction—that “isolated and purified” products of nature were patent eligible as new things—became ingrained in patent law (5).

The *Parke-Davis* decision likely served as the legal basis for the first patents on genetic material: nucleotides. Soon after Francis Crick and James D. Watson famously discovered the molecular structure of DNA in 1953, several researchers began to patent nucleotide derivatives, some of them naturally occurring. In 1957, for example, Har Gobind Khorana, who in 1968 would receive the Nobel Prize in Physiology or Medicine for his work on deciphering the genetic code, received a patent for synthesized nucleoside polyphosphates (116). Similarly, in 1957, Charles Heidelberger, then a researcher at the University of Wisconsin, received US Patent No. 2,802,005, for a derivative

of uracil, one of the four nucleotide bases used in RNA (117). Researchers continued to patent nucleotides and their derivatives throughout the 1950s and 1960s, and there is little evidence that such patents generated much controversy or litigation—or much revenue.

As research in biology progressed, so too did the landscape of biological patents. The 1960s and 1970s realized major advances in molecular biology, including the elucidation of the genetic code (69), the discovery of reverse transcriptase (12), and the first successful sequence-specific synthesis of a DNA molecule (97). Beginning in the 1960s, researchers began to patent increasingly complex products of biology. One patent filed in 1969 claimed one strain of rapidly reproducing RNA (119). Another claimed a method of cell-free *in vitro* synthesis of proteins from an RNA template (118). Yet another claimed certain tRNA molecules (120). But again, few, if any, of these patents were ever enforced or, for that matter, widely commercialized.

Four watershed events, all amazingly occurring within six months in 1980, truly launched a commercial—and intellectual property—revolution in molecular biology. The first event was the US Supreme Court's June 16, 1980, decision in *Diamond v. Chakrabarty* (37). In 1972, Ananda Chakrabarty at General Electric applied for a patent on *Pseudomonas putida*, a strain of bacterium that he had transformed with several plasmids coding for hydrocarbon-digesting enzymes. It was the first patent application on a recombinant bacterium—and the first on any man-made living thing (35).

In September 1973, the PTO rejected Chakrabarty's patent application on the grounds that living organisms were not patentable subject matter (68). After a lengthy series of lawsuits, the Supreme Court rejected the PTO's theory, awarded Chakrabarty his patent, and conclusively declared that "anything under the sun that is made by man" was eligible for patent protection—living or otherwise (37).

The second event occurred four months later, on October 14, 1980: a public stock offering of Genentech, one of the world's first "biotech" companies. Founded by scientist Herbert W. Boyer of the University of California-San Francisco (UCSF) and venture capitalist Robert Swanson, the Genentech IPO offered one million shares at \$35 per share. On the first day of trading, its share price reached as high as \$88 (88). This bonanza, along with advances in and increased attention on molecular biology, set off a boom in venture capital investment of biotechnology companies. Because such companies, at least when making medical products, could not sell their products without first conducting lengthy clinical trials, the initial strength of biotech companies was—and still is—largely based on their patent portfolios (13).

The third event was the issuance of the first recombinant DNA patent—based on an invention by the same Herbert W. Boyer and Stanley Cohen—on December 2, 1980 (121). That patent, the result of research conducted in 1974 on a process of creating recombinant DNA, i.e., recombining genes, appeared to be the holy grail for geneticists (3). Rather than tedious mutational or crossbreeding studies, the Cohen-Boyer technology allowed genetics researchers to study—and create—genes in isolation. With increasing research into the function and characterization of restriction enzymes, recombinant DNA technology opened doors for researchers to both isolate and purify individual genes as well as create analogs of their own (26). (Despite the patent, Cohen's Stanford colleague, Paul Berg, won the 1980 Nobel Prize in Chemistry for inventing recombinant DNA.)

The last major event in this annus mirabilis occurred on December 12, 1980: the signing of the Bayh-Dole Act by lame-duck President Jimmy Carter (106). Prior to the Bayh-Dole Act, inventions created with any federal funding were owned, at least in part, by the federal government. Because many such inventions were created at large research institutions, such as universities, this discouraged institutions of higher education from commercializing their faculty's inventions and dissuaded research into the applied sciences. By allowing institutions themselves to be assignees

to, and hence owners of, their faculties' inventions, the Bayh-Dole Act encouraged universities to engage in patentable research, perhaps nowhere more actively than in the life sciences (84).

These events combined with the potential for lucrative industrial applications to recombinant DNA to spur a soft but rapid arms race in patenting molecular biology. In 1981—only six months after the 1980 watershed—Jack J. Manis, a researcher at the Upjohn Company in Michigan, received what is likely the first gene patent: a patent claiming a purified version of pUC6, a naturally occurring plasmid found in *Streptomyces spinosus* (122). The legal basis for Manis's patent rested in Judge Hand's decision seventy years earlier—that natural substances, isolated and purified from their surrounding environment, were legally “new” things, and therefore patentable subject matter. Manis's patent was shortly followed by patents on oligonucleotides (123), hybrid plasmids (125), and bacteriophage DNA (124).

The first human gene patent was not far behind. In 1982, researchers at UCSF patented the gene for chorionic somatomammotropin, *CSHI* (126). The gene was vitally important in fetal growth and development but also had numerous therapeutic benefits. Previously, however, the gene's protein product was available only through painstaking extraction from cadavers—obviously limiting the quantity that could be produced, but also widely believed to be a safety risk. The *CSHI* patent disclosed the isolated 654 base-pair sequence of the gene, as well as technologies to make recombinant versions of the hormone in bacteria. More practically, the technologies disclosed in the *CSHI* patent simultaneously mitigated the safety concerns with cadaver-sourced somatomammotropin while presenting the opportunity for virtually limitless production (81).

The benefits of this technology led to the first gene patent war. Lured to Genentech, then a nascent company, one of the patent's coinventors, Peter H. Seeberg, stole several clones used by UCSF researchers in expressing somatotropin in bacteria. Genentech went on to use these clones to develop Protropin, the first commercially available recombinant therapeutic. The success of Protropin (by 1999 it had generated almost \$2 billion in revenue for Genentech) led to a vicious, wide-ranging, and long-lasting lawsuit between UCSF and Genentech. The parties settled in 1999, with Genentech agreeing to pay UCSF and its researchers \$200 million, \$50 million of which went toward building the UCSF campus that dominates San Francisco's Mission Bay today (136).

As genetic sequencing advanced, so did genetic patenting. From 1982 until the announcement of the Human Genome Project in October 1990, more than a thousand US patents claimed genes or genetic sequences (120). Still, the majority of such patents focused on the workhorse tools of molecular biology: cloning vectors (129), bacteriophage DNA (125), and purified plasmids (127). Few were patents on full-sequence human genes.

The Human Genome Project, however, changed that calculus. The method originally used in the Human Genome Project relied, at least in part, on sequencing mRNA transcripts found in a variety of tissues. Because the mRNA transcripts were, by their nature, processed after transcription from the genome, the resulting sequence contained only a portion of the expressed gene. These expressed sequence tags (ESTs) were instrumental in the infancy of the Human Genome Project (3). Craig Venter, then a researcher at NIH, pushed for patenting of these ESTs, even though little (or nothing) was known about their respective genes' functions. Still, the ESTs appeared to satisfy the conditions of patentability: they were new, insofar as they were synthetic chemicals; useful because they could help to locate important stretches of natural occurring genetic sequences; and nonobvious to the degree that researchers were previously unfamiliar with the underlying mRNA transcript (91).

In 1991, in an effort to appeal to private industry, then-NIH Director Bernadine Healy announced in the *New England Journal of Medicine* that her agency would seek patent protection for the ESTs generated by the project (57). This decision sparked an outcry in the research community: James Watson, at that point the head of the US Human Genome Project and the National

Center for Human Genome Research, who had earlier taken a strong position against gene patents, resigned from his position in 1992 at least partially in protest. Healy herself left soon afterward in a change of presidential administrations. The new NIH leadership withdrew its EST patent applications, only to have its private partners pursue them by the thousands (91).

After stops and starts at the PTO, the US Court of Appeals for the Federal Circuit declared that ESTs were not patentable except in the rare cases where the application showed a precise, biological function sufficient to fulfill patent law's utility requirement (67). Notably absent from the Federal Circuit's decision was a discussion on whether ESTs were ineligible for patent protection, i.e., whether as putative products of nature they were not patentable subject matter even if they were useful. The decision, therefore, left the door open for patents on full-length genes. And so, contemporaneously with the Human Genome Project, thousands of patent applications were filed that claimed isolated and purified human genes (31). The legal propriety of this strategy would not be resolved until 2013—about a quarter-century after the Human Genome Project began.

SOCIAL AND POLITICAL REACTIONS TO BIOLOGICAL PATENTS

Most issues in patent law instill little passion in the public at-large. Biological patents—patents on life—seem to be different. Intellectual property issues have consequently been at the forefront of social controversies over the recent advances in molecular biology. The five-justice majority decision in *Diamond v. Chakrabarty* acknowledged this context:

The briefs present a gruesome parade of horrors. Scientists, among them Nobel laureates, are quoted suggesting that genetic research may pose a serious threat to the human race or, at the very least, that the dangers are far too substantial to permit such research to proceed apace at this time. We are told that genetic research and related technological developments may spread pollution and disease, that it may result in a loss of genetic diversity, and that its practice may tend to depreciate the value of human life (37).

The four-justice dissent, too, took issue with the technology involved in Chakrabarty's invention, calling the patent question a matter that "uniquely implicates matters of public concern" (37). But both opinions ultimately sidestepped the social and ethical quandaries of biotechnology, saying that those were issues for Congress, not for the courts (37).

This approach did not prevent public reaction. To the contrary, along with more academic ethical analysis (87), social concerns over biological patents grew and evolved after *Chakrabarty* was decided, focusing on patents' roles with regard to research subjects, indigenous peoples, and nonhuman animals. These concerns took various forms, including demonstrations, petitions, and campaigns by nongovernmental organizations (NGOs). The decision in *Chakrabarty* was the birth of not one movement against patents, but of several overlapping movements against biological patents on nonhuman animals; human things; issues related to indigenous peoples, biopiracy, and genetically modified organisms; and, finally, gene patents.

Patents on Transgenic Animals

Chakrabarty immediately provoked a broad range of legal commentary. But the broader public response seems to have been muted, perhaps because Chakrabarty's *Pseudomonas* bacteria were neither charismatic nor cute. Patents on laboratory mice, however, did generate public interest. In 1984, Harvard filed for a patent on behalf of two of its faculty who had invented a genetically altered mouse modified to be particularly susceptible to cancer and dubbed the "Harvard Oncomouse."

The PTO granted the patent in 1988, including a claim to “a transgenic nonhuman mammal whose germ cells and somatic cells contain a recombinant activated oncogene sequence introduced into said mammal” (130). The patent generated some controversy—and unsuccessful challenges—in the United States, but proved more controversial elsewhere.

In Canada, the patent examiner rejected Harvard’s claims to the mouse itself on the ground that higher life-forms were not inventions for the purposes of Canadian patent law. That decision was upheld in the first two levels of review but overturned by the Canadian Federal Court of Appeal in 2000. On appeal, the Supreme Court of Canada—in a narrow five to four decision, reminiscent of the split in *Chakrabarty*—reinstated the original position, holding that a life-form could not be a “manufacture” or “composition of matter” under the Canadian law (56). Harvard’s patent was issued in Canada in 2003 but without its claims to the mouse itself (73).

In Europe, Harvard was initially denied a patent outright but was granted one in 1993 on the ground that European law forbade the patenting of animal varieties but not of animals (74). Seventeen opponents appealed that decision, largely on the ground that the patent violated the “ordre public” or “moral” provision of European Patent Convention (107, 108). Harvard won, albeit with its claims limited from “mammals” to “mice” (94, 108).

These lengthy legal controversies kept the patents in the spotlight in Canada and Europe, fueling the “No Patents on Life” movement, supported by various NGOs, including Greenpeace International, the Council for Responsible Genetics, the (U.K.) National Anti-Vivisection Association, the Canadian Environmental Law Association, and the Action Group on Erosions, Technology and Concentration [previously known as the Rural Action Foundation International (RAFI), a Canadian NGO] (22, 94).

In the United States, the Harvard Oncomouse patent had more political consequences than the *Chakrabarty* decision. After *Chakrabarty*, the PTO received numerous applications for patents on animals. In 1987, after the Board of Patent Appeals and Interferences ruled that a patent should be issued for an artificially forced polyploidy oyster (64), the PTO announced that it would grant such patents, although not to the extent they encompassed human beings (93). This led to the introduction of several bills in the US Congress banning animal patents, none of which passed (61, 62, 90). The Harvard Oncomouse patent was issued in 1988 (130).

Human Patents

No one, as far as we can tell, has ever intentionally applied for a patent on a human being. But people have applied for patents on pieces of humans, human chimeras, and classes of life-forms (mammals) that, without restriction, would include humans. Each has been controversial, not just as patents on life but because they would constitute patents on humans.

One of the more famous social controversies over biologic patents concerned the case of John Moore’s spleen, the subject of a famous, widely taught California Supreme Court decision, *Moore v. Board of Regents of the University of California* (78, 82). In 1976, John Moore, a 32 year-old patient with hairy cell leukemia, underwent a splenectomy at the advice of his physician, UCLA Medical Center hematologist David Golde. Golde developed white blood cells from Moore’s spleen into a cell line he called Mo, short for Moore, which eventually showed unusual growth and high levels of production of immune-system-related proteins. With the help of the technology licensing office at UCLA, Golde applied for and received a patent on this cell line (128).

Moore eventually became aware of Golde’s patent and sued UCLA and Golde on more than twenty claims, including one for conversion—the wrongful exercise of ownership over someone else’s property, in this case, according to Moore, his cells. By the time the case reached the California Supreme Court in 1990, it had become a cause célèbre (112). Moore had been a witness

in a congressional hearing (111); the case was heavily covered by the popular press; and professors, academics, trade associations, and NGOs filed amicus briefs on either side. Ultimately, the California Supreme Court rejected Moore's ownership claims, sending the case back to trial to decide whether Golde had breached any duties to Moore as his physician (78, 82). The trial was never held; the case settled shortly after the remand (78).

The Moore decision, at its heart, was not about patents, although the patent was one of several reasons the majority gave for denying Moore's claim to an ongoing property interest. Still the case prompted publicity and concern about the patenting of the human body and its parts. Some of that was fed by Moore himself, as he continued to be used by anti-life-patent groups to speak out against intellectual property and biopiracy for many years (18). But the concerns raised in Moore's case have never fully been resolved. Although the most famous human cell line, the HeLa line, derived from the cervical cancer of Henrietta Lacks, was not originally patented, thousands of patents have subsequently been issued that involve the HeLa cell line (105). The legal, social, and ethical concerns with these patents were the subject of a 2010 bestselling book, Rebecca Skloot's *The Immortal Life of Henrietta Lacks* (105), and led to an unprecedented public agreement between the NIH and Lacks's descendants in 2013.

In other instances, NGOs have attempted to manufacture public attention directed to the social concerns over patenting. In 1997, for example, Stuart Newman, a cell biologist and cofounder of the Council for Responsible Genetics, filed US Patent Application No. 08/993,564, titled "Chimeric Embryos and Animals Containing Human Cells" (131). As its name would suggest, Newman's patent application—admitted to be political theater—attempted to claim embryos containing both human and nonhuman cells, such as chimpanzee cells (32). The PTO ultimately rejected the application in 1999 (45), reiterating a 1987 policy statement:

A claim directed to or including within its scope a human being will not be considered to be patentable subject matter. . . . The grant of a limited but exclusive property right in a human being is prohibited by the Constitution. Accordingly, it is suggested that any claim directed to a nonplant multicellular organism which would include a human being within its scope include the limitation "nonhuman" to avoid this ground of rejection (132).

Despite the PTO's rejection of Newman's patent application, every year from 2004 to 2011, Congress put a limitation on the PTO's budget, forbidding it to use appropriated funds "to issue patents on claims directed to or encompassing a human organism" (29). Ultimately, in the last day before passage of a large patent reform bill in 2011, Congress added an additional provision to the patent statute, Section 33, forbidding patents containing "a claim directed to or encompassing a human organism." Despite the provision's many ambiguities and other problems, ably cataloged by Professor Yaniv Heled, the law is fundamentally a codification of a preexisting policy (58).

The European Patent Organization had reached a similar, but broader, result. It incorporated into its structure a 1998 European Union directive that bans patenting "the entire human body in all its developmental phases" as well as processes for cloning human beings, processes for modifying the germ-line genetic identity of human beings, and the use of human embryos for industrial or commercial purposes (38).

Indigenous Peoples, Developing Countries, and Genetically Modified Crops

Another set of patent controversies reached the public in the 1990s and 2000s, involving indigenous peoples' and developing countries' relationships with Western patents on indigenous technologies. One particularly difficult dispute involved the Human Genome Diversity Project (HGDP),

an effort in which one of us (H.T.G.) was deeply involved. This project, launched in 1992, aimed to collect cell lines from at least 20 individuals from 500 different populations around the world to better understand the evolution, history, and migrations of the human species (20). Opposition was initially led by RAFI, which successfully built opposition by, among other things, dubbing the Project's request for blood samples "the Vampire Project." More substantively, opponents of the HGDP stressed concerns about the possible use of genetic research on indigenous peoples to discriminate against them or to divert attention away from such populations' more immediate problems. Individuals from and groups of indigenous peoples took up the argument, from the World Council of Indigenous Peoples to individuals or small groups of activists in Nevada, New Zealand, and the Philippines (49–51, 55, 72). Ultimately, the HGDP never received substantial funding. It did, by the early 2000s, piece together a substantial and diverse collection of cell lines (19)—widely available to researchers—but never came close to its initial goals.

Perhaps the most interesting example of indigenous concerns about biological patenting does not concern the HGDP, but arose from an NIH patent. In the early 1990s, anthropologists in Papua New Guinea made contact with members of a group in the isolated upper Sepik River valley, the Hagahai, who had had very little, if any, contact with outside civilization. Medical tests discovered that some of the studied Hagahai were infected with a local variant of HLTV-I, a common retrovirus implicated in leukemia. With NIH support, researchers made cell lines from blood drawn from Hagahai people and—at the request of an anthropologist working with the Hagahai, who wanted them to benefit from the cell line—patented them with an agreement that 50% of any profits would be returned to the group (95). But in 1995, RAFI targeted the Hagahai cell lines as a case of biopiracy (40, 47), a charge picked up—in many cases, sensationally—by parts of the global press:

He's out there somewhere in the wild gorges of the Yuat River, hunting pig, harvesting yam, a young tribesman whose heart belongs to the jungle—but whose blood belongs to the US government (53).

After Papua New Guinea officials became involved, the NIH decided to abandon the patent, although the cell lines remained available for exploitation (40).

Developing nations had their own set of concerns apart from their indigenous peoples about Western firms patenting—and monopolizing—DNA from endemic species. A more recent example concerned the neem tree, native to India. In 1994, the European Patent Office granted a patent to the US Department of Agriculture and W.R. Grace Co. for "a method of controlling fungi on plants" by applying oil from the neem tree (44). The patent sparked outrage in India, where the neem tree had been used for various medicinal and agricultural purposes for centuries. The patent was viewed as theft not just of an Indian plant but of traditional Indian medical knowledge. The Indian Research Foundation for Science, Technology and Ecology, and other environmental groups, succeeded in having the patent overturned in 2000 (60) and in defeating W.R. Grace's appeal in 2005.

The broader effect of the developing world's concern was the creation of the Convention on Biological Diversity, which was completed in 1992 at a meeting at Rio de Janeiro and entered into force in 1993 (30). The Convention commits the member states to protect biodiversity. More tangibly, although it commits member countries to sharing their biological resources with researchers from elsewhere, it requires prior consent of the parties sharing genetic resources or traditional knowledge. It also requires that the results of such research, including commercial benefits, be shared with the countries that provided the resources. It is not clear that the Convention has led to much sharing of the benefits of genetic research, although in many countries it has coincided with increased regulation of biological and genetic researchers from foreign lands.

Finally, the continuing global controversy over genetically modified (GM) crops plays into fears about gene patenting. Although much of this fight revolves around the safety or appropriateness of consuming crops that are modified by modern genetic methods, it has also been affected by the commercial context of many of the GM crops: the ownership and patent enforcement of such seeds by a single company, Monsanto. As GM crops for some staples have begun to dominate fields, the patent ownership over such crops by a single company has caused concern (135). Monsanto's arguably heavy-handed efforts to enforce its licensing provisions to prevent farmers from saving seeds to plant in subsequent years has only exacerbated these concerns. Its early interest in finding a terminator gene to prevent reseeding—although abandoned—has not been forgotten (75). Monsanto publicly renounced any plans to use the technology in 1999, but the belief that it does use it, or wants to, has been hard to kill.

Gene Patents

Gene patents, per se, came late to the party. The United States and many other countries began issuing gene patents from the early 1980s, generally with little or no public knowledge or opposition. It was not until much later that opposition to patents on genes themselves, as opposed to patents on animals or humans, began to grow. Part of that concern was academic—a belief that preexisting human genetic sequences were not inventions to be owned—but part of specific opposition came from more practical concerns.

One set of early concerns with gene patents focused on restrictions on downstream applications of those genes, such drug targets or recombinant protein products (14). This led to several national reports on the topic by a variety of organizations: the US National Institutes of Health Working Group on Research Tools in 1998 (115); the Nuffield Council in Britain (87); and the National Academies of Science in 1997 (85) and 2006 (86). Another concern focused on the potential of gene patents to slow research on and clinical tests for genetic diseases. In 2003, for example, Mildred Cho, Jon Merz, and others published a widely cited empirical study of how gene patents were interfering with both research and clinical genetics laboratories (24). Much of the problem involved Myriad Genetics and breast cancer risk testing, thus sharpening public scrutiny on Myriad specifically (48).

By 2006, the issue of gene patenting began to attract popular attention. Appended to his techno-thriller, *Next*, Michael Crichton argued for five recommendations, including “Stop patenting genes” (33), advice he repeated in a February 2007 op-ed in *The New York Times* (34). Soon afterward, Representatives Xavier Becerra and Dave Weldon introduced a bill in 2007 to ban future patenting of DNA sequences (63). Their bill garnered some public attention but ultimately went nowhere. In other countries, legislation to ban gene patents was introduced but ultimately failed as well. The argument against gene patents did not go unanswered. Industry, of course, largely defended gene patents. But so did some patient advocates, notably Sharon Terry, the highly respected leader of Genetic Alliance, a consortium of different genetic disease groups (110). The arguments continued, but without a single judicial decision against the patentability of genes, resistance seemed futile.

Summing Up the Social Controversies Over Biological Patents

Did any of these legal, political, and social movements around biological patents make a difference in the ultimate legal position of gene patents? It is impossible to know. They clearly had some effect on the Convention on Biodiversity, and potentially the Canadian court decision banning the patenting of “higher” animals. Did it affect the US Supreme Court's eventual decision in its *Myriad* case? At the very least, it kept open questions about the legitimacy of these kinds of patents

that helped inspire the plaintiffs, and their counsel, to pursue the decisive case of *Association for Molecular Pathology v. Myriad Genetics, Inc.*, to which we now turn.

ASSOCIATION FOR MOLECULAR PATHOLOGY V. MYRIAD GENETICS, INC.

In 1990, Mary-Claire King, then a researcher at the University of California, Berkeley, discovered that a single gene located on Chromosome 17q21, later named *BRCA1*, was responsible for a large number of early-onset breast cancers (52). The clinical importance of King's finding spurred an international race to locate the gene precisely, to clone it by making separate copies of it, and then to sequence the clones. In 1994, a research team at the University of Utah, headed by Mark Skolnick, was the first to clone and sequence *BRCA1* successfully (80). Thirteen months later, Michael Stratton at the Institute of Cancer Research in the United Kingdom identified another gene linked to early-onset breast and ovarian cancer, which he named *BRCA2* (137, 138). Although Stratton published a truncated *BRCA2* sequence in his paper, the Skolnick team published a complete sequence only months later (109).

Unlike King and Stratton, Skolnick and his team were particularly aggressive about seeking patent protection for their discoveries. Contemporaneous with their papers on *BRCA1* and *BRCA2*, the Utah researchers applied for seven patents to protect their work in a variety of forms. Generally, these patents covered three groups of technologies related to *BRCA1* and *BRCA2*: the isolated forms of *BRCA1* and *BRCA2*; cDNAs, primers, and probes useful in sequencing the two genes; and methods of using *BRCA1* and *BRCA2* sequencing to predict early-onset breast and ovarian cancer risk (6). The inventions were assigned to the University of Utah and the other patent owners pursuant to the inventors' employment and grant agreements. Those assignees (the patent owners) then licensed the patents to Myriad Genetics, a Utah-based diagnostics company that Skolnick and his colleague, Peter Meldrum, had founded in 1991.

Myriad's focus quickly became clear. One of us (H.T.G.) helped organize a session at the 1996 conference of the International Association of Bioethics on breast cancer and genetic testing; Skolnick, to an audience of 300 bioethicists, gave a very poorly received talk for that audience on the great financial potential of providing *BRCA1* and *BRCA2* tests to millions of American women. In 1998, almost immediately after its patents issued, Myriad began to enforce its intellectual property against several high-profile clinicians performing *BRCA1*- and *BRCA2*-based cancer risk assessments. Myriad offered expensive licenses to—or threatened to sue—researchers at the University of Pennsylvania, Albert Einstein College of Medicine, the National Cancer Institute, and Yale University for continuing to provide information to their breast cancer research subjects on their *BRCA1* and *BRCA2* status. Most capitulated, but Myriad's aggressive enforcement strategy—up until then, unheard of for holders of gene patents—raised the ire of numerous scientific organizations, including the Association for Molecular Pathology, the American College of Medical Genetics, the American Society for Clinical Pathology, and the College of American Pathologists (11).

While Myriad was making enemies with its *BRCA1* and *BRCA2* patents, thousands of other gene patents that arguably covered genetic tests were causing no controversy. Almost all other gene patents were either licensed broadly on very reasonable terms, not actively enforced, or both. Myriad stood out as the only aggressive commercial holder of gene patents, and one whose patented tests covered breast and ovarian cancer, common diseases with great social and political salience. Yet for more than a decade, no one challenged Myriad's patents.

Around 2006, however, the issue of gene patenting caught the attention of the American Civil Liberties Union (ACLU), whose science advisor at the time, Tania Simoncelli, began looking

into the issue as part of her mission to identify important emerging issues in science, technology, and civil liberties. After several years of discussions with researchers, health care workers, patient advocates, and others, the ACLU filed suit against Myriad in federal court in New York in May 2009, as counsel for a host of plaintiffs—scientific organizations, clinicians, cancer patients, and patient advocacy groups (11).

Ten months later, Judge Robert W. Sweet issued a resounding—and surprising—ruling against Myriad. In a 152-page opinion, he declared all of Myriad’s patent claims invalid for lacking patentable subject matter, pointedly casting doubt on the classical reading of *Parke-Davis*. In particular, Judge Sweet rejected the notion that *Parke-Davis* concerned itself with patentable subject matter, tying the decision instead to patent law’s novelty standards. Even considering *Parke-Davis* as a patentable subject matter decision, ruled Judge Sweet, the decision did not stand in contradiction to numerous other cases that required not mere “isolation and purification” of a natural product, but “something more.” Further, Judge Sweet found it significant that the composition of matter claims on the *BRCA1* and *BRCA2* genes were not for the purpose of making physical use of the actual molecule, but for using the information the molecule encoded (11). Judge Sweet’s decision, both sweeping and radical at the time, received national attention (98).

Myriad then appealed the decision to the US Court of Appeals for the Federal Circuit, which split Judge Sweet’s decision in two: it affirmed the trial court’s ruling that the patent claims on methods of analyzing *BRCA1* and *BRCA2* to assess cancer risk were invalid, but it rejected Judge Sweet’s ruling that the patent claims on either the isolated *BRCA1* and *BRCA2* genes, or the cDNA, primers, and the probes that went with them, were invalid. As for the former, the Federal Circuit ruled that Myriad’s method claims were invalid as abstract ideas—that their method of “‘comparing’ or ‘analyzing’ two gene sequences . . . [were] only abstract mental processes” (6). As for the latter ruling, however, the court held that Judge Sweet erred by failing to consider that an isolated gene was, at least chemically speaking, a new thing. Because a gene’s chemical bonds with its chromosome had been cleaved to isolate it, this made the isolated forms of *BRCA1* and *BRCA2* new things for patent law purposes and consequently patentable (6).

The plaintiffs then appealed to Supreme Court, which, a few days after it decided *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, another patent opinion concerning medical diagnostics, granted review of the *Myriad* decision, vacated the Federal Circuit’s decision, and remanded the case back to the Federal Circuit for reconsideration in light of *Mayo* (7). After the Federal Circuit issued substantially the same opinion in its second consideration of Myriad’s case, the Supreme Court again granted the plaintiffs’ request for review of the Federal Circuit decision. It agreed to hear the case to decide the question framed by the plaintiffs’ attorneys as simply, “Are human genes patentable?” (8).

Anticipation of the Supreme Court’s decision ran high and predictions about the outcome of the case were mixed. After largely refusing to hear appeals from the Federal Circuit for the first twenty years of its existence, beginning in the mid-2000s the Supreme Court began to grant review of Federal Circuit cases and had often reversed its rulings. Many of the reversals revealed tension between the Federal Circuit and the Supreme Court on the appropriate level of clarity to impose on patent law standards. Some commentators and patent lawyers believed that the Federal Circuit’s arguably impolitic—and certainly terse—rebuff of the Supreme Court’s earlier attempt to have the Federal Circuit reconsider its first decision in light of *Mayo* guaranteed a reversal. Others saw the Federal Circuit’s opinion as conforming to the holistic, standards-based approach on patentable subject matter typically advocated by the High Court.

The Court finally decided *Myriad* on June 13, 2013. In a crisp ruling, the Court held that “a naturally occurring DNA segment is a product of nature and not patent eligible merely because

it has been isolated, but that cDNA is patent eligible because it is not naturally occurring” (10). Notable for its brevity, the unanimous opinion, written by Justice Thomas, merely declared that “separating [a] gene from its surrounding genetic material is not an act of invention” (10), because the Utah researchers, in identifying the *BRCA1* and *BRCA2* sequences, did not alter the gene itself. By contrast, because cDNA does not exist in nature, being created through the rather artificial process of reverse transcribing mRNA in vitro, Myriad’s patent claims on cDNA were, at the least, patentable subject matter (10).

To many, the Court’s decision ended the surrounding debate as to whether human genes, at least with the same sequence as found in nature, were, in fact, patentable subject matter. After several other patent law opinions drafted by the High Court provided little concrete guidance to patent practitioners, the decision—or, at the very least, its outcome—provided clarity to a long vexing area of biotechnology law (28). It was also lauded by many in the biotechnology industry as keeping intact the patent protection available for synthetic DNA, widely viewed as the most commercially valuable class of claims in Myriad’s patents, a position strongly argued by an amicus brief from Dr. Eric Lander, a prominent researcher in the Human Genome Project and the field (9).

But the decision also raised numerous questions: Was *Parke-Davis* dead, or did the Court make an exception to the doctrine simply for gene patents? If cDNA, primers, and probes were patentable subject matter, were they patentable in light of patent law’s novelty, utility, and nonobvious requirements? And would next-generation high-throughput genetic sequencing—a far cry from the old-fashioned Sanger sequencing method used by Myriad—infringe on Myriad’s remaining patent claims?

Myriad wasted little time cuing these issues up for another federal court to decide in the months following the Supreme Court’s ruling. After several companies announced that they would start offering *BRCA1* and *BRCA2* testing in light of the Supreme Court’s decision, Myriad sued them in federal court in Utah, Myriad’s home state, on Myriad’s remaining patent claims covering *BRCA1* and *BRCA2* cDNA, primers, and probes. Other companies preemptively sued Myriad, seeking a declaration that their activities would not infringe Myriad’s patents.

Myriad’s strategy to obtain home-field advantage quickly backfired, however. In another lengthy trial court opinion, Judge Robert Shelby surprised much of the patent bar by declaring that although patent claims on cDNA, primers, and probes were generally patentable subject matter, Myriad’s specific claims were ineligible because their products could not be differentiated from the unpatentable isolated genes themselves (65). Although Judge Shelby’s decision was not a final ruling—it concerned only whether Myriad was entitled to a pretrial injunction—Myriad Genetics appealed, once more, to the Federal Circuit. On December 17, 2014, the Federal Circuit, again somewhat surprisingly, affirmed Judge Shelby’s analysis concerning Myriad’s specific claims (66). The last of the remaining cases settled on February 16, 2015, with Myriad quietly dismissing its claims. Shortly before, on February 3, 2015, it had released its quarterly fiscal report, which was generally poor. The same day Peter Meldrum, its long-time CEO, announced his retirement, effective at the end of June (101).

Thus, after sixteen years of threatened or actual litigation, almost none of Myriad’s claims on its original seven patents constitute patentable subject matter. All three groups of claims—the isolated forms of *BRCA1* and *BRCA2*; cDNAs, primers, and probes; and methods of using *BRCA1* and *BRCA2* sequencing to predict early-onset breast and ovarian cancer risk—have been invalidated at all three levels of the federal court system.

On one hand, this is surprising, given gene patents’ seeming stability since the 1980s and through the Human Genome Project. But on the other hand, the *Myriad* litigation came at a time when parties—and courts—have begun to pay more attention to patent law and the effects of aggressive patent monopolies on businesses. The Supreme Court, in its decision, noted that

“Myriad’s patents would, if valid, give it the exclusive right to isolate an individual’s *BRCA1* and *BRCA2* genes” (10). This offhand statement highlighted Myriad’s adversaries’ core concern: that these patents would, in essence, allow one entity the exclusive right to isolate an individual’s genetic material, and therefore, use that analysis in genetic diagnostics. After the *Myriad* case, therefore, the future of genetic diagnostics is likely to see substantial change, at least for *BRCA1* and *BRCA2* testing.

THE FUTURE EFFECTS OF MYRIAD

One result of the Supreme Court’s *Myriad* decision has become clear in the months since it was issued: the company’s patent-based monopoly on *BRCA1* and *BRCA2* testing in the United States has been broken. Competitors have entered the market, fought off Myriad’s last-ditch lawsuits, lowered prices, and, perhaps, improved services. But what are the wider implications of the *Myriad* decision for gene patents and for patents in general in biotechnology research and industry? This section looks at four areas of possible impact: the future of gene patents outside the United States; the future of gene patents in the United States; the effects of the *Myriad* case on research and industry; and the search by interested parties for other forms of monopoly protection.

Non-US Patents

Patents are creatures of domestic law; that is, they can only be enforced within the country in which they are issued. Accordingly, decisions on patenting by the US Supreme Court or the PTO have no binding effect on patenting decisions in other countries. This leads to several disparities in the texture of international patenting. For example, and as discussed earlier, Canada bars patents on “higher animals,” whereas the European Patent Convention has a strong bar against patenting human embryos.

Nonetheless, over the past thirty years, all major patent regimes have allowed gene patents with more or less the form and scope of US patents before *Myriad*. Individual countries or organizations have ruled against particular gene patents—opposition by a group of French laboratories prevented Myriad from receiving any but very limited protection under European patent law—but not against gene patents as a whole (104, 133). Recently, the Federal Court of Australia ruled in February 2013 that Myriad’s claims were affirmatively patentable in Australia, with the High Court of Australia hearing oral argument on this issue in June 2015 (36). But as yet, we have surprisingly not seen tests in other countries as to whether the US position on *Myriad* will be more broadly adopted. It is worth noting that even in countries outside the United States where Myriad had been granted patents, those patents were not generally stringently enforced. Local laboratories, often government-owned, likely ignored them or simply refused to comply with licensing requirements (50). Gene patents may be officially dead in the United States, but could live on, at least weakly, in other countries.

US Patents

In the United States, though, it now seems clear that gene patents are “not only merely dead, but . . . really most sincerely dead” (54). Because Myriad did not appeal the Federal Circuit’s invalidation of its patent claims on methods of conducting *BRCA* testing, and in light of the Supreme Court’s recent decisions on patentable subject matter, patent claims directed to methods of conducting genetic risk-assessments are now ineligible. This is a consequence of the Supreme Court’s decision in *Mayo*, forbidding patents on comparison-based diagnostic tests as mere abstract ideas (77). Furthermore, in its *Myriad* decision, the Supreme Court invalidated all patent claims

directed to isolated genomic DNA (10). And in their affirmation of the Utah trial court's opinion rejecting Myriad's claims to cDNA, primers, or probes of particular genes, the Federal Circuit has crystallized the ineligibility of such technologies (66).

To be sure, one can still patent DNA sequences that are not found in nature, including some cDNA transcripts as well as completely novel DNA sequences. But such sequences would need to substantially differ from a naturally occurring sequence. What substantially means in this context may well be an important point for the courts to clarify. But, all in all, there is little left at this point for gene patents.

Effects of *Myriad* on Research and Industry

This extinguishing of long-held intellectual property norms is likely to have little effect, at least as far as genetic research is concerned. By and large, gene discovery—associating particularly genes or sequences of DNA with traits—has been undertaken by academic researchers with government or private funding. And although tens of thousands of gene patents have been issued in the United States, few have played important commercial roles. *CFTR*, mutated versions of which are responsible for cystic fibrosis, has long been patented and owned by the University of Michigan, Johns Hopkins University, and Toronto's Hospital for Sick Children. These patents have been licensed on nonexclusive terms for very moderate payments. As a result, genetic testing for cystic fibrosis has long been available widely and cheaply (21). The same has been true for *HTT*, the gene that, in some variants, causes Huntington's disease (100), as well as for the genes that, when mutated, cause Tay-Sachs disease and Canavan disease (27). It is simply unlikely that the loss of such modest royalties would stop academic research in this area.

The loss of the ability to patent diagnostic uses of gene patents could, however, lessen incentives for discovering new connections between particular genomic sequences and diseases or traits. Ironically, however, here the Supreme Court's decision in *Mayo*—not *Myriad*—will be important. By prohibiting patents on diagnostic technologies, *Mayo* could inhibit the commercialization of “big data” genetic discoveries. But, again, that seems unlikely to be significant. Furthermore, patents on using specific genes for gene therapy appear to remain viable. To the degree such technologies become commercially viable, patent protection for them might become significant.

One important caveat exists to this relatively optimistic scenario. *Myriad* dealt with gene patents, or, more specifically, with patents on particular sequences of DNA as compositions of matter. It found that naturally occurring DNA sequences could not be patented because they are products of nature. It is at least conceivable that courts could extend this rationale beyond genes and DNA to other naturally occurring molecules. The loss of composition of matter patent protection for naturally occurring molecules produced by, say, fungi that are discovered to be effective antibiotics might have significant effects on their development, even though *Myriad* would not deny patent claims for the molecule's use as an antibiotic. The *Myriad* opinion does not speak of any molecules other than DNA and RNA. Unlike Judge Sweet's district court opinion, however, it offers no reason to treat nucleic acids as special. Some scholars have suggested that the Court's silence on this difference stems from its recognition that nucleic acids, unlike other natural products, have an informational component: their sequence (16).

Other Protections

Finally, patents are not the only sources of monopolies or necessarily the most effective (43). US drug law provides “regulatory exclusivity” for some approved drugs, preventing other firms from selling the same drug or biological product in the United States for varying periods—ranging

anywhere from six months to twelve years under current law, depending on the circumstances. The loss of some patent protection may lead the affected firms to seek greater protection from regulatory exclusivity, either through the existing methods or through lobbying for new and wider exclusivities.

In the genetic testing area, another path to monopoly might be through the device approval process. FDA views genetic tests as regulated medical devices when used to predict disease risk or course or treatment response. It has, thus far, largely chosen not to regulate them under the so-called laboratory-developed test (LDT) exclusion. In October 2014, FDA issued a draft guidance discussing its current plans to bring those LDTs under some form of regulation (113). It may well be that a firm could get some protection from competition by being approved as an LDT or as a companion diagnostic, another FDA term. It is possible that such approvals would force competitors to get their tests approved. Although this may not, in and of itself, be a large barrier to entry, it would increase the expense of competition. What will happen ultimately with the LDT Draft Guidance remains deeply uncertain. Interestingly, on December 19, 2014, the FDA approved Myriad's BRCAAnalysis test as a companion diagnostic for use in determining whether patients have a form of ovarian cancer responsive to a particular anticancer drug, Lynparza (114). Were this route to provide Myriad Genetics with another form of monopoly to genetic diagnostic testing after *Myriad*, it would be indeed ironic.

But Myriad—after all of its litigation losses—still possesses another form of monopoly: data exclusivity. Some variants of the *BRCA1* and *BRCA2* genes are well known from widespread experience to increase a patient's risks for some cancers. Other variants are equally confidently known not to increase those risks. But the risk of many variants is unknown. They are neither commonly found in families at normal cancer risk nor are they known in enough individuals who developed cancer to be labeled as high-risk. These are called variants of unknown significance (VUSs) (23).

As the only laboratory testing people for *BRCA1* and *BRCA2* mutations in the United States from 1996 until 2013, Myriad collected and analyzed information on the disease states of the people it tested as well as on the genetic variations they had. In 2004, it largely stopped sharing the results of these analyses with outside researchers, retaining its database on information on former patients.

This database should allow it to determine whether particular variants are dangerous, safe, or of unknown significance much more effectively than other firms. The ability to call VUSs more accurately should be a substantial market advantage (23). Although one group, led by Dr. Robert Nussbaum of UCSF, is attempting to reconstruct Myriad's database by contributions from its customers and their physicians, Myriad's database might provide a useful medical, and hence market, advantage for years to come (46, 71). Myriad's patents may be dead, but the monopoly position they created, although weakened, may linger on.

CONCLUSION

The history of gene patents is a fascinating one: a twisting tale of science, money, culture, and courts, where new technologies created new legal problems. The story now seems largely, although not entirely, ended. Neither the problem of gene patenting nor its resolution seems to have created major difficulties. When all was said and done, they appear to have generated more controversy than true social harms (except, perhaps, to people who faced high prices for *BRCA1* and *BRCA2* testing). While history rarely repeats itself, we will likely continue to see versions of this story played out in the future, both close and distant. New discoveries in biology—in neuroscience, in stem cell research, in genome editing—will pose new social and legal challenges. We should be vigilant to

spot, careful to consider, and ready to act on them, quickly. The gene patent controversies lasted nearly thirty-five years. We must aspire to do better.

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