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Cease or Persist? Gene Patents and the Clinical Diagnostics Dilemma

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"He who receives an idea from me, receives instruction himself without lessening mine; as he who lights his taper at mine, receives light without darkening me."

– Thomas Jefferson, August 13, 1813

Executive Summary:

Patent protections on biomedical innovations help incentivize the development of new devices and drugs. In the field of clinical diagnostics, however, patents on human DNA can impede the development of better test methods and delay patient access to clinical care. An oft-cited example is the case of Myriad Genetics, in which patents on two genes linked to hereditary breast and ovarian cancer (BRCA1/2) prevented university labs from developing and providing testing for high-risk patients.

Myriad's actions have roused the ire of researchers, clinicians and patient interest groups within the healthcare community and have led to government action in many countries. This is not, however, the first controversy over the role of gene patents in biomedical technology. Since 1980, when the Supreme Court granted patentability to life forms and Congress made federally funded research patentable, various researchers and firms have attempted to monopolize genomic discoveries through aggressive patenting strategies. Members of the biotechnology industry argue that these patent-backed monopolies promote innovation by encouraging private investment in basic research. Critics, however, warn that these monopolies can impede innovation by preventing others from building on the findings of the patent holder. By preventing researchers and clinicians from accessing key segments of the human genome, gene patents can create a harmful legal environment that undermines the development of new clinical diagnostics. Many point to the Myriad controversy as an example of how gene patents can block research critical to the study of a major hereditary disease.

In an effort to evaluate these critics' arguments in context, this essay will study the prevailing ideas behind their claims in four stages: It will: 1. Discuss the theories behind the patenting of DNA fragments using historical examples of past gene patent controversies, 2. Use the Myriad BRCA1/2 case to examine the impact of gene patents on public research and healthcare systems, 3. Address recent policy suggestions from the US Department of Health and Human Services and 4. Trace the development of the ongoing court battle over Myriad's remaining patents. The essay will then explore the current progress of genomic scale sequencing technology, and suggest that the infringement liability exemption is the best means of securing research and diagnostic access to patented genes. By drawing insights from theory, jurisprudence and empirical evidence, this paper will argue that Congress should propose this policy in the spirit of Article 1.8.8 of the Constitution and Title 35 of the United States Code. While the exemption avoids the "Gordian knot" solution of eliminating all gene-related patents, it presents a safer solution that avoids inadvertent shocks to other research fields, such as therapeutics development. By striking a better balance between incentives for private investment and protections for scientific inquiry, this rule would help Congress, the courts and federal agencies pursue the goal of scientific progress as expressed in our nation's constitution.

Introduction:

Last December, clinicians, researchers and patients represented by the American Civil Liberties Union (ACLU) petitioned the Supreme Court for a rehearing of *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office et al*.[1] In its 2-1 ruling on July 29, 2011, the three-judge panel representing the Court of Appeals for the Federal Circuit (CAFC) had upheld Myriad's product patent claims on the BRCA1/2 genes.[2] The majority ruling from the CAFC asserted that these patents were valid because isolated DNA fragments were "not a purified form of a natural material, but a distinct chemical entity."[3] Counsel for the plaintiff, however, argued that that court failed to properly consider the fact that these "gene fragments with the altered chemical structure…[already] exist in nature."[4]

How did the semantics of DNA become the basis for such heated legal debate? One reason is the issue's relevance to the debate over human gene patents in biomedical research. By aggressively patenting the genetic mutations behind hereditary predispositions for breast and ovarian cancer, Myriad Genetics managed to land in the eye of an ongoing policy storm over biomedical patent policy.[5] Proponents of gene patents assert that they promote access to new research by encouraging firms to invest in new discoveries. They warn that eliminating gene patents will cause firms to abandon the pursuit of critical medical technologies, because weak

[1]The case was *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office et al*. until after the CAFC ruling, which removed the USPTO (United States Patent and Trademark Office) as party to the case. The case is now referred to as *Ass'n for Molecular Pathology et. al. v. Myriad Genetics et. al.*

[2] *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office et al*., 653 F.3d 1329 (Fed. Cir. 2011). Although the court ruled that the method claims were no longer patentable in light of the Supreme Court's ruling in *Bilski*, it upheld Myriad's 'composition of matter' claims on the normal and mutated sequences of the BRCA1/2 genes, e.g. claims 1, 2, 5 under U.S. Patent 5,747,282.

[3] *Id.* at 1352.
Note that on March 26, 2012, the Supreme Court decided to grant the petition for certiorari but vacated and remanded the case back to the CAFC. The effects of this decision will be discussed later in this essay.

[4] Christopher A. Hansen, "Plaintiffs-Appellees' Petition for Panel Rehearing," (August 25, 2011): 1. *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office et al.,* 653 F.3d 1329 (Fed. Cir. 2011).

[5] E. Richard Gold and Julia Carbone. "Myriad Genetics: In the Eye of the Policy Storm," *Genetics in Medicine* 12 (2010): S49.

patents would make it more difficult for them to prevent freeriding and protect profits. In response, opponents argue that these patents allow harmful monopolies that reduce patient access to better care. While gene patents can create substantial economic incentives for developers of biologic diagnostics and therapeutics, they can also stymie subsequent medical progress and reduce downstream research by monopolizing access to fundamental discoveries in the human genome.

In the US today, gene patent policy continues to be treated as a technical and administrative matter relegated to oversight and review by the USPTO. The arguments raised against the BRCA1/2 patents suggest that this passive approach is inadequate for the regulation of intellectual property rights over the human genome. In 2011 alone, the American Cancer Society anticipated approximately 230,480 new cases of invasive breast cancer, 21,990 new cases of ovarian cancer and a combined 54,980 deaths due to the two diseases.[6] Despite the fact that more reliable and affordable BRCA1/2 testing will help identify patients with hereditary predispositions, target them for intensive surveillance and ultimately help save their lives, Myriad's BRCA1/2 patents continue to prevent researchers from providing second opinion testing and more cost-effective tests. On the other hand, eliminating gene patents might have crippling effects on the biotechnology industry's ability to develop therapeutics for these and other chronic diseases. According to the Biotechnology Industry Organization (BIO), the majority of biotechnology firms in-license early-stage discoveries.[7] Recent studies suggest that new biotechnology-related drugs cost on average over $1.2 billion to bring to market, and

[6] Statistics from *Breast Cancer Facts & Figures 2011-2012*. Atlanta: American Cancer Society, Inc., (2011): 2, and the Ovarian Cancer National Alliance at <www.ovariancancer.org>
39,520 deaths were due to breast cancer and 15,460 deaths were due to ovarian cancer.
[7] *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office and Myriad Genetics, Inc*., 702 F. Supp. 2d 181 (S.D.N.Y. 2010) (slip op., at 77).

successfully gain approval only 30% of the time.[8] Absent patent protection, biopharmaceutical developers might face greater difficulty in procuring new projects and protecting them.

As a critical component of US healthcare policy, gene patents are part of a greater "social contract"[9] designed to balance between private interests and public wellbeing. While these restrictions on the use of knowledge are designed to reward individuals for their inventions, they ultimately entail a quid pro quo – patent holders must disclose information that will enhance the social benefit derived from the claimed technology. In order to attain the ultimate goal of biomedical innovation, then, gene patent policy must ensure that follow-on, "downstream" research is not disproportionally impeded for the sake of rewarding patent-holders upstream. The human cost imposed by these patents cannot be justified otherwise. While upstream innovation is a necessary component of new product development, it is not a sufficient condition for the creation of those clinically effective drugs and DNA sequencers that will help save lives.

In the last half decade, Myriad has refused to provide data from its testing business to the National Institutes of Health's (NIH) Breast Cancer Information Core (BIC), citing its concern that its competition might benefit from it.[10] This patent-backed monopoly over critical information has blocked the efforts of geneticists and researchers seeking to study the demographics of those genetic mutations related to breast and ovarian cancer. For the last eighteen years, Myriad has enforced its monopoly rights on both the isolated DNA fragments that code for BRCA1/2 and the ability to perform diagnostic testing for those genes. In the absence of a robust research exemption from infringement liability following the Federal

[8] Brief for the Biotechnology Industry Organization as Amicus Curiae, 25. *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office et al*., 653 F. 3d 1329 (Fed. Cir. 2011).
[9] Geertrui van Overwalle. "Turning Patent Swords into Shares," *Science* 330 (2010): 1630.
[10] Andrew Pollack. "Despite Gene Patent Victory, Myriad Genetics Faces Challenges," *New York Times*, 24 August 2011.

Circuit's ruling in *Madey v. Duke University*,[11] Myriad's actions highlight a current imbalance between incentives and access in US patent policy – one in which the social distortions and economic inefficiencies of patents are outweighing their marginal social benefits.[12] By impeding the development of more advanced gene diagnostics and blocking clinical inquiry into a patient's own DNA, this imbalance may undermine the goal of scientific progress sought in Article 1, Section 8, Clause 8 of the US Constitution, and lead to grave consequences for women at risk of breast and ovarian cancer.

Though the Myriad controversy may seem at first to be the exception to the norm, it is rather an extension of a gene patent debate that has been going on over the past three decades. Since the passage of the Bayh Dole Act in 1980, breakthroughs in gene sequencing and manipulation have catalyzed growing concern over the fact that patents can hinder innovation as well as support it. As new discoveries in biotechnology translate into biomedical innovations, the restrictive effects of gene patents become increasingly apparent. In order to fully understand the current debate surrounding Myriad's BRCA1/2 patents, then, we must first understand the background and development of this debate, including the theoretical arguments that have helped formalize it.

Background and Theory:

Biomedical patents: purpose and policy

In an earlier era, Sir Isaac Newton furthered his knowledge "by standing on the shoulders of giants." Were he alive today, he might be charged a fee. In the United States, Article 1.8.8 of the Constitution entrusts Congress with the power to grant patents in order to "promote the

[11] Madey v. Duke Univ., 307 F. 3d. 1351 (Fed. Cir. 2002).
[12] Stiglitz Decl., (19 January 2010): 5, 11-16. filed in *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office and Myriad Genetics, Inc.*, 702 F. Supp. 2d 181 (S.D.N.Y. 2010).

progress of science and the useful arts." Congress defines the conditions for patentability in Title 35 of the United States Code, which grants patents for inventions and discoveries that are useful, novel, and nonobvious.[13] According to Section 101, "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 this title."[14] Owners can license their patented findings on an exclusive basis so as to prevent others from selling, making or using them. In exchange, the law limits the patent's life to twenty years and requires that the patent application describe the finding in a way that would allow similarly skilled individuals to replicate it.[15] Furthermore, implicit exceptions within Section 101 deny patentability to claims on "Laws of nature, natural phenomena and abstract ideas."[16]

The main goal of patent policy is to bring new and useful discoveries into the public domain. By rewarding inventors with legal monopoly rights against pure market competition, patents allow the research community to learn from ideas that inventors might otherwise hide as trade secrets. They allow inventors to cover the high costs of research by exclusively licensing these rights to private investors, who bear the financial burden but also reap the economic returns on these discoveries. Although traditional proponents of laissez faire may object to the monopolistic elements of patents, most economists believe that the benefits gained through intellectual property rights outweigh their potential costs to market efficiency. In *How Markets Fail,* John Cassidy helps explain this view by elaborating on knowledge as a public good.[17] Research projects often involve a substantial amount in upfront investments, and thus require

[13] 35 U.S.C. §§ 101-103
[14] 35 U.S.C. §101
[15] 35 U.S.C. §112
[16] *Mayo et al. v. Prometheus*, 566 U.S. ___ (2012) (slip op., at 1); *Diamond v. Diehr*, 450 U.S. 175, 185 (1981); *Bilski v. Kappos*, 561 U.S. ___, ___ (2010) (slip op., at 5); *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980); *Le Roy v. Tatham*, 14 How. 156, 175 (1853); *O'Reilly v. Morse* 15 How. 62, 112-120 (1854).
[17] John Cassidy, *How Markets Fail: the Logic of Economic Calamities* (New York: Picador, 2009), 133-137.

long-term planning and stable revenues to recoup sunk costs. Because scientific knowledge is nonrival-in-use and rival firms attempt to freeride off of each other's discoveries, firms might not invest enough in basic research unless patents are available to ensure a reasonable profit. Patents can encourage investments by allowing patent-holding firms to retain a monopoly on basic scientific discoveries while they develop commercially applicable inventions from them.

In the 1980s, two developments in US patent policy broadly expanded the realm of patentable material and sparked an investment boom in the biotechnology industry. The first came in June 16, 1980, when the Supreme Court held in *Diamond v Chakrabarty* (by a 5-4 ruling) that genetically engineered bacteria were patentable under Section 101 of Title 35 U.S.C.[18] The profound significance of this case was that it extended patentability to life forms that were not yet explicitly patentable under federal statute. In writing the majority opinion, Chief Justice Warren Burger established that "the relevant distinction was not between living and inanimate things, but between products of nature, whether living or not, and human-made inventions." Because Chakrabarty had made a new organism by engineering it with recombinant DNA, it was a patentable 'composition of matter.'[19] The Supreme Court's decision became a major catalyst for investment in the biotechnology industry and the patenting of genetic material. By defining the range of patentability as "anything under the sun that is made by man," it allowed private investors to invest in biotechnology R&D with the hope of commercializing a broad portfolio of lucrative patents on life forms and DNA.[20]

The second major development came from outside of the courts. On December 12, 1980, Congress passed the Bayh-Dole Act to foster "the commercialization and allocation of rights in

[18] *Diamond v. Chakrabarty*, 447 US 309 (1980).
[19] Daniel Kevles. "Ananda Chakrabarty wins a patent: biotechnology, law, and society," *Hist Stud Phys Biol Sci*. 25 (1994): 132.
[20] Martin Adelman and Randall Rader, *Cases and materials on patent law, 2nd ed.* (St. Paul, MN: Thomson/West, 2003), 107-8.

inventions resulting from federally sponsored research and development."[21] Congress intended to achieve this goal by allowing universities and small businesses to patent and license federally funded research. Prior to Bayh-Dole, the government owned roughly 30,000 patents on federally funded research that had yet to be commercialized.[22] These unused assets were somewhat analogous to what Hernando de Soto refers to as "dead capital," in that they lacked "value as collateral for securing the interests of creditors."[23] Given the slumping economy at that time, there was a growing interest in generating revenue and building new businesses from this intellectual property. The legislators behind this act hoped that allowing universities and small businesses to patent federally funded inventions would help them attract private investment and encourage investors to commercialize their discoveries.[24]

By assigning researchers formal rights to their intellectual property and allowing private actors to exchange those rights, Bayh-Dole helped turn new discoveries into what Hernando de Soto would call "live capital." The act helped channel investments into thousands of new patents, companies and commercial products, and ultimately contributed to growth in the domestic economy.[25] As of 2003, "374 new companies based on an academic discovery were formed [and] 4,081 new companies [had] been formed based on a license from an academic institution."[26] By 2009, the latter number was over 4,500.[27] Over 2,500 new commercial

[21] Chester Moore. "Killing the Bayh-Dole Act's Golden Goose," *Tulane Journal of Technology & Intellectual Property* 8 (2006): 153.
[22] *Ibid*.
[23] Hernando De Soto." Dead Capital and the Poor," *SAIS Review* 21.1 (2001): 17.
[24] Arti Rai and Rebecca Eisenberg. "Bayh-Dole Reform and the Progress of Biomedicine," *American Scientist* 91, no.1 (2003): 52.
[25] Moore, 156.
[26] Alfred Berkeley. "The Economic Impact of University Technologies," *Journal of Ass'n of University Technology Managers* 16 (2004): 4.
[27] Samuel Loewenberg. "The Bayh-Dole Act: a Model for Promoting Research Translation?," *Molecular Oncology* 3 (2009): 91.

products between 1998 and 2003 relied on the licensing of university research,[28] and 657 new products were launched in 2010 alone.[29] In the field of biotechnology, the yearly average number of gene patents granted rose from 12 in the 1970s to 143 in the 1980s, and jumped to 1606 in the 1990s (Figure 1).[30] Though much of the new wealth of genetic knowledge in the 1990s was the result of the Human Genome Project, the rapid rise in patents also reflected the potency of the combination of *Diamond v. Chakrabarty* and the Bayh-Dole Act.

The anticommons threat to biomedical technology

Some critics, however, wondered whether the large number of new patents was indeed beneficial to biomedical innovation. Chief among them were Michael Heller and Rebecca Eisenberg, who were concerned that the growing number of patents on basic discoveries would ultimately prevent firms from using them to develop more useful applications. In 1998 they warned of a potential "tragedy of the anticommons," in which the fragmentation of intellectual property rights would prevent downstream innovators from gaining an "effective privilege of use."[31] Heller and Eisenberg proposed two hypothetical mechanisms by which this might result: either the fragmentation would require researchers to spend more than they can afford in license fees, or patent-holders would use "reach-through" agreements to impose disproportionate royalties on or take control of licensees' future inventions later in the game.[32] In the former situation, patents would fail to produce commercially useful inventions because each patent holder would try to maximize its profits from licensing fees and no researcher would be able to

[28] Chester Moore. "Killing the Bayh-Dole Act's Golden Goose," *Tul. J. Tech. & Intell. Prop.* 8 (2006): 155.
[29] Ass'n of University Technology Managers, US Licensing Survey FY2010.
[30] Sam Kean. "The Human Genome (Patent) Project," *Science* 331 (2011): 531.
[31] Michael A. Heller and Rebecca S. Eisenberg, "Can Patents Deter Innovation? The Anticommons in Biomedical Research," *Science* 280 (1998): 698.
[32] *Ibid*., 699.

buy enough licenses to invent a non-infringing product. In the latter scenario, researchers would access patented discoveries using reach through licensing agreements (RTLA) but then face the risk of being bankrupted by the royalties and restrictions subsequently imposed by the licensor.

To further illustrate Heller and Eisenberg's article, James Buchanan and Yong Yoon proposed a model that posited the anticommons theory as concept symmetric to the longstanding "tragedy of the commons." Using the stylized example of tickets to a busy parking lot, Buchanan and Yoon demonstrate that the tragedies of both the commons and the anticommmons "depend on the number of persons [or firms] assigned simultaneous rights."[33] When multiple ticket issuers both have exclusive property rights to the parking lot, anyone who seeks to use the lot must obtain a ticket from each owner and ultimately pay a higher price than they would for a single ticket. Thus, while productivity is reduced by excessively high usage in the commons, it is reduced by prohibitively high overhead cost in the anticommons. When multiple patents claim gene fragments that are complementary to each other for the purpose of diagnosing or treating a hereditary disease, each patent holder gains the ability to extract rents on anyone who attempts to develop the test or drug downstream. Granted, one could argue that market competition from other parking lots nearby could help bring down the high transaction costs created by the anticommons. In genetics research however, there's only one human genome. When a particular test or drug requires access to a specific target gene, one cannot simply invent around a patent that grants exclusive rights over the use of that gene.

Heller and Eisenberg's proposed "tragedy of the anticommons" spurred a great debate within the research community, and encouraged numerous other studies on the potential development of a biomedical anticommons. Facing the dramatic rise in patent applications for

[33] James Buchanan and Yong Yoon. "Symmetric Tragedies: Commons and Anticommons," *The Journal of Law and Economics* 43, no. 1 (2000): 4.

fragments of DNA not specifically tied to an end product (i.e., Express Sequence Tags, or ESTs, and Single Nucleotide Polymorphisms, or SNPs), a growing number of researchers became concerned that the Bayh-Dole Act's failure to distinguish between basic, research-enabling discoveries and inventions with direct commercial applications would eventually lead to the establishment of an anticommons in genetic research.[34] For researchers engaged in genomic sequencing during and after the Human Genome Project (HGP), the seriousness of these concerns soon became apparent.

Patent wars over the human genome

ESTs are fragments of complementary DNA (cDNA) that capture the end portions of a subject's expressed genes (Figure 2). Since they express a small fraction of a gene rather than the gene's entire sequence, they are used as identification markers for their respective genes. EST patenting creates an anticommons scenario because the development of end products such as therapeutics and diagnostics requires the use of multiple fragments.[35] In the 1990s, however, NIH researcher Craig Venter began to patent ESTs en masse by sequencing thousands of them through automated machines.[36] By 1994, he and the NIH had filed a claim for almost 7,000 of these fragments.[37]

In order to produce the thousands of patent applications at such a rapid pace, Venter attempted to patent the various ESTs before fully understanding the genes that they represented.[38] The methods he used were obvious to competent researchers in his field, but he

[34] Rai, 55.
[35] Heller, 699.
[36] Daniel Kevles and Ari Berkowitz. "The Gene Patenting Controversy: A Convergence of Law, Economic Interests, and Ethics," *Brooklyn Law Review* 67 (2002): 236.
[37] *Ibid*.
[38] *Ibid*., 237.

attempted to patent his sequences even in the absence of a clear inventive step. According to Nobel laureate James D. Watson, this was "sheer lunacy" given that "virtually any monkey" could conduct such research.[39] Despite the lack of new insight it generated, however, Venter's rent-seeking strategy seemed poised to lock up a significant portion of the human genome even before it could be adequately explored. As Genentech's lawyer put it, "If these things are patentable, there's going to be an enormous cDNA arms race."[40] In response to the concerns raised by Venter's efforts, the USPTO rejected his initial patent applications in 1992 and the NIH withdrew all of its EST patent applications in 1994. Venter, however, continued to file thousands of EST at a nonprofit cooperating with Human Genome Sciences Inc. Other companies such as Incyte Pharmaceuticals soon followed suit, filing claims on over 40,000 EST and planning to file for almost 100,000 each year.[41]

In 1998, Venter moved to Celera, a for-profit company that had adopted a slightly revised approach towards patenting these basic research-enabling markers. By using computerized genome databases to find known genes that had a structure similar to that found in a new EST, researchers at the company would guess at the function of the gene it represented and then use this explanation to apply for a patent on that EST.[42] This practice cast even further doubt on the utility grounds for Celera's new EST patents. The guessing game used to apply for the patents demonstrated not so much an aptitude for producing new and useful findings, but rather a willingness to conduct routine, mechanical work based on prior discoveries. Meanwhile, Celera continued to restrict public access to its EST findings out of concern that competitors would

[39] *Ibid*.
[40] *Ibid*.
[41] *Ibid*, 240.
[42] *Ibid*, 247.

"repackage their data and sell it in competition with them."[43] Ironically, the firm included in its own patent claims data that had already been made public by Human Genome Project researchers through the GenBank database.[44]

As the EST patenting competition built up steam, the race to patent SNPs raised an even more fundamental concern from the research community. SNPs are point mutations that affect the expression of individual genes (Figure 3). Whereas EST patents could be used to monopolize a specific method of identifying a target gene (using the claimed EST as a probe), SNP patents could claim the target gene itself. Without a license from the SNP patent-holder, researchers could be blocked entirely from studying correlations between a given mutation of a gene and its physical expression.[45] Such situations would create problems beyond the anticommons dilemma present in the EST patent race.[46] Instead of reducing public access by imposing higher transaction costs, the SNP patent completely blocked public access by monopolizing a fundamental discovery. In order to build as broad a monopoly as possible, many startup companies in the 1990s began to file for patents on these SNPs.

As the total number of claims leapt exponentially, the EST and SNP arms race triggered responses from both academia and government. In February 1996, the UK-based Wellcome Trust sponsored a strategy meeting in which researchers from the NIH National Center for Human Genomic Research agreed to the Bermuda rules, which required the release of all newly

[43] Rebecca Eisenberg. "Genomics in the public domain: strategy and policy," *Nature* 1 (2000): 73.
[44] *Ibid*.
[45] John Barton. "Patents, Genomics, Research and Diagnostics," *Academic Medicine* 77, no.12 (Suppl.) (2002): 1339-40.
[46] *Ibid*., 1340. For traits governed by a single gene, the issue here would be a restriction on a foundational discovery, not multiple rights to the same SNP. Most traits, however, are determined by the combined influence of multiple genes. In this situation, SNP patents on different genes that all affect a single trait would lead to an anticommons scenario in which multiple rights-holders would be able to mutually exclude each other from developing a comprehensive diagnostic test for the given trait. See the hypothetical argument made in by Barton for more details.

sequenced assemblies of DNA on a daily basis.[47] In March of 2000, the presidents of both the Royal Society of London and the US National Academy of Sciences warned that EST patents, although in the interests of short-term shareholders, would "not serve society well."[48] That same month, President Bill Clinton and Prime Minister Tony Blair issued a joint public statement asserting that "raw fundamental data on the human genome, including the human DNA sequence and its variations, should be made freely available to scientists everywhere."[49] In 2001, the USPTO finally clarified its utility guidelines towards patent claims on ESTs, requiring the identification of the represented gene and its function.[50]

Interestingly, some of the strongest responses towards the EST/SNP patenting craze came not from researchers and regulators but from leading firms within the biotechnology industry. In the mid 1990s, Merck partnered with Washington University in St. Louis to publish sequences of cDNA for the public.[51] Although Merck's former VP of research subsequently stated that the firm did not seek to purposely undermine anyone's intellectual rights,[52] the Merck Genome Initiative served in the earlier years as a means of responding to other firms' efforts to patent ESTs.[53] In the spring of 1999, ten pharmaceutical companies joined the Wellcome Trust to establish and fund a new private nonprofit, The SNP Consortium.[54] The Consortium made it its

[47] *Summary of the Principles Agreed at the first International Strategy Meeting on Human Genome Sequencing*, U.S. Department of Energy, Human Genome Project Information, (28 February 1996).
[48] Bruce Alberts and Sir Aaron Klug. "The Human Genome Itself Must be Freely Available to All Humankind," *Nature* 404 (2000): 325, quoted in Daniel Kevles and Ari Berkowitz, "The Gene Patenting Controversy: A Convergence of Law, Economic Interests, and Ethics," *Brooklyn Law Review* 67 (2002): 247.
[49] Eisenberg, *Genomics*, 71.
[50] *Utility Examination Guidelines*, 66 Fed. Reg. 1092 (Jan. 5, 2001)
[51] Rebecca Eisenberg. "Intellectual Property Issues in Genomics," *Trends in Biotechnology* 14 (1996): 304.
[52] Alan Williamson. "The Merck Genome Indexing Project," *Drug Discoveries and Therapeutics* 4, no.3 (1999): 118.
[53] Eisenberg, *Genomics*, 72. By releasing them to the public and establishing them as prior art, although this strategy became irrelevant with the new USPTO utility guidelines regarding ESTs in 2001.
[54] Arthur Holden. "The SNP Consortium: Summary of a Private Consortium Effort to Develop an Applied Map of the Human Genome," *Biotechniques* 32 (2002): S23. The ten companies were: Bayer Group AG, Bristol-Myers Squibb Company, Glaxo Wellcome PLC, Aventis, Monsanto Company, Novartis AG, Pfizer Inc, Roche Holding Ltd., SmithKline Beecham PLC, and Zeneca Group PLC. The initial funding totaled $53 million.

explicit objective to "manage publication of the resulting SNP map in a manner intended to maximize the number of SNPs that enter the public domain (as that term is understood in patent law)."[55] In essence, the perceived threat of balkanization was so great that the pharmaceutical industry ultimately decided to release SNP data to the public.[56] Rather than publish its findings immediately like the researchers who followed the Bermuda rules, the Consortium filed Statutory Invention Regulations (SIR) to the Patent Office. While this practice delayed the release of the Consortium's data to a quarterly basis, it allowed the Consortium to prevent other firms from using the released findings data to file their own patents.[57]

The development of strategies such as the Consortium within the biomedical technology industry reflected a growing discrepancy between the original purpose of patents and the practices allowed by gene patent policy. Despite patent policy's intended role as a means of incentivizing innovation, the continuous stream of patent claims from firms such as Incyte and Human Genome Sciences was driving up the cost of downstream innovation on more developed, useful products such as therapeutic drugs. The trickle had become a torrent, and leading drug manufacturers such as Pfizer and SmithKline Beecham were paying millions of dollars just to gain access to patented genetic information.[58] In 1995, then Chairman of the Council of Economic Advisers Joseph Stiglitz warned that because "one innovation builds on another," "the breadth and utilization of patent rights can be used not only to stifle competition but also have

[55] *Ibid*.
[56] Rai, 55.
[57] Eisenberg, *Genomics*, 72. SIRs have attributes similar to those of patents but do not grant the right to exclude others from "making, using, selling or importing the invention." They also require the applicant to waive the right to pursue a patent for a certain length of time.
[58] Lori Andrews. "The Gene Patent Dilemma: Balancing Commercial Incentives with Health Needs," *Houston Journal of Health Law and Policy* 2 (2002): 85.
"Pfizer reportedly paid $15.75 million to Incyte Pharmaceuticals for access to their DNA database and SmithKline Beecham has paid $125 million to Human Genome Sciences for access to its genetic information."

adverse effects in the long run on innovation."[59] Economist Carl Shapiro followed up in 2001 with his warning of the "patent thicket," which asserted that the thicket of patent rights on the complementary components of downstream products was creating holdup problems by exposing product developers to higher costs and potential infringement liability.[60]

A failure to protect free inquiry

In order to address and avoid this barrier to innovation, the NIH developed a set of guidelines for recipients of its research grants. Designed to encourage the sharing of biomedical and genetic research tools developed with public funding, the guidelines stated that "proprietary rights in research tools that do not require further development may function more as a tax on commercial development than as a source of rights to preserve the viability of end products and to motivate further investment."[61] Much of the momentum behind these guidelines came from NIH Director Harold Varmus, who had established the working committee behind the guidelines and had begun his term by removing Venter's initial EST claims in 1994. Under Varmus, the NIH worked to expand researchers' access to patented genetic research tools held by patent holders and their exclusive licensees.[62] While respecting patent holders' and licensors' rights to exclude commercial competitors from using their intellectual property, the NIH attempted to worked out an explicit "research exemption" that would protect university research from liability for patent infringement.

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[59] Carl Shapiro. "Navigating the Patent Thicket: Cross Licenses, Patent Pools and Standard-Setting," *Innovation Policy and the Economy* 1 (MIT Press 2001) at n.1.
[60] *Ibid*, 139-144.
[61] *Principles of Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Resources*, 64 Fed. Reg. 28205, 28206 (May 25, 1999). Cited in Andrews, *Dilemma*, 85.
[62] For example, in 1999 Varmus negotiated a Memorandum of Understanding (MOU) with Du Pont that allowed NIH funded researchers to use the Oncomouse despite Du Pont's exclusive license to Harvard University's patent on it. See: Sasha Blaug, "Managing Innovation: university- industry partnerships and the licensing of the Harvard mouse," *Nature Biotechnology* 22, no.6 (2004):761-3.

Because these liability exemptions had to be negotiated on a case-by-case basis, university researchers often invoked the common law research exemption when an explicit agreement was not available. Stemming from Judge Learned-Hand's decision in the appellate ruling *Whittemore v. Cutter*, the common law research exemption provided an affirmative defense for those who infringe patents "merely for philosophical experiments, or for the purpose of ascertaining the sufficiency of the machine to produce its described effects."[63] In 2002, however, the Federal Circuit ruled in *Madey v. Duke University* that universities could be sued for patent infringement despite their non-profit status.[64] In its ruling in favor of the plaintiff, the court argued that any act "in furtherance of the alleged infringer's legitimate business" going beyond "strictly philosophical inquiry" did not qualify as exempted experimental use.[65] By including nonprofit university research in its broad definition of "legitimate business," this case rendered the common law research exemption effectively null.[66]

In light of the concerns raised by the EST/SNP patents and this new threat of infringement liability for basic genomic research, US Congressmembers Lynn Rivers (D-MI) and Dave Weldon (R-FL) introduced the Genomic Research and Diagnostic Accessibility Act ("GRDAA") to the House floor on March 14, 2002. Though it did not attempt to remove human genes from the realm of patentability, the GRDAA proposed an infringement liability exemption for noncommercial research on genetic sequence information and protection against infringement

[63] *Whittemore v. Cutter*, 29 Fed. Cas. 1120 (C.C.D. Mass. 1813).
[64] *Madey v. Duke Univ*., 307 F3d 1351 (Fed. Cir. 2002). *cert. denied* 539 U.S. 958, *appeal denied* 78 Fed. App'x 105 (Fed. Cir. 2003) (per curiam), *partial summary judgment denied* 336 F Supp. 2d 583 (M.D.N.C. 2004).
John Madey had sued Duke University for using lab equipment that he had patented and brought to the school when he was hired as a professor there.
[65] *Id*., 1362.
[66] *Id*. According to the ruling, "educating and enlightening," as well as the pursuit of "grants, students and faculty," all comprise a university's "legitimate business." Because the patented equipment could be used to conduct research that will ultimately further those goals, Duke University was not exempt from liability for infringing on Madey's patent.

remedies for physician-conducted gene testing for medical purposes.[67] To address the broader issue of patentability, Rivers and Weldon introduced a companion bill, the Genomic Science and Technology Innovation Act.[68] This companion bill called on the White House Office of Science and Technology Policy to begin a study on federal patent policy towards genes and its impact on the development of new technologies.[69] Combined, the acts were designed to address both the immediate public health need for clinical diagnostics and long-term goals for biomedical innovation. Unfortunately, the bills died in committee and Rivers was unable to win her reelection bid. Weldon sponsored a subsequent bill (the Genomic Research and Accessibility Act, or "GRAA") with Xavier Becerra in 2007, but the GRAA was worded too broadly and failed to gain enough support to pass through committee.[70]

Since then, the USPTO has for the most part determined de facto policy towards human gene patents. Despite public commentary in favor of stricter regulations over gene patents, the USPTO's policies have allowed for the rapid expansion of gene patentability. While proponents of expansive intellectual property rights point to the rapid growth of the US biotech industry as a vindication of this position, opponents have argued that the combination of *Madey* and the growing number of gene patents have imposed an increasingly restrictive IP regime that slows downstream innovation and delays access to clinical diagnostics. With the curtailment of the common law research exemption to only that which is unrelated to the "legitimate business" of an institution, Bayh-Dole might have the ironic effect of increasing the risks associated with research and innovation while reducing the risks for those who invest in patenting it. Although

[67] *Genomic Research and Diagnostic Accessibility Act of 2002,* H.R. 3967, 107th Cong. (2002).
[68] *Genomic Science and Technology Innovation Act of 2002,* H.R. 3966, 107th Cong. (2d Sess. 2002).
[69] *Id*.
[70] By attempting to bar patents on any "nucleotide sequence, or its functions or correlations, or the naturally occurring products it specifies," the bill threatened many patents that were conducive of and critical to innovation (e.g., patents for the synthesis of recombinant DNA not already found in the human genome).

an observable, widespread anticommons scenario has yet to emerge, the past history of gene patenting has raised important questions and issues that have yet to be fully explored.

Current practice and the clinical diagnostics dilemma:

The answer to these questions, however, is not simply a matter of per se patentability for all DNA. As noted earlier, one reason that the Becerra-Weldon bill failed to make it out of committee was that its scope was not designed proportionally to the problem. Although it succeeded in publicizing legitimate concerns over the effects of patents on the development of genetic diagnostics, the Becerra-Weldon bill also extended beyond the Rivers-Weldon bill and attempted to cover any nucleotide sequence, including those that were synthetically designed for use in therapeutic drugs. The radical nature of this proposal drew a strong response from the biotechnology industry, which lobbied to defeat Becerra-Weldon before it was put to a vote. In his testimony to House Committee on the Judiciary, Subcommittee on the Courts, the Internet, and Intellectual Property in October 2007, attorney Jeffrey Kushnan from BIO asserted that "Concerns that basic research will face significant new obstacles from patent litigation are unfounded and not borne out by experience, either from before or after the *Madey* decision."[71]

Mr. Kushnan's comment conveniently ignores the fact that public concern over the significant obstacles that surfaced in the EST and SNP patent race played a large role in stemming the tide of junk patents and avoiding potential patent litigation. It does, however, help illustrate a critical point regarding current practices in the field of genetic research. As Dr. Jon Soderstrom explained in the same House Committee hearing, forbearance on the part of patent

[71] Kushnan, Jeffrey. Statement to the House, Committee on the Judiciary. *Stifling or Stimulating – the Role of Gene Patents in Research and Genetic Testing*, Hearing, 30 October 2007 (Serial No. 110-6): 17.

holders and exclusive licensors often allow for a de facto research exemption.[72] Given that most researchers agree with the general consensus that naturally occurring genes in the human body should not be patentable, [73] there seems to be a culture of forbearance in the biomedical research community that reduces the need for a legal defense.

Outside of clinical diagnostics, many studies have shown that the Heller and Eisenberg's hypothesized mechanisms are not widely substantiated by empirical data. The National Academy of Sciences estimates that 3,000+ new gene patents have been issued per year since 1998, adding up to over 40,000 patents to governments, universities and for-profit entities ranging from large firms the startups.[74] Even with the large number of patents and the wide range of interests behind them, studies in the U.S. and other large, developed economies have found that anticommons problems have been fairly infrequent.[75] Within the U.S., a study showed only 1% of academic biomedical researchers reporting a project delay due to patents held by other researchers.[76] Given the empirical data above, it seems that researchers have heeded Heller and Eisenberg's warning and have largely avoided the anticommons problem. Workaround agreements such as royalty offsets have prevented RTLAs and license stacking from driving projects to a loss.[77] Because researchers can try to invent around certain types of patented discoveries, conduct their research offshore or challenge the validity of the patent,

[72] Christopher Holman. "Recent legislative proposals aimed at the perceived problem of gene patents," *Biotech Briefing ABA Section of Sci. & Tech. Law, Chicago, I.L.* (2008).
[73] Isaac Rabino. "How Human Geneticists in the US View Commercialization of the Human Genome Project," *Nature Genetics* 29 (2001): 15-16.
[74] Timothy Caulfield et al. "Evidence and Anecdotes: an Analysis of Human Gene Patenting Controversies," *Nature Biotechnology* 24, no.9 (2006): 1092.
[75] *Ibid*.
[76] *Ibid*.
[77] John Walsh et al. "Research Tool Patenting and Licensing and Biomedical Innovation," in *Patents in the Knowledge-Based Economy* by Wesley M. Cohen and Stephen A. Merrill, (*Washington, DC: National Academies, 2003),* [299].

patent holders outside of the clinical diagnostics space often have an incentive to avoid raising royalties beyond reasonable levels.[78]

For clinical diagnostics, however, individual patent holders can still bear a disproportionately restrictive impact on medical innovation. As mentioned earlier, diagnostic tests for mutations in specific genes cannot simply invent around patents claiming full rights to the target genes themselves. Although it is currently in the process of seeking public commentary regarding potential reforms,[79] the USPTO still allows patents on foundational discoveries for which no workaround solutions exist. These patents can prove to be a critical obstacle for developers of new diagnostic methods. Because universities and firms are limited in their ability to identify, evaluate and pursue opportunities for further development, the individual patent holder is less likely to maximize the potential uses of a given discovery in the way that multiple innovators would.[80] If the patent holder maintains exclusivity over an entire area of research, then, it could significantly stunt progress and impose the ultimate cost on those whose lives might be saved through subsequent inventions.

Recent evidence supports the argument that gene patents exert a restrictive effect on innovation in the field of clinical gene testing. One survey by Merz et al. showed that out of 119 US laboratories engaged in genetic testing for hemochromatosis, 30% of them either gave up or stopped developing their tests after patents were issued on the HFE gene.[81] Almost all of the 119 laboratories had known of the patent, and half had received cease-and-desist letters from the exclusive licensor for the patents. In a phone survey by Cho et al., about a quarter of the respondents "reported that they had stopped performing a clinical genetic test because of a patent

[78] *Ibid*., 323.
[79] *Request for Comments and Notice of Public Hearings on Genetic Diagnostic Testing*, 77 Fed. Reg. 3748 (Jan. 25, 2012).
[80] J. Walsh, 291.
[81] Jon Merz et al. "Diagnostic testing fails the test," *Nature* 415 (2002): 577.

or license."[82] Out of the thirty respondents who comprised that group, nearly a third of them cited the BRCA1/2 patents currently held by Myriad Genetics (Figure 4).[83]

As noted earlier, the SNP race demonstrated the importance of securing research access to basic discoveries and taking preemptive action against the development of biomedical anticommons. If the government is to continue using patents to effectively promote biotechnology R&D, it must keep in pace with current technology and address anticommons issues proactively. While workaround solutions may help avoid the need for constant policy revision, holding blind faith in the benevolence of patent holders may be a foolhardy decision. In order to foster socially useful science while preserving the economic value of patent rights as collateral, policymakers must delineate the standards of patentability in a way that promotes both access to foundational discoveries and stronger intellectual property rights.

Due to the recent testimonies of many researchers and the relatively high level of social awareness of breast cancer, the BRCA1/2 issue has become a particularly visible controversy. Myriad, however, claims that it never blocked research on either gene.[84] In the words of former Myriad president Gregory Critchfield, "If you give test results back to patients, it crosses over the line, and it's no longer a simple research test. [It] is really a very bright line."[85] Many researchers, however, argue that Mr. Critchfield's assertion is not a practical assessment of Myriad's effects on clinical "research." Cho asserts that sharing clinical test results is often a necessary part of furthering scientific research.[86] In Merz's view, "There is no clear line to be drawn between clinical testing and research testing, because the state of the art of genetic tests is

[82] Mildred Cho et al. "Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services," *Journal of Molecular Diagnostics* 5, no.1 (2003): 7.
[83] *Ibid*., 6.
[84] Gold, S44.
[85] J. Walsh, 318.
[86] *Ibid*., 319.

such that much more clinical study is necessary to validate and extend the early discovery of a disease gene. Thus, the restriction of physicians from performing clinical testing will directly reduce the knowledge about these genes."[87] Though Myriad can argue that patents are necessary to incentivize private investment in research, it cannot argue that enforcing its patents poses no harm to research on clinical diagnostics.

By forcing university researchers and healthcare providers to abandon their work on developing better clinical tests for patients, Myriad has stirred up the healthcare community and raised serious doubts regarding the validity of its patents. On the other hand, biotechnology industry experts have provided strong reasons against a complete ban on gene patents. Though the anticommons theory is not an entirely new, its recent emergence with the expansion of gene patentability makes one to wonder about its potential long-term consequences. The following case study on the BRCA1/2 controversy will attempt to explore these dimensions of the gene patent debate, and learn how they will affect the future of clinical diagnostics in the US.

The Myriad Case:

The patenting of BRCA1/2

The discovery of the BRCA1/2 genes was the cumulative result of research conducted by scientists from around the world. The search for the first BRCA gene involved a fierce competition between seven major research teams across five countries, and led to the creation of the International Breast Cancer Linkage Consortium in 1988.[88] Funding came from a large number of sources, including public institutions such as the U.S. National Institutes of Health. Two years later, a U.S. team led by Mary Claire King from the University of California at

[87] *Ibid*., 318.
[88] DT Bishop et al. "Preface to the breast cancer linkage consortium papers," *American Journal of Human Genetics* 52 (1993): 677.

Berkeley announced the location of BRCA1 on chromosome 17.[89] Needless to say, the scientific community received the news with much enthusiasm.

However, it was a different research group – one led by Marc Skolnick at the University of Utah's Centre for Genetic Epidemiology – that ultimately acquired the patents for BRCA1. Researchers seeking to patent the BRCA1 gene had to determine both the normal and mutated sequences of the gene. Using a vast pedigree of Mormon families that he had recorded since the 1970s, Skolnick was able to trace the hereditary path of breast cancer by cross-linking the pedigree with the Utah cancer registry.[90] This study fueled the group's future research, and with $5 million from the National Institutes of Health (NIH) Myriad began to sequence mutations of the BRCA1 gene.[91] To secure more funds for the project in the meantime, Skolnick's team separated itself from the university's genetic center and incorporated as Myriad Genetics in 1991.[92] By promising the large pharmaceutical firm Eli Lilly licensing rights over diagnostic kits and therapeutics developed from BRCA1, Myriad was able to raise $2.8 million ($1 million in equity, $1.8 million in licensing royalties) from the firm even before it received any patents.[93] In August of 1994, Myriad filed its first patent application over sequences for BRCA1 and its mutations. After three years and multiple revisions from applicant, the USPTO granted Myriad in December 1997 a patent covering 47 different mutations of the BRCA1 gene.[94] In the next six months, Myriad was issued seven additional patents on sequences of BRCA1 and diagnostic methods used to test for the gene.[95]

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[89] Jeff Hall et. al. "Linkage of early-onset familial breast cancer to chromosome 17q21," *Science* 250 (1990): 1684.
[90] Bryn Williams-Jones. "History of a Gene Patent: Tracing the Development and Application of Commercial BRCA Testing," *Health Law Journal* 10 (2002): 129-130.
[91] Janice E. Graham et al. "Actor-Network Theory: a tool to support ethical analysis of commercial genetic testing," *New Genetics and Society* 22 (2003): 282.
[92] Gold, S41
[93] *Ibid.*
[94] US 5,693,473. US Patent Office. <http://www.uspto.gov/>
[95] Gold, S41.

Interestingly, however, another US firm managed to get a patent for the normal BRCA1 sequence months before Myriad did. After licensing King's research on BRCA1, Oncormed filed for a patent on the "consensus sequence of the human BRCA1 gene" in February 1996 and received a patent in August 1997.[96] At first, Oncormed and Myriad sued each other for patent infringement. In May 1998, however, Myriad bought Oncormed's BRCA1/2 patents for an "undisclosed" sum.[97] Throughout the 1990s, Myriad persisted in consolidating patent rights over both BRCA1 and BRCA2. In September 1994, a UK-based, multinational team led by Michael Stratton became the first to announce the location of BRCA2. The team published the genetic sequence by December 1995, and the Cancer Research Campaign (the charity fund supporting the research) filed for a patent in the UK. Myriad, however, managed to file for a patent in the US a day before the article was published. Claiming that its sequence was more complete than Stratton's, Myriad successfully applied for and received patents on the BRCA2 gene, its mutations and the processes by which it would be detected.[98]

Given the number teams working on the discovery and sequencing of BRCA1/2, it is unclear whether the patents granted to Myriad were necessary for the identification of the genes. For BRCA1, it is clear that patents played an important role in attracting funding for research. Both Oncormed and Myriad sequenced the genes in order to patent them. While the $5 million from NIH funded much of Skolnick's initial work, the private investments from Eli Lilly and other prospective shareholders gave Myriad the additional boost it needed to complete its cross-linkage analysis. In the absence of a large nonprofit such as CRC, Myriad's anticipated patents on BRCA1 were critical to the firm's ability to secure private funding. For BRCA2, however, the Cancer Research Campaign (CRC) charity provided sufficient funding for Stratton's team's

[96] E. Marshall. "The battle over BRCA1 goes to court; BRCA2 may be next," *Science* 278 (1997): 197.
[97] *Ibid*.
[98] Gold, S41.

sequencing of the gene. Although the CRC sought to patent Stratton's discovery, its intent was to secure broad availability of the gene by preventing other entities from patenting and restricting it.[99] Thus, even if Myriad had not patented BRCA2, scientists would have been able to rely on Stratton's research to develop tests for it.

Questions also remain as to the appropriateness of the patents. By granting Oncormed and Myriad patents concurrent on the same gene, the USPTO created a legal mess in which each party sued the other for infringement.[100] Although the issue was eventually settled out of court, it raises questions regarding the original validity of patents issued by the USPTO. Furthermore, the BRCA1/2 patents granted Myriad a broad monopoly over foundational discoveries first made by Mary Clare King and Michael Stratton. When asked about the suspicious timing of Myriad's BRCA2 patent, Stratton stated that Myriad had capitalized on an information leak at his workplace, the Institute of Cancer Research.[101] According to one citation network analysis, researchers around the world still tend to believe that Michael Stratton's team was the first to sequence BRCA2.[102] In light of Stratton's comments, the study suggests that the scientific community is somewhat doubtful of the validity of Myriad's claims to the BRCA2 sequence.

Although patent rights played a critical role as a financial incentive for startup firms such as Myriad and strategic investors such as Eli Lilly, they were less of an incentive for the researchers who directly contributed to the discovery of the genes. Both Stratton and King intended to license their discoveries openly rather than restrict other researchers' access to them, and this reflected the general culture in the geneticist community against the aggressive use of

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[99] Robert Cook-Deegan. "Gene Patents," in *From Birth to Death and Bench to Clinic: The Hastings Center Bioethics Briefing Book for Journalists, Policymakers, and Campaigns*, ed. Mary Crowley (*Garrison, NY: The Hastings Center, 2008)*, 71.
[100] Williams-Jones, 312.
[101] James Meek. "Money and the meaning of life," *The Guardian*, 17 January 2000.
[102] Parthasarathy Decl. (24 August 2009): 6, filed in *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office and Myriad Genetics, Inc.*, 702 F. Supp. 2d 181 (S.D.N.Y. 2010).

patents on human DNA. Myriad, however, would block others from benefiting from its own findings despite its heavy reliance on the work of others. Rather than license its genes to other research teams that had developed their own diagnostic tests, Myriad would choose to kill market competition by forcing researchers to shut down their labs and clearing their products out of the market. Ultimately, the broad scope of the BRCA1/2 patents would undermine the development of improved diagnostic techniques by preventing academic labs from applying them in clinical studies. Given the limited role that the patents played in the discovery and identification of the BRCA1/2 gene, it is difficult to argue that the utility initially generated by the BRCA1/2 patents was enough to justify broad restrictions on subsequent research.

Business development and domestic concerns

Through its nine patents on BRCA1/2, Myriad consolidated its exclusive rights over all applications involving the two genes.[103] Although it claimed that its long-term goal was to develop therapeutic treatments for breast cancer, the firm started by building a diagnostics business based out its facilities in Utah. To launch its diagnostics business, Myriad built a $30 million laboratory[104] and began to market the three subsets of its BRACAnalysis® test: the comprehensive test ($2600 for complete sequence of BRCA1/2), the single site test ($295) and the 3-mutation multisite test ($450 for mutations prevalent in the Ashkenazi Jewish population).[105] Patients who did not have relatives already tested for BRCA1/2 would receive the comprehensive test, while the single site test would be given to relatives of patients for whom a mutation was found. The logic of the system was that the relatives of patients testing positive would only have to test for the mutation already discovered in family.

[103] *Id.*, 6.
[104] Gold, S42.
[105] Williams-Jones, 134.

Myriad sought to build its business by drawing together a large network of professionals, providers and payors within the healthcare industry. It provided training for physicians and clinicians, whom they relied on for patient referrals. The firm also made agreements with large health management organizations such as Kaiser Permanente and Blue Cross/Blue Shield to provide testing for their patients, and had its tests covered by over 390 insurers by 1999.[106] Throughout this process, Myriad marketed its test as the "gold standard" for breast cancer diagnostics.[107] Laboratory tests were kept in-house, with the exception of follow-up single-site tests that were sometimes licensed to local labs. The firm claimed that its method of full sequencing was superior to other methods because it checked each individual nucleotide in the BRCA code to specifically locate each point mutation.[108]

By the time Myriad settled its patent disputes, however, other methods had already become commercially available. At the University of Pennsylvania, Dr. Arupa Ganguly at the Genetics Diagnostics Laboratory (GDL) had created a faster, cheaper test that used gel electrophoresis to detect mutations in the DNA.[109] At the Genetics and IVF Institute (GIVF), patients were given tests that used protein truncation testing (PTT) or single stranded conformational polymorphism (SSCP) in addition to local DNA sequencing. Despite Myriad's claim that its sequencing method was the gold standard, PPT or SSCP had the added benefit of detecting large re-arrangement and deletion mutations that weren't always detected Myriad's sequencing method.[110] To eliminate this potential source of competition, Myriad wrote cease-and-desist letters to both GDL and GIVF in early 1998.[111]

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[106] *Ibid*., 136.
[107] Gold, S63.
[108] Williams-Jones, 135.
[109] Parthasarathy Decl., 10.
[110] Williams-Jones, 135.
[111] Gold, S42.

Although the first letter was enough to convince GIVF to quit its tests, GDL argued that its tests fell under the common law research exemption. Because its clinical tests had been restricted to subjects who were enrolled under the National Cancer Institute's (NCI) Cancer Genetics Network and its research protocols, GDL asserted that they were beyond the reach of Myriad's patents.[112] Myriad disagreed, however, and maintained that GDL was providing a commercial service as long as it disclosed the results of its tests to patients. It sent a total of four letters, two to GDL co-Director Dr. Haig Kazazian and two to University of Pennsylvania general counsel Robert Terrell, accusing the University and the GDL of patent infringement and demanding written assurance that the testing would be stopped.[113] To avoid a protracted lawsuit for which it lacked the resources, GDL eventually abandoned its project. With GDL out of the picture, Myriad reached a Memorandum of Understanding (MOU) with the NCI that allowed it to provide its testing services to NCI researchers and offer discounted prices only when they were paid for in grant funds.[114] This move allowed Myriad to expand its market share and draw more revenue from public funds without reducing its revenue from private insurers and patients.

From a policy perspective, one of the more worrisome aspects of Myriad's negotiations with the GDL was that they resulted in Myriad determining the boundary between exempted research and commercial infringement.[115] The line between clinical research and commercial diagnostic services is grey, fuzzy and difficult to determine, and allowing the patent-holder to determine the boundary seems foolhardy at best. In the case of BRCA1/2, Myriad's enforcement of its patents impeded the provision of services critical for clinicians and their patients. With the closure of Ganguly's lab at the GDL, cancer-counseling clinics at New York University,

[112] Parthasarathy Decl., 12.
[113] Ganguly Decl. (18 August 2009): 3-4. *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office et al*., 702 F. Supp. 2d 181 (S.D.N.Y. 2010).
[114] Gold, S42.
[115] Parthasarathy Decl., 13.

Columbia University and Georgetown University stopped sending their samples to GDL and lost the ability to pursue a second opinion other than Myriad's.

Through its aggressive actions against the GDL, Myriad dissuaded other university labs at Yale, Columbia, and Emory from providing their own full sequencing and large rearrangement services for BRCA1/2 despite their capacity to do so immediately.[116] This became a critical problem for patients who received test results that had variants of unknown significance (VUS), genetic mutations for which Myriad did not know if they were indicative of increased susceptibility to cancer. According to Director Harry Ostrer at the NYU Langone Medical Center (the main plaintiff in this case), Myriad's monopoly on BRCA1/2 testing prevented him and other researchers from studying the VUS to determine their meaning.[117] Dr. Wendy Chung, Director of Clinical Genetics at Columbia University, noted that as of 2005 a disproportionate number of the 1,433 test results with VUS were from racial minorities (i.e. African Americans, Asians and Hispanics) because of the limited data on patterns of genetic variation within minority populations.[118] Given the high price of Myriad's testing services and the firm's decision to not accept Medicaid patients, Dr. Ostrer worried that Myriad might not see a sufficient financial incentive in addressing the VUS predominant in patients from underprivileged racial minority groups.[119] Although university labs were ready to engage in clinical research addressing the VUS in these patient populations, Myriad's patents were preventing them from doing so.

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[116] Matloff Decl., Chung Decl., Ledbetter Decl., *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office and Myriad Genetics, Inc*., 702 F. Supp. 2d 181 (S.D.N.Y. 2010).
[116] Gold, S42.
[117] Ostrer Decl .(11 August 2009). *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office and Myriad Genetics, Inc*., 702 F. Supp. 2d 181 (S.D.N.Y. 2010).
[118] Chung Decl., (30 July 2009): 5. *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office and Myriad Genetics, Inc*., 702 F. Supp. 2d 181 (S.D.N.Y. 2010).
[119] Ostrer Decl., 7.

By eliminating BRCA1/2 testing at university labs, Myriad's aggressive actions also raised civil rights concerns regarding patients' access to their own genetic information. By preventing clinicians from reporting test results to patients and allowing for the marginalization of racial minorities due to disparate VUS rates, the firm's practices violated the right to free inquiry under the First Amendment and raised concerns regarding equal protection under the Fourteenth Amendment. When Myriad stated that it did not seek to restrict research in any way, it meant that Dr. Chung and other NCI researchers were allowed to sequence the BRCA1/2 gene for their own use but forbidden to sequence it for patients. Because Myriad's patents blocked researchers from disseminating the pure information expressed in patients' genes, they undermined the right to free inquiry by preventing the transmission of knowledge and thought. The patents also discouraged university investment in translational research critical to resolving the VUS,[120] including those that were found disproportionately in racial minorities. Patients of color were placed at greater risk because Myriad's BRACAnalysis® test results generated unresolved VUS, and this raised concerns about racial inequality regarding access to accurate testing. Myriad addressed the VUS issue by improving its test over time. In terms free inquiry, however, it was clear that Myriad's decision to prevent other labs from providing BRCA1/2 testing was violating the patient's right to seek a second opinion.

By eliminating opportunities for second opinion testing, Myriad's restriction of free inquiry would place patients at greater risk of misdiagnosis. As mentioned earlier, the use of large-rearrangement tests such as PPT helped other laboratories find structural mutations that weren't detected by Myriad's sequencing test. Myriad, however, did not employ large rearrangement testing until much later. In 2001, French researcher Dominique Stoppa-Lyonnet

[120] Ledbetter Decl., (20 August 2009): 4-7. *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office and Myriad Genetics, Inc.*, 702 F. Supp. 2d 181 (S.D.N.Y. 2010).

and her colleagues reported that they had found a previously undetected mutation in a French family previously studied by Myriad.[121] Meanwhile, Mary Clare King conducted a study of 300 high-risk women previously studied by Myriad and used alternative methods to identify previously undetected BRCA mutations in 12% of those subjects.[122] In light of these findings, Myriad admitted that some large rearrangement mutations would escape detection by its original test, and continued to work on an additional test that was eventually completed in 2006. The firm has asserted that throughout this time, it did not seek to shut down other laboratories offering alternative, individualized tests designed to catch these large rearrangements.[123]

The testimony of Genetic Counseling Director Ellen Matloff at the Yale Cancer Center suggests otherwise. In her written statement to the Southern District Court of New York, Ms Matloff noted that "Myriad's continuous and systematic assertion of its BRCA patents [had] resulted in the elimination of other genetic testing options available to [her] and [her] patients that could [have been] cheaper, better and more appropriate."[124] As it had done with GDL, Myriad sent a cease-and-desist letter to the Yale DNA Diagnostics lab in late 2000. The Yale lab, which had previously offered Ms Matloff BRCA1/2 analysis at $1600, stopped its tests after receiving the letter. In 2005, Ms Matloff requested Myriad's permission for the Yale lab to test her patients for the large rearrangements in the BRCA genes that Myriad's test had missed. Despite the fact that it did not yet provide such tests, Myriad denied the request. Ms Matloff 's patients were thus denied access to alternative individualized tests that could have led to a better outcome. Although Myriad eventually released its own version of the test (the BART®) later

[121] Gold, S45.
[122] Tom Walsh, et al. "Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer," *JAMA* 295 (2006): 1379.
[123] Gold, S45.
[124] Matloff Decl., (12 August 2009): 4. *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office and Myriad Genetics, Inc*., 702 F. Supp. 2d 181 (S.D.N.Y. 2010).

on, it charged an additional $650[125] premium that most insurers were not willing to pay. Because many nationwide insurers have chosen not to bear the additional cost of covering Myriad's BART®, patients are left with no choice but to bear the full burden of the cost or forgo the test. Ms Matloff notes that were it not for Myriad's threat to sue, other laboratories would have been able to provide these tests earlier and at a much lower price.[126]

Given this evidence regarding Myriad's business practices in the US, it is difficult to deny that the broad scope of Myriad's BRCA patents led to restrictions on clinical researchers' access to the BRCA genes, and cost some patients the opportunity for earlier and more accurate detection. Though Myriad insists that it never blocked the research use of its BRCA patents, this claim implies a rather narrow definition of "research" that excludes much of the clinical testing that university labs attempted to do. According to Director David Ledbetter at the Emory Medical School's Division of Medical Genetics, "sequencing will only cover 70% of the causative mutations" linked with breast cancer but "structure causes 30%."[127] Despite the fact that nonprofit labs in multiple universities had the ability to test for the additional 30% and find the cases of hereditary breast cancer that Myriad missed, Myriad used its patents to prevent the provision of such tests. Meanwhile, those patients who ultimately bore the cost of this decision lost the opportunity for early diagnosis and an improved chance of survival.

In light of these issues, Myriad came across to many researchers as a firm that was determined to maximize its profits even at the cost of scientific inquiry and patient health. Although the firm's decisions were reasonable and perhaps even necessary in terms of protecting its profits and its shareholders' interests, the human cost imposed by the restrictions on university clinics intensified the firm's clash with patients and medical professionals. As Myriad

[125] *Ibid.*
[126] *Ibid.*
[127] Ledbetter Decl., 4. Determining the structure requires the use of large rearrangement testing.

built a reputation for its aggressive business strategy, it eventually triggered hostile reactions from abroad as well.

Global expansion and reactions abroad

With its business growing in the United States, Myriad attempted to expand its global market share by acquiring patent rights abroad. The firm was at first successful in obtaining patents in Canada, Europe, Australia, New Zealand and Japan.[128] In order to sell its product, Myriad selected a licensee for each region and gave it the exclusive right to market all BRCA tests in that region. As it had done in the states, it usually allowed licensees conduct the follow-on tests while keeping all comprehensive testing in its main laboratory in Utah.[129] Due to opposition within the countries' healthcare systems, however, this business model met with limited success. Both in Europe and in Canada, Myriad's patents eventually met with staunch opposition from healthcare professionals, policymakers and patients who believed that the broad scope of Myriad's patents was not aligned with their goals.

Passed in 1998, the European Union (EU) Directive 98/44 on the Legal Protection of Biotechnological Inventions required EU member states to enact laws permitting patents on human genes by 2000. Most states, however, did not enact such legislation until several years after the deadline.[130] When the European Patent Office (EPO) issued Myriad its patents on BRCA1/2 in 2001, France had yet to provide a statutory protection for patents on human genes. The delay reflected the French scientific community's wariness towards such patents, and was prolonged by opposition from researchers such as Stoppa-Lyonnet who had stood against

[128] Gold, S43
[129] Ibid., S49.
[130] Natividad Lorenzo. "The European Patent System: Certification Systems in the European Union and Practices Useful to the MERCOSUR countries." *Project: Support for the Development of Biotechnologies in the MERCOSUR Biotech ALA/2005/017-350 Agreement,* (2008): 31-33.

Myriad's aggressive use of its patents. Thus, when Myriad offered to license its test to the Institut Curie (a leading French non-profit research foundation) and researchers at other French laboratories, it did not receive a response. Instead, it faced opposition from the Institut Curie and 16 other French laboratories against its patents through the Opposition Division at the EPO.[131]

There were both political and scientific motives behind the specific strategy taken against Myriad. From a political standpoint, the French Ministries of Health and Research expected that the opposition procedure at the EPO would strengthen the government's bargaining position against Myriad while allowing the government to refrain from a direct declaration against gene patents.[132] By providing public support for the Institut Curie's challenge but avoiding direct participation, the ministry officials hoped to negotiate a licensing agreement more in favor of French laboratories while keeping the policy window open for fulfillment of EU Directive 98/44. If there were no window, there would be no credible argument for Myriad to license in France all. If Myriad were to license its rights in France, the government would at least have the opportunity to try broadening access to the patented genes by extending compulsory licenses in the name of public health.

Institut Curie, however, had independently grounded reasons to challenge the patents. Whereas the Ministries ultimately pursued a policy that would acknowledge Myriad's patents, the Institut and other French labs were opposed to adhering to them at all.[133] Specifically, researchers such as Stoppa-Lyonnet were concerned that Myriad's testing protocols would ultimately detect fewer BRCA mutations despite charging a higher price. As mentioned earlier, research done by French labs had suggested that a significant portion of testable BRCA mutations were going undetected by Myriad's test. As with the case of the Yale DNA

[131] Williams-Jones, 138.
[132] Gold, S55.
[133] Williams-Jones, 138.

Diagnostics lab, Institut Curie feared that it would no longer be able to provide its own test, which it claimed was better than Myriad's test because the former provided the large rearrangement testing yet missing in Myriad's methods. Furthermore, it warned that Myriad's insistence on keeping tissue samples for all comprehensive BRACAnalysis® tests back in Utah would prevent French researchers from building their own database for BRCA mutations.[134]

Institut Curie's challenge against Myriad's patents soon drew support from groups in a number of other European countries. Genetics societies and patients' associations from Germany, the United Kingdom, Austria, Switzerland and other countries joined in the opposition against Myriad, further motivated by the concerns over the firm's alleged failure to provide adequate counseling and follow-up care for patients.[135] Myriad attempted to reach an agreement with the French Ministry of Health, but the Ministry failed to continue negotiations after a power change in the June 2002 national elections.[136] Left to the decision of the EPO, Myriad's initial patents were significantly reduced. The Opposition Division of the ECJ affirmed that, based on the European Patent Convention, Myriad's patent (EP 705 902) could not claim the isolated BRCA1 gene or use it to prevent others from developing diagnostics for it.[137]

Subsequent responses in individual European countries also led to more restrictive policies on gene patents. Belgium enacted a research exemption as a direct answer to the public debate stirred by Myriad's patents.[138] Germany passed legislation in 2005 that removed absolute substance protection and protected new applications of patented genes from infringement

[134] Gold, S45.
[135] Benjamin Coriat et al. "Are 'strong patents' beneficial to innovative activities? Lessons from the genetic testing for breast cancer controversies," *Industrial and Corporate Change* 14 (2005): 1216.
[136] Gold, S55.
[137] Coriat, 1218.
[138] Geertrui Van Overwalle et al. "Reshaping Belgian Patent Law: The Revision of the Research Exemption and the Introduction of a Compulsory License for Public Health," *Chizaiken Forum* 64 (2006): 42.

lawsuits.[139] In France, a new amendment in 2004 enabled the government to issue compulsory licenses on patented diagnostics.[140] While the exemption and specificity requirements used by these countries fell short of rejecting gene patents outright, they clearly represented a step back from an absolute guarantee of broad patent rights over genes.

In Canada, policymakers also moved to curtail Myriad's patent-backed monopoly. Because provincial governments were largely in charge of directing Canada's public payer healthcare system, opposition originated at the provincial level. In 2000, Myriad reached a marketing agreement with MDS Laboratory Services in Canada and began to offer its testing services to health officials in the provinces. As it had proposed in Europe, Myriad wanted to keep laboratory testing in-house rather than provide the diagnostic kits. This was new to Ontario's provincial healthcare system, which usually relied on diagnostic kits that let hospitals provide the tests themselves.[141] Hospitals in Canada were already providing their own BRCA tests to patients on a research basis, and by April 2000 these tests were fully covered under public health insurance.[142] Cognizant of the resistance that Myriad's business model had faced in Europe, the Ontario Health Ministry and the other provinces' health ministries chose to consult first with various researchers and laboratories and delayed their response to Myriad.[143]

By the spring of 2001, MDS and Myriad had yet to receive an answer. Tired of waiting for the Ministry's response, Myriad sent cease-and-desist letters to the authorities in Ontario, Alberta, Quebec, and British Columbia, insisting that any "funding, directing or contracting with others to perform genetic testing services" would be in infringement of exclusively licensed

[139] Christopher Ann. "Patents on Human Gene Sequences in Germany: On Bad Lawmaking and Ways to Deal With It," *German Law Journal* 7, no.3 (2006): 286.
[140]Gold, S55.
[141] *Ibid*., S51.
[142] Fiona Miller et al. "When research seems like clinical care: a qualitative study of the communication of individual cancer genetic research results," *BMC Medical Ethics* 9, no.4 (2008).
[143] Gold, S51.

patents and subject to litigation.[144] The wording was used to extend the infringement charge to not just the hospitals performing the test, but to the provincial governments that paid for them as well. Threatened with legal action, Ontario Premier Mike Harris and Health Minister Tony Clement asserted that the public payments made to Ontario hospitals for their BRCA tests were not in infringement of Myriad's patents.[145] As for the hospital clinics, Harris and Clement determined that the health needs of Canadian women justified their decision to provide BRCA1/2 testing. Although the average cost of a BRCA1/2 test in Ontario was $1150, Myriad demanded $3850 for each test.[146] According to spokesperson Gord Haugh, the Ontario health ministry decided that adhering to Myriad's demands would have set an insupportable precedent.[147]

When attempted negotiations between the Minister Tony Clement, MDS and Myriad fell apart (Myriad presented a letter from the US ambassador threatening trade sanctions), the Ontario government approached the federal Patent Policy Directorate. The Directorate, however, attempted to avoid the issue and demanded that Ontario provide more substantial evidence of a real and present crisis.[148] The Directorate's failure to facilitate a workable settlement between Myriad and the provinces led to further deterioration of relations between the two sides. In British Columbia, authorities attempted to comply with Myriad's patents by stopping tests at the B.C. Cancer Agency, but ultimately failed. Under Myriad's prices, patients faced a price hike that the public health insurance system could not afford to pay.[149] Methods to work around

[144] *Ibid*.
[145] Williams-Jones, 142.
[146] Laura Eggerton. "Ontario defies US firm's genetic patent, continues cancer screening." *Canadian Medical Association Journal* 166, no.4 (2002) 494.
[147] *Ibid*., 494
[148] Gold, S53.
[149] Williams-Jones, 142.

Myriad's patents were unsatisfactory, and in 2003 the BC Ministry of Health Services allowed the BCCA to reengage in testing for BRCA mutations.[150]

In the end, Myriad was unable to enforce its patents in Canada because of two main reasons: 1. conflicts between its business strategy and the publicly funded provincial healthcare systems and 2. a lack of policy coordination in the Canadian government at the federal level. Federal action was delayed due to disagreements between Health Canada (the national health department) and the Patent Policy Directorate, and the latter's decision to not intervene. In 2004, Health Canada and the Directorate asked the Canadian Biotechnology Advisory Committee (CBAC) for its recommendation on the issue.[151] Although CBAC has suggested the implementation of a narrowly tailored research exemption, Canada has yet to clarify its official policy.[152] Myriad, meanwhile, has abandoned its attempts at market exclusivity in the country.

The challenges that Myriad faced in Europe and Canada were again due to the clash of interests between the firm and healthcare professionals, but with a greater emphasis this time on the role of clinical research in the national healthcare agenda. In Canada, France and many other European nations, health insurance was socialized and public spending comprised as larger share of national healthcare expenditure. As a result, the debate over Myriad's gene patents focused on the fact that they would prevent public and nonprofit cancer research clinics from developing tests that would improve patient access to critical health-related information. On the other hand, political decision-making (and a lack thereof) also played a critical role in determining the outcome of the conflicts in France and Canada. Ministry officials' decisions to not engage in proactive dialogue with Myriad encouraged it to take more unilateral actions, which were interpreted as a sign of aggressiveness and hostility. Although some delay was necessary for

[150] *Ibid.*
[151] Gold, S53
[152] *Ibid*., S54.

policymakers to gather information and insight from various researchers and clinicians, some policymakers (e.g. at Canada's Patent Policy Directorate) may have used the lack of empirical evidence as an excuse to avoid the responsibility of articulating a specific policy framework for regulating the patents.[153] Altogether, these reactions had the effect of antagonizing Myriad's breast cancer testing business, and intensifying the clash between the firm's patents and clinical research around the world.

Lessons from Myriad

What does the story of the BRCA1/2 patents tell us about patent policy toward human genes? At a most basic level, it points to the need for a better articulation of policy goals. In light of the issues that arose from the patenting of the genes and their monopolization in the clinical diagnostics space, it is clear that there are pressing reasons to limit the enforceability of patents on human DNA. Allowing patents to restrict genetic research and product development can lead to outcomes that are seriously detrimental to the innovation and progress, and can bear a negative impact on the health of thousands of patients each year.

Myriad's interaction with other research clinics, clearly demonstrated the extent to which gene patents could violate the obligations of medical professionals, the rights of patients and the goals of healthcare systems. At the University of Pennsylvania, Institut Curie and the Ontario hospital system, physicians involved in BRCA1/2 clinical research had an ethical duty to reveal the test result to the patient when asked. Given this issue mentioned earlier by Merz and Cho, Myriad's assertion that it supported the research use of BRCA1/2 was inconsistent with its practice of preventing research clinics from sharing test results. Its attempt to draw a "very bright line" failed to achieve its purported dual goal of promoting research while punishing

[153] *Ibid*., S60.

infringers. By directly and indirectly forcing the closure of in-house BRCA1/2 testing labs at U.S. universities and hospitals in British Columbia, Myriad preventing physician-run laboratories from providing second opinion testing and new tests that it did not yet cover. For all hereditary breast cancer patients and particularly for those from economically underprivileged racial minority groups, Myriad's business model seems to have been neither clinically sound nor ethically justifiable.

On a separate note, the Myriad story also suggests that governments seeking investment in biomedical technology should narrow their patent policies to a range that is more in line with their healthcare policy goals. While it seems that Myriad's aggressive actions against infringers may have been partly to blame for its mixed success abroad, it is also true that government officials in both France and Canada exacerbated the conflicts by failing to communicate clear restrictions to patent enforcement in a timely and credible manner. Both France and Canada had expansive patent policies that were not in line with their more socialized healthcare systems. Instead of guaranteeing Myriad limited exclusivity rights in exchange for specific concessions in its enforcement practices (e.g., full exclusivity over the distribution of its own testing kits in exchange for a liability exemption protecting preexisting tests in public hospitals), government officials in France and Ontario failed to address the uncertainty over the practical level of protection that could be afforded to Myriad's patents. As a result, Myriad chose to enforce its patents aggressively and ended up in protracted lawsuits that hurt its growth. This increased uncertainty weakens intellectual property rights by undermining their potential value as "live capital" – as effective incentives for private investment. To incentivize further private investment in genetic diagnostics, governments will have to establish patent policies as social

policies that they can expect to enforce. In the US, Congress will have to decide where the pragmatic balance between incentives and access should lie.

While it is true that healthcare in the US is less socialized than those of France or Canada, our nation's more privatized model also requires the greater regulation of patents on human genes. The story behind the BRCA1/2 patent controversy shows that in clinical testing, gene patents' harmful effects on market competition can outweigh their potential benefits as incentives for investment. From a fiscal standpoint, these patents go against the goal of the Bayh-Dole Act and fail to align with the purpose of NIH funding. From an efficiency standpoint, the patents undermine the federal goal of containing costs through improved technology. In the US today, the high cost of care for chronic conditions such as cancer skew national healthcare expenditure so that the most chronically ill 1% of all patients require 20% of total national spending. By helping potential cancer victims avoid more expensive treatments, reduce the risk of tumor recurrence and take advantage of available preventive measures, timely and accessible clinical diagnostics could significantly reduce their total cost of care.[154] Given that national health expenditures are expected to reach 32% of GDP within the next twenty years,[155] the fiscal and economic considerations provide strong justification for patent policy reforms supporting better genetic testing.

By halting the development of new tests at university labs and preventing second opinion testing, Myriad BRCA1/2 patents undermined the scientific inquiry that they were supposed to promote. Despite the Bayh-Dole Act's original goal of promoting innovation through patents on

[154] Kevin S. Hughes et al. "Cost-Effectiveness of the Identification of Women at High Risk for the Development of Breast and Ovarian Cancer," in *Management of Patients at High Risk for Breast Cancer*, ed. Victor G. Vogel. (*Malden, MA: Blackwell Science, 2001)*: 262-3.
According to one estimate, the use of preventive interventions such as prophylactic mastectomy may save over $1000 per life-year in treatment costs for women in their thirties with a BRCA1/2 mutation.
[155] William Kissick. "Recollections on Government and Health Care," *Connecticut Medicine 74* (2010): 557.

university research, the BRCA1/2 patents led to the aggressive stifling of innovation in clinical testing at university laboratories. This raised critical policy questions tied to the promotion of both clinical science and fundamental civil rights. In light of these issues, researchers and advocates in the have called upon the Department of Health and Human Services to pursue a statutory liability infringement exemption on the research and diagnostic uses of patented genetic sequences.

The SACGHS Report:

Suggestions for US policy

To address the gene-patenting dilemma from the healthcare policy perspective, the U.S. Health and Human Services Department (HHS) commissioned a fact-finding task force from the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) to determine the impact of gene patents on clinical diagnostics development and patient access to gene testing. From October 2006 to September 2009, the SACGHS task force collected evidence through an extensive literature review and a compendium of case studies for 10 clinical conditions.[156] In March 2010, the committee reported that patents on genetic discoveries "do not appear to be necessary for either basic genetic research or the development of available genetic tests."[157] Citing the American College of Medical Genetics, the report reaffirmed that "genetic tests are typically well developed and being delivered BEFORE patent holders seek to control the testing."[158] While noting university technology managers' and biotechnology firms' assertions that gene patents have acted as a significant incentive for funding from outside investors, the

[156] *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests*. Public Health Service, Secretary's Advisory Committee on Genetics, Health and Society (SACGHS), 2010.
[157] *Ibid.*
[158] *Ibid.*

report also noted that exclusive licensing and the high transaction costs for licensing these patents have created significant hurdles in the treatment of rare hereditary disorders.[159]

In addition to the BRCA1/2 test, the report included case studies on the development of clinical diagnostics for hereditary hearing loss, spinocerebellar ataxias, Long QT Syndrome, Canavan disease and hereditary hemochromatosis. In all of these cases, clinical gene tests were available on the market before the gene patent holder offered its own. These studies showed that other diagnostic companies (e.g. Athena Diagnostics, PGxHealth) "[had] adopted similar or even more aggressive business models and [had] shut out university laboratories from offering genetic testing for [the hereditary] diseases." [160] By clearing the market of these preexisting tests, gene patents were limiting the availability of current tests, preventing competitors from improving the tests and blocking qualified physicians from providing valuable second opinions to patients whose test results were unclear.

Of course, incentivizing investment in genetic discoveries is not the sole reason given for issuing patents. Proponents of gene patents have argued that without patents, academic geneticists would resort to trade secrecy rather than promote open science. According to the SACGHS report, however, this argument misses the point: the primary goal for researchers is to get published, and in order to win recognition they must reveal their findings as early as possible. Reverse engineering also reduces the viability of trade secrecy as an effective competitive

[159] *Ibid*., 29-30. The report also notes that in a public comment on the draft of the SACGHS report, the president of Gene Dx (company that develops genetic test for rare hereditary disorders) stated that, "For a rare disorder…it may take several years for a laboratory to recover the initial development costs due to the small number of individuals who will be tested. The additional expense associated with negotiating a license of a patent, and paying the up-front and ongoing royalties, can be a strong disincentive to a commercial laboratory in its selection of genetic tests to develop and offer to the community…gene patents have a severe negative impact on the development, and thus the availability of genetic testing for rare disorders…"

[160] Julia Carbone. "DNA Patents and Diagnostics: Not a Pretty Picture," *Nature Biotechnology* 28 (2010): 784-91.

strategy.[161] Given this environment, the report suggests that trade secrecy in the absence of patents is neither preferable nor practical for genetic researchers as a substitute for patents. While patents might allow and encourage the disclosure of some information while providing proprietary rights, trade secrecy prevents researchers from pursuing prizes for their findings and often fails to exclude others from engineering substitute versions of their inventions.

While emphasizing that there are incentives for disclosure other than patent rights, the report goes on to note that patents may even fail to promote disclosure and end up reducing public knowledge. According to the Innovation Partnership, a nonprofit IP consultancy, "The argument that patents promote progress through the required disclosure of the new invention is not substantiated by empirical evidence. [Patent specifications are] drafted as broadly as possible while disclosing little. Most scientists admit they rarely consult patents to identify useful information."[162] One major study showed that gene patents could even have a dampening effect on the proliferation of scientific publications about their claimed gene. In 2009, Kenneth Huang and Fiona Murray published a study tracing the effects of patents on follow-on research about their respectively claimed genes. Using a mathematical model in which "public citations to each paper" acted as a proxy for follow-on research, they studied 1,279 papers and measured their respective citations.[163] The results showed that the number of citations was on average 5% lower than predicted for papers that were published jointly with a gene patent, and almost 10% lower when the patented gene indicated a hereditary predisposition for a human disease.[164]

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[161] SACGHS, *Gene Patents*, 27. "…secrecy is not a viable option for many inventors, because their inventions would be reverse engineered…In the area of genetics particularly, Randal J. Kirk and his coauthors have observed that 'trade secret protection is largely impractical for biotechnology and genetic material due to…the ease with which these products can be reverse engineered.'"
[162] *Ibid*., 27.
[163] Kenneth, Huang et al."Does Patent Strategy Shape the Long-run Supply of Knowledge? Evidence from Human Genetics," *Academy of Management Journal* 52 (2009).
[164] *Ibid*.

In its six recommendations to HHS Secretary Sebelius,[165] the SACGHS highlighted the need to create exemptions from infringement liability for researchers and providers of clinical diagnostics.[166] The committee argued that while improving access and quality in genetic testing, this exemption would allow firms to continue seeking gene patents and enforce them in the development of therapeutics. Notably, the committee also recommended that HHS "ensure equal access to clinically useful genetic tests" in light of the fact that they "will be increasingly incorporated into medical care." By establishing equity as a key issue in this debate, the committee echoed the VUS concerns in the Myriad debate and highlighted the systemic discrimination that could emerge in the clinical diagnostics space due to the business strategies and pricing practices of a sole provider.

Dissent and rebuttal

Some members of the SACGHS, however, disagreed with the recommendations that were published in the committee report and attached a statement of dissent. Emphasizing the investor's desire to secure a sufficient return on investment, the statement claimed that the creation of an exemption would endanger the pursuit and development of many discoveries due to the "increasing complexity" and "higher evidentiary standards" involved in developing genetic tests. Regarding the issue of pricing and equitable access, the dissenters argued that health plans were "free to refuse coverage and payment even if every laboratory in the country

[165] SACGHS, *Gene Patents*, 97-100.
The six recommendations are:
1. Support the Creation of Exemptions from Infringement Liability
2. Promote Adherence to Norms Designed to Ensure Access
3. Enhance Transparency in Licensing
4. Establish an Advisory Body on the Health Impact of Gene Patenting and Licensing Practices
5. Provide Needed Expertise to USPTO
6. Ensure Equal Access to Clinically Useful Genetic Tests
[166] *Ibid*,, 100.

offers a test," and that equitable access to clinical testing was "a commercial objective more than a patient access issue" because clinicians could already order tests from patent-holding providers. Perhaps most tellingly, the dissenters did not believe that there was "any credible evidence that the quality of testing performed in sole source laboratories is routinely or demonstrably subpar in any way to what which is done in multiple laboratories"[167] and refused to believe that "modifying the gene patent system and protections it offers through exclusive licensee agreements would result in multiple laboratories performing proprietary tests with better quality than generated by current and developing oversight of quality assurance undertaken by these agencies and laboratories themselves."[168]

Barring a complete rejection of the numerous studies and testimonies provided by the researchers, health providers and patients involved in the *Myriad* case, the latter statements made by the dissenting statement to the SACGHS report appear questionable at best. The declarations of Ms Matloff, Dr. Ostrer and Dr. Ledbetter, the research of Mary Clare King and Dominique Stoppa-Lyonnet, and the personal experience of those patients who bore the social cost of Myriad's restrictive practices provide at least a credible case with demonstrable evidence of the adverse effects of patent-backed monopolies on clinical testing for heritable diseases. In the ACLU's current public education campaign regarding gene patents, Ms Kathleen Maxian shares her experience of suffering from advanced-stage ovarian cancer due to a BRCA1/2 mutation in her family that Myriad's tests failed to catch. Myriad's "comprehensive" BRACAnalysis® test had failed to detect the mutation in her sister, which if detected would have allowed Ms Maxian to seek preventive measures in the earlier stages of her condition (and improve her chances for

[167] SACGHS, *Statement of Dissent from Ms Aspinall, Dr. Billings and Ms Walcoff*.
[168] *Ibid*.

survival). The company's pricing policies and guidelines had withheld complementary BART® testing from Ms Maxian's sister.

Of course, it would be hyperbolic to declare that Myriad's patents should be revoked because of a single incident. It would also be unfair to expect Myriad to provide free testing for all patients – the firm states on its website that less than 1% of patients on average will test positive in BART® after testing negative in BRACAnalysis®.[169] It would be wrong, however, to claim that Myriad did right by preventing Ms Matloff from providing large rearrangement testing to patients who could not get it through Myriad. Patients in situations similar to that of Ms Maxian were restricted to Myriad's linear method of sequencing despite the fact that the Yale center was willing and able to provide the large rearrangement test that captured mutations left undetected by Myriad's BRACAnalysis®. This was clearly a patient's rights issue – a matter of civil rights and human decency, not merely of patent rights and commercial gain.

The dissent's implicit claim that gene patent holders are not culpable for high prices and limited access because insurers are "free to refuse" is also rather weak. It is true that many insurers have chosen not to cover BART® testing, perhaps because Myriad has so far refused to incorporate it into its purportedly "comprehensive" BRACAnalysis® sequencing test. Large insurers such as Kaiser Permanente, however, have expressed their desire to increase access to BRCA1/2 testing for all patients who might benefit from it. In fact, Kaiser would even lower costs by providing these services in-house. According to Senior Vice President Dr. Jed Weissberg, if it were not for Myriad's patents on the isolated BRCA1/2 fragments, Kaiser Permanente would be able to launch a nationwide BRCA1/2 testing program within months.[170] This January, Kaiser followed up in the *Myriad* case by filing an amicus brief in support of the

[169] *Myriad for Professionals – BRACAnalysis® Large Rearrangement Test (BART)*. Myriad Genetics website, accessible at https://www.myriadpro.com/BRAC_BART
[170] Personal phone communication with Dr. Jed Weissberg, 12 February 2012.

ACLU's petition to the Supreme Court. Arguing on behalf of the plaintiff, the brief noted that Myriad's pricing system often makes it prohibitively difficult for Kaiser's genetic counselors to get tests for relatives of patients outside the Kaiser system. This is a critical issue when the patient has a misleadingly low individual risk but a higher familial risk, and increases the chance that the patient will suffer from a failed detection similar to the one that affected Ms Maxian and her sister. Kaiser asserted that Myriad's monopoly over BRCA1/2 testing is making it "practically impossible" acquire complete familial information regarding BRCA1/2. Mentioning Myriad's test for colorectal cancer, it argued that there are critical benefits to be gained from having multiple providers and a wider range of testing options. Affirming that it would provide its own BRCA1/2 screening internally in the hypothetical absence of Myriad's patents, Kaiser declared that it could conduct BRCA1/2 diagnostics in a way that would be more appropriate and patient specific than Myriad's fixed menu of services.[171]

Perhaps the most defensible argument made by the dissenting members of the SACGHS is that the infringement liability exemption on gene patents would reduce the incentive for private investors to fund the development of new genetic tests. Even this, however, is a disputable claim. Though the statement seems sound at first, this claim fails to address the possibility that private investors may be driven to new genetic tests that do not rely gene patents such as those owned by Myriad. With the major advancements made in the past decade towards next generation, genomic scale sequencing technologies such as whole genome and whole exome[172] sequencing, patents on isolated fragments of DNA have become less relevant as a

[171] Brief for Kaiser Permanente as Amicus Curiae, *Ass'n for Molecular Pathology et al. v. Myriad Genetics et al.*, U.S. (Jan. 13, 2012).

[172] The exome is the collective whole of a person's exons, which are the parts of the person's genome that code for all of her physical traits. While whole genome sequencing processes both the exons and the introns (noncoding segments), whole exome sequencing isolates and tests only the coding segments of the genome (Figure 5). This essay will refer to the two tests collectively as "genomic scale sequencing." Although whole genome sequencing is yet too costly for widespread use, exome-sequencing technology is currently a cost-effective option. As will be

means of securing revenue streams. For currently available methods such as whole exome and micro-array testing, they have even become a legal hindrance. Genetic diagnostics manufacturers such as Illumina, Life Technologies and Pacific Biosciences pursue revenue streams from high-throughput processing technology rather than economic rents on patented DNA sequences. Market competition encourages them to lower the cost of sequencing on a per amplicon basis,[173] and the cost of sequencing an entire human genome has fallen (in light of recent academic findings) from over $10,000 to just $1,000[174] - over $2000 cheaper than Myriad's BRACAnalysis®.

When asked whether the advent of genomic scale sequencing would create downward pressure on Myriad's revenue, Mark Capone, president of Myriad's laboratory division, argued that data analysis costs are still too high and that these technologies will not be accurate enough to be used in a clinical setting for at least the next four years.[175] Consulting firm DeciBio, however, expects that the currently dormant market for next generation sequencing will grow to somewhere between $700 million and $1.1 billion by 2015.[176] Meanwhile, universities across the nation are working with a $416 million grant from the US National Genome Research Institute (USNHGRI) to develop more effective methods of analysis and translate basic research into genomic medicine.[177] Given the unsustainably high price of Myriad's $3,000+ BRACAnalysis® test (plus an additional $700 for BART®) and the rapid advance of genomic scale sequencing,

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discussed later, the isolated DNA patents still held by Myriad prevent clinicians from providing whole exome sequencing tests.

[173] Personal communication with Shrikant Mane, Director of Yale Center for Genomic Analysis, 3 February 2012. An amplicon is a DNA nucleotide produced by either natural or artificial amplification.

[174] Bill Hathaway. "Yale one of first institutions to get powerful new DNA sequencing technology," *Yale News,* 10 January 2012.

[175] Pollack, *New York Times,* 24 August 2011.

[176] Monica Heger. "Demonstrating Cost Effectiveness of Clinical NGS is Key to Payor Reimbursement, Hospital Uptake," *GenomeWeb,* 22 February 2012.

[177] Ciara Curtin. "New Genome Sequencing Program Aims to move Discoveries Closer to the Clinic," *GenomeWeb,* 1 February 2012.

Goldman Sachs issued a sell rating on Myriad's shares last year.[178] Although other equity research analysts may remain positive about the company's prospects, there are strong signals in both the market and academia suggesting that the future for investors will be in patented sequencing technology, not patented genes.

While it does not provide a political strategy for implementing its recommended liability exemption, the SACGHS report helps clarify many of the arguments made for and against exemption regulations for gene patents in clinical testing. Myriad's patents on isolated fragments of the BRCA1/2 sequence may be responsible for 88% of its current revenue,[179] but they represent an outdated mindset that is reminiscent of the EST and SNP race of the 1990s. By pursuing a business strategy built around the extraction of rents on the use of new upstream research, companies such as Myriad, Incyte and Human Genomic Sciences adopted gene-patenting practices that reduce patient access to timely care and threaten the development of downstream products.

Although de facto arrangements between universities and firms have been sufficient to prevent the rise of a widespread anticommons in genetic research, the development and use of clinical diagnostic methods such as genomic scale sequencing and micro-array analysis raises the issue of impeded downstream innovation yet again.[180] Although the BRCA1/2 controversy may seem to be an outlier due to the particularly vocal opposition from the breast and ovarian cancer community, the SACGHS case studies show that it is not the only case of aggressively enforced gene patents contributing to adverse public health results. Aggressively enforced gene patents could prevent researchers from using whole exome and micro-array tests to look for the claimed

[178] Pollack, *New York Times,* 24 August 2011. Current rating is neutral.
[179] *Ibid.*
[180] Although the recent CAFC ruling on Myriad may allow for a workaround solution to Myriad's patents for whole genomic sequencing, lawyers are yet unclear as to whether the inclusion of BRCA1/2 in whole exome and genome sequencing will be liable for patent infringement.

genes. Given these concerns, it seems highly advisable that Congress and the courts at least consider the possibility of invoking an infringement liability exemption for clinical genetic testing. In the meantime, the courts will continue to debate the question of whether human genes should be patentable at all.

In the Courts - the "dual nature" of DNA:

Despite the AMP's 2-1 loss at the CAFC in July, recent developments at the Supreme Court suggest that this debate is far from over. On March 26, 2012, the Supreme Court granted the ACLU petition. It vacated the CAFC's judgment upholding Myriad's patents on isolated DNA, and remanded the case for further consideration in light of the Court's recent ruling in *Mayo et al. v. Prometheus*. In *Prometheus*, the Supreme Court unanimously revoked Prometheus' blood test patents under 35 U.S.C. § 101 because they claimed processes failed to deliver significant utility beyond the laws of nature.[181] The test determined the correct dosage for a drug by measuring changes in blood metabolite levels after the administration of different doses, and the patents claimed the idea of inferring the correct dosage by correlating the metabolite levels with their respective dosages. According to the court, the patents covering the test methods failed to assure that they were "genuine applications of laws," rather than "drafting efforts designed to monopolize [laws of nature]."[182] The act of removing and analyzing the blood did not constitute a patentable step, because it did not add significant utility beyond a restatement of natural phenomena.[183]

[181] *Mayo et al. v. Prometheus*, 566 U.S. ___ (2012) (slip op., at 8).
[182] *Id.*, (syllabus to slip op., at 2)
[183] *Id.*, (slip op., at 19)

While the ACLU intimates that this decision "bodes well for the ultimate outcome of the Myriad case,"[184] Myriad claims that the ultimate impact of the Supreme Court's ruling in Prometheus will be of little to no significance. In the words of Gregory Castanias, a lawyer representing the firm, "We don't believe that that decision really changes the landscape with regard to our case at all."[185] Although the plaintiffs in both *Myriad* and *Prometheus* have argued that the respective patents in question claim laws of nature, *Myriad* differs from *Prometheus* in that *Myriad* focuses on 'composition of matter' patents rather than method patents. As Dr. Robert Cook-Deegan from the former SACGHS task force puts it, the remaining debate in *Myriad* is "about a thing rather than a method."[186] Almost all of Myriad's method patents were revoked by the July CAFC decision, on the basis that comparing two DNA sequences in order to determine a BRCA1/2 mutation is an abstract idea that cannot be patented.[187] Myriad's 'composition of matter' patents on the isolated DNA, however, are valid according to CAFC because these physical fragments are allegedly of a "markedly different chemical nature."[188] The plaintiffs in *Myriad* have argued that these fragments are still essentially products of nature. Although Supreme Court has remanded *Myriad* in light of the *Prometheus* ruling, it has not yet explicitly affirmed the plaintiffs' view.

The conflicting interpretations held by Myriad and the ACLU regarding the Supreme Court's latest decision ultimately reflect an issue of semantics that emerges from the "dual nature" of DNA. As noted by Myriad Genetics' Dr. Joseph Straus during the district court

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[184] Sandra Park from the ACLU, quoted by Alison Frankel. "Could SCOTUS Prometheus Ruling be the End of Gene Patents?" *Thomson Reuters*, 21 March 2012.
[185] Andrew Pollack. "Justices Send Back Gene Case," *New York Times*, 26 March 2012.
[186] *Ibid*.
[187] *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office et al*., 653 F.3d 1355-57 (Fed. Cir. 2011).
All method claims were revoked except for claim 20 of '282, because claim 20 claimed a method of screening potential therapeutics that went beyond mere abstract comparison of correlations observed from nature.
[188] *Id.* at 1352.

hearing of this case, "On the one hand, [isolated DNA] are chemical substances or molecules. On the other hand, they are physical carriers of information, i.e., where the actual biological function of this information is coding for proteins."[189] The CAFC decision holds that isolated DNA fragments become distinct when the researcher breaks the covalent bonds connecting them to the rest of the subject's genome.[190] The issue with this claim is that the physical isolation of a segment of the human genome does not change the information it contains. As Dr. Robert Nussbaum from UC San Francisco explains it, the information contained in a gene is found in the arrangement of the nucleotide bases in the DNA, and this sequence does not change whether the DNA is in the body or in a test tube. Isolating the DNA does not make it "structurally and functionally distinct," and "to claim otherwise is to confuse a gene with the machinery that regulates how that gene is expressed."[191] Myriad's patents allow the firm to monopolize the extraction of a person's genetic information but fails add significant utility beyond the laws of nature. Presumably, the plaintiff will argue that this violates the Supreme Court's ruling that mere "drafting efforts designed to monopolize" are unpatentable.

The issue before the CAFC, then, is whether the removal of a naturally occurring DNA fragment from its cellular environment is sufficient to make the entire entity patentable as per 35 U.S.C. §101. Interestingly, the judges' opinions in the July CAFC ruling reflect a rather mixed stance towards this view. In the CAFC's 2-1 ruling against the plaintiffs in July, the two judges in the majority fail to articulate a common standard for identifying patentable discoveries. While

[189] *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office and Myriad Genetics, Inc.,* 702 F. Supp. 2d 181 (S.D.N.Y. 2010) (slip op., at 122-3).
[190] *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office et al., 653* F.3d 1353 (Fed. Cir. 2011). Judge Lourie explains that, unlike the case of purified adrenaline in *Parke-Davis & Co. v. H.K. Mulford Co.,* isolating DNA is chemically changed - not purified from a physical mixture. Emphasizing that the covalent bonds connecting it to other genetic material must be broken, he claims, "when cleaved, an isolated DNA molecule is not a purified form of a natural material, but a distinct chemical entity" (at 1352).
[191] Nussbaum Decl., (18 January 2010): 14. *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office and Myriad Genetics, Inc.,* 702 F. Supp. 2d 181 (S.D.N.Y. 2010).

Judges Alan Lourie and Kimberly Moore both agree that isolated DNA fragments have chemical characteristics that are "markedly different" from those of naturally occurring DNA, they differ in their explanations of why isolated DNA should be a patentable product. According to the official majority decision written by Judge Lourie, Myriad's claims are "drawn to patentable subject matter" because they are on molecules that have "a distinctive chemical identity…from molecules that exist in nature."[192] Judge Moore, however, writes a separate, concurring decision to emphasize that the claims must also have "the potential for significant utility."[193]

Although this split in reasoning seems rather subtle at first, this difference highlights the conflict between the two judges' views on the nature of DNA. By focusing exclusively on the chemical identity of isolated DNA, Judge Lourie argues that isolation itself is a sufficient condition for patentability. In his view, "It is the distinctive nature of DNA molecules as isolated compositions of matter that determines their patent eligibility, rather than their physiological use or benefit."[194] He insists that the "claimed isolated DNA molecules are distinct from their natural existence," and that "their informational content is irrelevant to that fact." In conclusion, Judge Lourie asserts that "the patent eligibility of an isolated DNA is not negated because it has similar informational properties to a different, more complex natural material," and that genes are "best described in patents by their structures rather than their functions."[195]

While concurring with Judge Lourie's claim that isolated DNA is not a product of nature, Judge Moore asserts that this alone does not "make isolated DNA so 'markedly different' from chromosomal DNA so as to be per se patentable subject matter."[196] Unlike Judge Lourie, she

[192] *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office et al., 653* F.3d 1351 (Fed. Cir. 2011).
[193] *Id.* at 1360. Citing *Chakrabarty*, 447 U.S. at 310, 100 S.Ct. 2204.
[194] *Id.* at 1353.
[195] *Id.*
[196] *Id.* at 1365. Citing *Chakrabarty*, 447 U.S. at 310, and *Cf. Funk Bros*, 333 U.S. at 130-31: "(Creation of 'a new and different composition' of bacterial strains was nevertheless not patentable subject matter)."

attempts to address the plaintiff's argument regarding utility by arguing that the isolation of naturally occurring DNA fragments sufficiently increases their functional utility as well. She argues that the process of extraction, the use of short fragments as primers and the development of diagnostic tests are all non-natural interventions that add utility to both the chemical and informational component of isolated DNA fragments.[197] The difference between her logic and Judge Laurie's reasoning becomes most apparent in her discussion of isolated DNA fragments that are too large to be used as primers, in which she states, " Whether an isolated gene is patentable subject matter depends on how much weight is allocated to the different structure as compared to the similarity of the function to nature."[198]

The significance of this split in reasoning between Judges Laurie and Moore is that the latter's argument may be more amenable to change in light of the Supreme Court's *Prometheus* ruling. Judge Moore's logic – unlike Judge Laurie's – allows for a calibration of patent policy towards isolated DNA.[199] Whereas Judge Laurie's reasoning provides a blanket defense for the patentability of any strand of isolated DNA because of its altered ends, Judge Moore's inclusion of functional utility in her determination of patentability acknowledges the possibility that "the patents in this case might well deserve to be excluded from the patent system."[200] The Supreme Court's decision to vacate Judge Laurie's ruling may lead Judge Moore to reassess whether the incremental utility generated by Myriad's patents goes sufficiently beyond the laws of nature that provide DNA with its informational utility. Along with Judge Bryson's dissenting view that "isolated genes are not materially different from the native genes" because "the only material change made to those genes from their natural state is the change that is necessarily incidental to

[197] *Id.* at 1365-66.
[198] *Id*. at 1366.
Moore decides against that conclusion out of adherence to the recent history of USPTO practice (at 1367).
[199] *Id.* at 1372.
[200] *Id.* at 1373. She insists, however, that this is a matter for Congress to decide.

the extraction of the genes," Judge Moore's reasoning balances the CAFC ruling more evenly than a strict 2-1 division.

According to ACLU lawyer Chris Hansen, the plaintiffs in the CAFC case did not lose 2 to 1, but lost "1.51 to 1.49."[201] Aside from Judge Moore's ruling and the Supreme Court's granting of certiorari, the ACLU's odds in the upcoming CAFC rehearing may also benefit from the support of the US Department of Justice (DOJ) and the past Solicitor General. Leading up to the July hearing at the CAFC, the DOJ filed one of the 29 amicus briefs issued in response to the ACLU lawsuit. Although the DOJ brief is technically "in support of neither party,"[202] it undermines the defendant's claims to the BRCA1/2 genes by stating that "genomic DNA that has merely been isolated from the human body, without further alteration or manipulation, is not patent-eligible."[203] As an amicus, the DOJ attempts to set a future standard by which the patentability of a particular genetic discovery could be determined based on its novelty and the informational utility it generates. At a most basic level, this standard is built on the premise that fragments of naturally occurring genomic DNA (gDNA) are products of nature but novel sequences of complementary DNA (cDNA) are patentable inventions. According to the brief:

> "New and useful methods of identifying, isolating, extracting, or using genes and genetic information may be patented…as may nearly any man-made transformation or manipulation of the raw materials of the genome, such as cDNAs. Thus, the patent laws embrace gene replacement therapies, engineered biologic drugs, methods of modifying the properties of plants or generating biofuels, and similar advanced applications of biotechnology."[204]

At the CAFC oral argument session in April, then-acting-Solicitor General Neal Katyal explained the government's position against patents based on the mere isolation of naturally

[201] Statement by Christopher Hansen, made at the conference "Gene Patents: Advancing Medicine or Capturing Humanity?" organized by the Information Society Project at Yale Law School, 14 February 2012.
[202] Brief for the United States as Amicus Curiae in Support of Neither Party, 18. *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office et al*., 653 F. 3d 1329 (Fed. Cir. 2011).
[203] *Id*. at 10.
[204] *Id.*, 11.

occurring sequences of DNA. In asserting that the isolated DNA coding for the BRCA1 polypeptide[205] falls outside the scope of §101, Katyal argued that isolated DNA is not patentable if it codes for a sequence that is naturally present in the human chromosome.[206] Unlike Judge Sweet of the district court, who ruled in favor of the plaintiffs, Katyal did not claim that isolated DNA is merely the "physical embodiment of [genetic] information."[207] He also disagreed, however, with Judge Lourie's claim that isolated DNA is a novel chemical entity just because of the fact that covalent bonds are broken during its extraction. Katyal noted that according to Judge Lourie's logic, even elements such as lithium would be patentable because it is found in nature within "salts with covalent bonds."[208] Echoing the voice of one biologist from the 1990s who claimed that patenting ESTs would be "like trying to patent the periodic table"[209], Katyal insisted that nobody would think that "the third element in the periodic table" would be patentable just because it has to be chemically extracted from its natural state.[210]

While satisfying neither party in the Myriad case, the DOJ position best illustrates the point that innovation requires a balance of private incentives and public access. Tradeoffs must be made, and must be clearly defined in order to guarantee sufficient access to the human genome for researchers and clinicians. The evidence provided by the SACGHS strongly suggests that Judge Laurie's ruling and the USPTO's de facto patentability policies fail to secure the constitutional goal of promoting innovation and the general welfare. Judge Moore notes that

[205] Claim 1 of Myriad's '282 patent: "An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2. Katyal established that the oligonucleotide claims (claims 5 and 6) fell outside of §101 as well.
[206] Recording of Oral Argument held on 4 April 2011, for *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office et al., 653* F.3d 1329 (Fed. Cir. 2011).
[207] *Id.*
[208] *Id.*
[209] Christopher Anderson. "US Patent Application Stirs up Gene Hunters, 353 Nature 485 (1991), supra note 14 at 485.
[210] Recording of Oral Argument held on 4 April 2011, for *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office et al., 653* F.3d 1329 (Fed. Cir. 2011). Katyal also used the example of changing uranium 238 to uranium 235 as an example in which breaking covalent bonds does not create a new patentable chemical entity.

the USPTO has granted patents on isolated DNA for the past 35 years, but this does not seem to reflect a "split in the government" as much as it suggests a deviance in USPTO practices from federal policy. During the EST/SNP patenting race and now again, the executive branch and its agencies (i.e. NIH) have expressed concern over the detrimental effect gene patents have had on open access to foundational scientific discoveries. Recently, the legislative branch has also taken steps towards curtailing the continued expansion of gene patentability under the USPTO.

Although Congress fell short of eliminating gene patents in 2007, it took a significant step last year towards greater regulation of patents on isolated DNA. In the America Invents Act (AIA) passed last September,[211] Congress required the USPTO to study and report on the effects of current patent policy on gene testing.[212] By expanding the definition of prior art and establishing a post-grant opposition procedure to challenge patents, it also opens doors to future patent counterstrategies such as those used by Merck Genome Initiative, SNP Consortium and Dominique Stoppa-Lyonnet in the fight against patents on EST/SNPs and other isolated DNA. While the AIA applies broadly to patents in other sectors as well (e.g. technology, telecommunications), its provisions seem to suggest that the federal government does not support Judge Laurie's overly expansive view of human gene patentability.

Ultimately, the continued legal debate over the Myriad BRCA1/2 patents emphasizes the need to protect the flow of clinically valuable information conveyed through isolated genomic DNA. As Justice Breyer points out in the *Prometheus* ruling, patent protection is a double-edged sword that can incentivize new discoveries but also slow down innovation.[213] In order to

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[211] *America Invents Act of 2011*, H.R. 1249, 112th Cong. (2011). The Leahy-Smith America Invents Act was passed by Congress and signed into law by the president on September 16, 2011. It switches the US patent system from a "first to invent" to a "first to file" basis, expands the definition of prior art used to determine patentability and establishes an opposition procedure to challenge patents after they have been granted.

[212] *Request for Comments and the Notice of Public Hearings on Genetic Diagnostic Testing*, 77 Fed. Reg. 3748 (Jan. 25, 2012)

[213] *Mayo et al. v. Prometheus*, 566 U.S. ___ (2012) (slip op., at 23).

promote the sciences and the useful arts, US patent policy must ensure that downstream innovators in clinical diagnostics are able to isolate parts of the human genome without being threatened by infringement lawsuits. The per se patentability rule espoused by Judge Laurie and past USPTO policy fails to strike the proper balance between private incentives and scientific inquiry. In order to tailor a better policy solution for the development of clinical diagnostics, Congress should pass a rule that limits the restrictive impact of current patents while preserving patent incentives for other biomedical products.

The Liability Exemption – in Support of the SACGHS Proposal:

As the courts continue to study *AMP v. Myriad Genetics* and the case for gene patent policy reform, clinical diagnostic technology persists in its steady advance. For women at risk of hereditary breast and ovarian cancer, however, Myriad's patents on isolated DNA continue to block affordable and reliable testing from other providers such as Kaiser Permanente and the Yale Cancer Center. Given the broad impact of patent laws across a wide range of scientific fields, the best policy solution for the near future may be an infringement liability exemption limited to the research and diagnostic use of patented genes. As Justice Breyer noted in *Prometheus*, changing patentability rules to solve issues within a specific field may lead to unforeseen consequences in others.[214] While leaving patent protections in place for their use in the development of biologic therapeutics, the liability exemption would allow university labs and health insurers to develop more accurate and cost-effective testing systems. Biopharmaceutical

[214] *Id.*, (slip op., at 24).

companies would continue to use their patents to attract investment, and also keep the twelve-year market exclusivity policy recently granted by the government. [215]

Opponents of the liability exemption have argued, however, that this policy would reduce innovation and decrease access to new diagnostic technologies. They insist that without the right to exclude others from the use of isolated genomic DNA, clinical diagnostics manufacturers will not be able to develop and deliver new tests. The claims they have advanced, however, seem rather weak in light of the facts surrounding the development of the BRCA1/2 tests.

As noted in the Myriad case study, the evidence suggests that patents were not necessary for the development of the BRCA1/2 test – university researchers such as Mary Clare King and Michael Stratton had already discovered the genes, and researchers such as Dr. Ganguly had already developed BRCA1/2 diagnostics independent of Myriad's patents. Myriad used its patents to clear the market of these preexisting tests.[216] Myriad notes, however, that the patents, by giving the firm monopoly control over the market, allowed it to invest in the marketing and physician education necessary for the delivery of BRCA1/2 testing to patients.[217] The issue with this statement is that although the monopoly may have encouraged Myriad to increase its direct-to-consumer (DTC) marketing, the firm's marketing and education tactics were unnecessary for the delivery of BRCA1/2 testing to the public.[218] The firm's DTC "public awareness campaign" was designed to manipulate preexisting public anxiety about hereditary breast cancer, and it left

[215] Hunter Rost. "US healthcare reform reflects changing life sciences industry." *Financier Worldwide Global Reference Guide 2010: Biotech and Pharmaceuticals* (2010): 4.
The Approval Pathway for Biosimilars grants biotechnology companies 12 years of market exclusivity on new drugs starting after FDA approval. This is different from a patent but achieves the same effect in terms of protecting market share.
[216] SACGHS, *Gene Patents*, 90.
[217] Richard Marsh, General Counsel for Myriad Genetics, comment made at the conference "Gene Patents: Advancing Medicine or Capturing Humanity?" organized by the Information Society Project at Yale Law School, February 14, 2012.
[218] SACGHS, *Gene Patents,* A-34.

out most of the critical information necessary for the public' education about BRCA1/2.[219] Myriad paid sales account managers to provide physician "training," but it blocked qualified physicians and counselors from obtaining the full information from its test beyond the summary it provided.[220] Myriad's publicity efforts increased demand for the firm's products but impeded the provision of quality genetic counseling and medical decision-making necessary for the judicious use of BRCA1/2 testing. According to health insurer Kaiser Permanente, which has covered Myriad's BRCA1/2 test since 1997, the monopoly over clinical research has ultimately had "negative effects on patient health."[221]

Other opponents to the liability exemption have claimed that patent protections on isolated DNA are necessary to encourage open science and reduce trade secrecy. However, evidence from the SACGHS seriously undermines these claims. As mentioned by the Innovation Partnership in the SACGHS report, patents disclose very little and do not provide researchers with all the information necessary to replicate and improve the discovery. Trade secrecy in the absence of these patents is weak because of the ease with which the covered products are reverse engineered.

Combined with patents, however, trade secrecy can be used to hoard data critical to the improvement of diagnostics for the target gene. Diagnostics producers can use this tactic to prolong their market monopoly beyond the life of their patents. Despite the ethical implications of this tactic, Myriad has decided to use this as its growth strategy in the coming years. Around 2008, the firm stopped submitting mutation data from its test results to the Breast Cancer

[219] Ellen Matloff et al. "Direct to Confusion: Lessons Learned from Marketing BRCA Testing," *The American Journal of Bioethics*, 8 (2008) 7.
[220] Amicus Brief for *Kaiser*, 8.
[221] *Id.*, 10.

Information Core (BIC).[222] When asked about the matter, Mark Capone stated that Myriad sought to prevent competitors from benefiting from its investment in the BRCA1/2 mutations. Perhaps with a tinge of irony reminiscent of Celera's restrictions on its data, this decision has had a negative impact on the clinical research community that found the BRCA1/2 genes in the first place. Myriad' data hoarding strategy has made it more difficult for researchers in the BIC consortium to study the demographics of the BRCA1/2 mutations and identify those with the strongest links to cancer.[223] Granted, Myriad's attempts to preserve its informational advantage might have been justified if it produced sufficient utility to the public in return. As noted earlier however, the advent of genomic scale sequencing has made Myriad's technology rather anachronistic. According to Mary Clare King, "Science has moved beyond what [Myriad] can do. It's not good for the science and it's not good for the patients and their clinicians if they cannot have the most complete, up-to-date information."[224] In 2010, King published findings suggesting the application of "next generation sequencing to mutation detection for patients at high risk of breast cancer."[225]

Until this technology becomes widely applicable, Myriad plans to maintain its market dominance in BRCA1/2 diagnostics by using its private database to compete on the basis of reliability (2% VUS rate). This plan, however, is built on a rent-seeking monopoly strategy not in line with the broader goal of social utility espoused in Article 1.8.8 of the Constitution. The Genomics Law Report draws attention to this observation in its coverage of the *Myriad* debate, noting that "the hoarding of immensely important clinical data does not seem likely "to promote

[222] Swisher Decl., (19 August 2009): 6. *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office and Myriad Genetics, Inc*., 702 F. Supp. 2d 181 (S.D.N.Y. 2010).
[223] Statement by Mark Capone, President of Myriad's laboratory division, quoted by Andrew Pollack, *New York Times*, 24 August 2011.
[224] Pollack, *New York Times*, 24 August 2011.
[225] Tom Walsh et. al. "Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing," Proceedings of the National Academy of Sciences, 8 June 2010.

the Progress of Science and the useful Arts." [226] Through a liability exemption extending to the research and diagnostic use of patented genes, Congress would be able to undo the negative public health effects of this diagnostic monopoly while keeping patent protections in place for therapeutics manufacturers.

Given the massive efforts at NHGRI and universities across the nation to translate genomic scale sequencing technology to clinical practice in the next four years, it is highly unlikely that maintaining research and diagnostic exclusivity over patented fragments of naturally occurring DNA will be a sensible strategy for innovation in the future. As noted by King, current whole exome sequencing technology makes the issue already anachronistic for the genetic testing industry. According to Dr. Allen Bale at the Yale School of Medicine's DNA Diagnostic Lab, "With very little tweaking, exome sequencing will be as good [as] or better than what Myriad has to offer. Turnaround time may be a problem in the near term, but not for long. We are switching to exome sequencing for all genetic tests that involve panels of genes…as long as there are no patent issues."[227] Along with the trade secrecy issue, this fact might help explain why Myriad CEO Peter Meldrum commented (rather ironically), "If I had my druthers, I would not want to go into a new market in a heavy-handed fashion, trying to enforce patents."[228] In the long run, Myriad and other firms in the genetic diagnostics space plan to rely on genomic scale sequencing, not tests for individual conditions.[229]

For this transition to succeed, however, it is of critical importance that researchers and clinicians are able to test genomic scale sequencing in the clinical laboratory setting. Although the CAFC's reversal of Myriad's method patents may allow a legal workaround for whole

[226] John Conley et al. "How Will Myriad Respond to the Next Generation of BRCA Testing?" *Genomics Law Report*, 1 March 2011.
[227] Personal communication via email, 12 February 2012.
[228] Pollack, *New York Times*, 24 August 2011.
[229] *Ibid*.

genome sequencing, there is still significant concern as to how Myriad's remaining BRCA1/2 patents will affect the new sequencing methods. While some argue that whole genome sequencing can circumvent Myriad's remaining patents by using computerized searches of the entire raw genomic sequence (as opposed to physically isolating the target sequences),[230] the necessary software is still in the early stages of development and the hypothetical defense has yet to be tested in court. Because whole exome and micro-array tests still rely on the isolation of target sequences of DNA, clinicians who use those tests to look for BRCA1/2 mutations will still be subject to infringement lawsuits.

In the future, the development of advanced analytic software for whole genome sequencing may eventually allow researchers to circumvent Myriad's patents. Currently, however, isolated DNA patents still pose a legal risk for genomic scale sequencing and prevent the use of available whole exome sequencing technology. Because of Myriad's patents, geneticists continue to leave out BRCA1/2 in their sequencing activities out of concern that Myriad will sue for infringement. When asked if the Yale DNA Diagnostics lab would be prevented from reporting the results for BRCA1/2 mutations drawn from whole genome sequencing, Dr. Allen Bale answered that "there is absolutely no doubt that Myriad would send a cease and desist order should we report results of BRCA1 and BRCA2 testing based on whole genome sequencing." A liability exemption would allow Dr. Bale and other geneticists to research the diagnostic application of genomic scale sequencing to BRCA1/2, unhampered by Myriad patents.

Granted, one could point to the costs and risks involved in the biopharmaceutical industry and claim that such a move would reduce incentives for developers of new genetic tests. In the district court hearing of *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark*

[230] Steven Salzberg et al. "Do-it-yourself genetic testing," *Genome Biology* 11 (2010): 404.

Office et al., Myriad cited a recent BIO survey of diagnostic and therapeutic biotechnology companies in which "77% of the respondents without approved products indicated that they expect to spend 5-15 years and over $100 million developing a commercial product."[231] The issue with that argument, however, is that the BIO statistic lumps diagnostics and therapeutics together when in fact genetic test developers face much lower overhead expenses than biopharmaceutical developers. Unlike pharmaceutical manufacturers, developers of laboratory diagnostics do not have to create new active ingredients that require FDA approval. Although companion diagnostics for therapeutics and diagnostic testing kits are subject to FDA regulation, laboratory tests conducted by clinicians does not require FDA trials.

In fact, diagnostic monopolies built through patents on isolated DNA can actually hinder the development of a companion test for a new therapeutic drug. In its public testimony to the USPTO regarding exclusive gene patents, FORCE[232] noted that Myriad did not seek FDA approval for its diagnostic tests. Despite Myriad's claims that patents like its own have helped foster innovation, FORCE notes that the firm's patents have prevented others from developing an FDA-approved BRCA test, which in turn has hindered the efforts of drug companies who seek to gain FDA approval for therapeutics such as PARP inhibitors.[233] As noted by the SACGHS, patents on human genes are not a critical incentive for the invention and commercialization of genetic diagnostics.[234] Given the continual rise in national healthcare expenditures and the potential savings from new technologies, a liability exemption that creates opportunities for more

[231] *Ass'n for Molecular Pathology et al. v. U.S. Patent and Trademark Office and Myriad Genetics, Inc.*, 702 F. Supp. 2d 181 (S.D.N.Y. 2010) (slip op, at 77).
[232] "Facing Our Risk of Cancer," a nonprofit organization dedicated to education, support and advocacy for breast and ovarian cancer.
[233] FORCE Testimony to the USPTO, published on FORCE website on February 18, 2012. Myriad's test has slowed the drug companies clinical studies by forcing them register subjects for studies from the wider pool of breast and ovarian cancer patients instead of using genetic test results to select those who are hereditary carriers.
[234] Gold, S49.

cost-effective clinical research while preserving patent protection for novel products and processes seems to be the best policy solution available at this time.

Conclusion:

By studying the history of the gene patenting controversy in greater detail, one can see that patent policy on human genes is, like healthcare, a cultural as well as a scientific issue. It challenges traditional capitalist theories by requiring governments to adapt market incentives to changing social needs, through rules that may serve as exceptions to the theories of self-regulating markets and efficient intellectual property rights. It must deliver quantifiable results towards an abstract goal, whether it is the promotion of innovation, health, or long-term innovation in the protection of health. Such broad agendas require a certain degree of flexibility – an exception to the rule that allows for a continued balance between the dual goals of incentivizing the pursuit of knowledge and disclosing new findings. Examples of such exceptions can be found in copyright law, the patenting of surgical methods and even in the Bayh-Dole Act, which grants the NIH march-in rights for situations in which the patent-holder fails to "achieve practical application of the subject invention." This last exception, however, has never been used and is effectively defunct. In order to promote innovation in downstream genetic testing and the "useful art" of clinical diagnostics, Congress should consider the passage of a clinical exemption for patents on isolated DNA.

In the long run, technological progress in genome sequencing and analysis might eventually inspire a more appropriate standard for gene patentability. For now, however, there is an urgent, demonstrable need for an infringement liability exemption covering the research and diagnostic use of isolated human DNA. Delaying the clinical application of techniques such as

whole-exome sequencing in order to protect existing patents on BRCA1/2 and other genes is not the way to ensure continued scientific progress. With the coming of personalized medicine, an increasing number of patients will rely on more comprehensive genetic tests to determine whether they have a hereditary predisposition for not just breast cancer, but a myriad of other chronic diseases. Accurate test results would help physicians target high-risk patients for early detection and treatment, and ultimately help save lives.

One cannot deny that the liberalization of biomedical patent policy in *Diamond v. Chakrabarty* and the Bayh-Dole Act had a significant role in driving the rapid progress of biotechnology. Yet *Chakrabarty* adhered to an implicit rule against patenting laws of nature, and the Bayh-Dole Act acknowledged the common law research exemption (at least until *Madey*). Removing these protections threatens downstream innovation – the goose that ultimately lays the golden eggs. Patents imply a quid pro quo – as noted by Justice Breyer in *Prometheus*, they act as a double-edged sword. Although they can help promote innovation through private incentives, they can also impede it by preventing free inquiry and restricting access. Heller and Eisenberg's hypothetical "tragedy of the anticommons" has yet to fully rear its ugly head, but the BRCA1/2 controversy has demonstrated that there must be limits to the enforceability of patents on isolated fragments of human genomic DNA. In order to preserve the balance struck by the Constitution between the social distortion and utility created by patents, Congress should enact a research and diagnostic exemption designed to improve access to information. Otherwise, we may fail to promote the balanced progress of science and the useful arts that gave patents their social value in the first place.

Thus, while there are strong reasons not to ban all gene patents outright, there are compelling reasons to limit their enforceability to more socially and economically reasonable

bounds. Granted, stronger protection of formal intellectual property rights can help innovators attract more private investments from creditors and shareholders. At a general level, the economic incentive created by stronger patents seems to help advance scientific knowledge by addressing the market failure that stems from its nonrivalrous nature as a public good. A ban on all gene-related patents might threaten not just therapeutics manufacturers but the patients who rely on them as well. The private incentive that gene patents provide, however, is just one means to an end rather than the end itself. If patent policy is to improve quality of life standards for society as a whole, it must be aligned with the nation's social goals of biomedical innovation and patient access to timely care. While these goals may be shaped in part by the structural necessities of the market, they will hopefully allow for a more practical and sustainable balance between the costs and benefits of technological progress.

Figure 1: Average yearly number of DNA patents issued, by decade
Source: Data from the DNA Patents Database at Georgetown University, found in Sam Kean, "The Human Genome (Patent) Project," *Science* 331 (2011): 531.

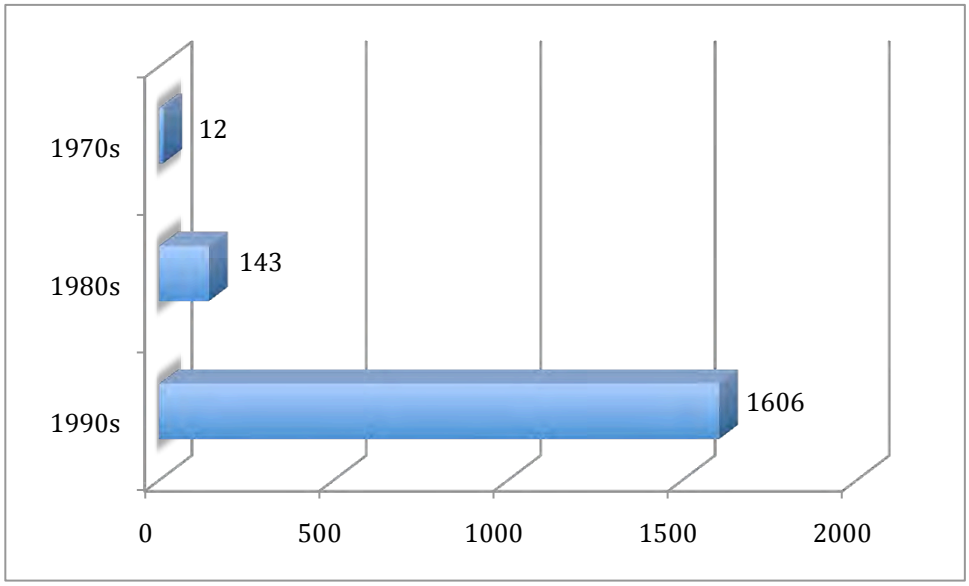
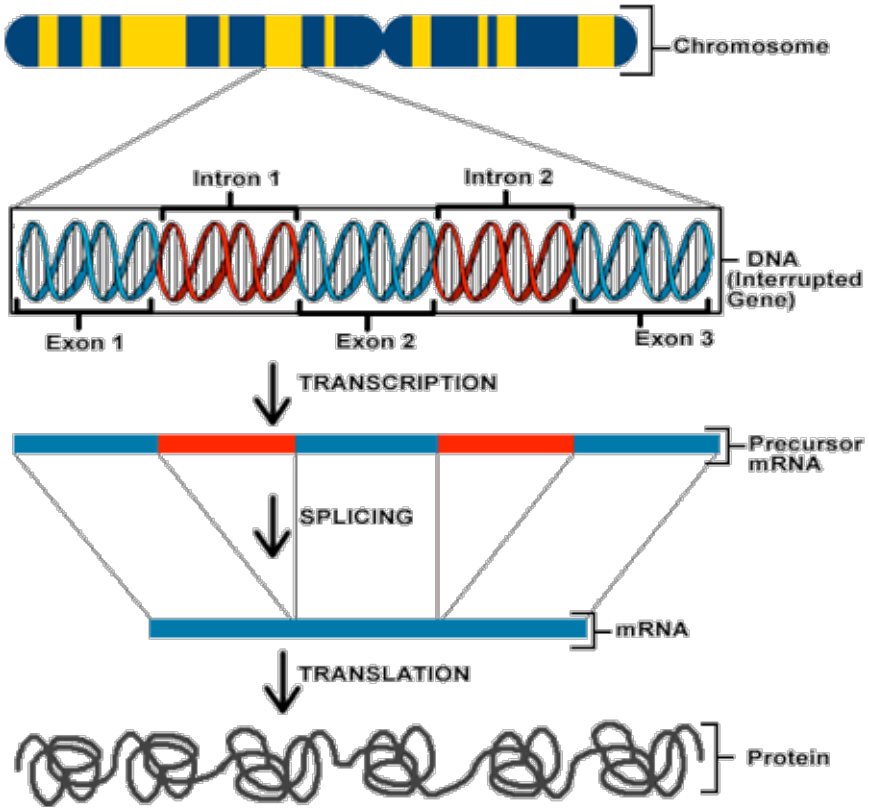
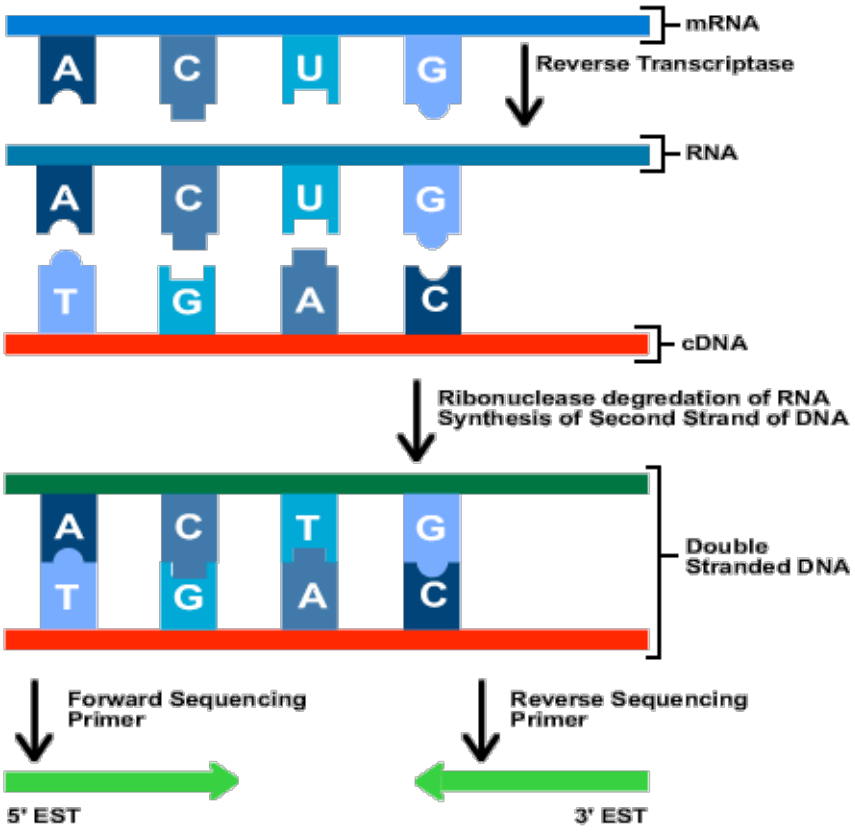


Figure 2: Visual representation of the role of Express Sequence Tags
Source: National Center for Biotechnology Information
http://www.ncbi.nlm.nih.gov/About/primer/est.html

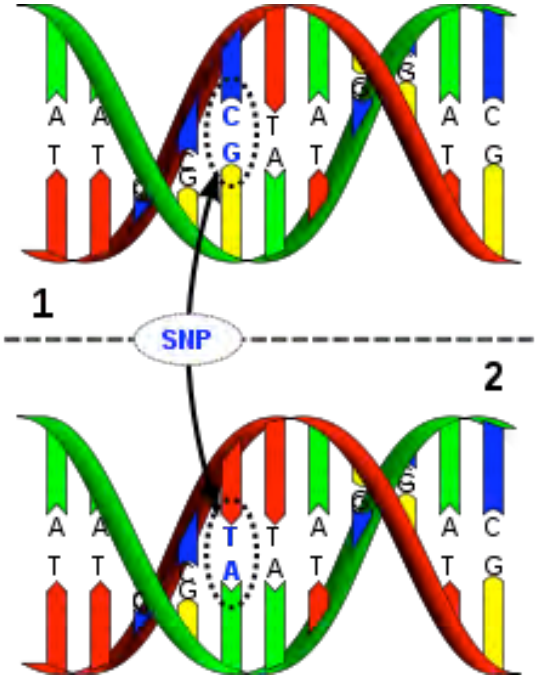


Genes are areas of the human genome that code for physical traits, which are expressed as proteins. The sections of DNA that are expressed are called exons, and they are transcribed into mRNA (another nucleic acid that acts as a template for protein synthesis during translation). As this graphic shows, the regions of DNA that aren't physically expressed (introns) are not included in the process of transcription, so that the mRNA includes only the genetic information that codes for the trait. *cont'd*



Because mRNA is not stable outside of the human body, researchers capture and store its sequence by converting it to cDNA. ESTs "tag" genes by capturing either the beginning (5' EST) or ending (3' EST) portion of this cDNA sequence. When mRNA is transcribed from DNA and again when cDNA is synthesized from mRNA, the sequence is preserved due to complementarity rules between the nucleotides (A with T/U, C with G). The cost of the technology behind EST synthesis is very low.

Figure 3: Visual representation of Single Nucleotide Polymorphisms (SNPs)
Source: US Department of Energy: Human Genome Project Information, SNP Fact Sheet



Wikipedia image: http://en.wikipedia.org/wiki/File:Dna-SNP.svg

Single Nucleotide Polymorphisms are point mutations that affect only the given base pair and leave the rest of the sequence unchanged. Although they do not always affect the amino acid sequence that determines protein structure, when SNPs lead to the expression of a different amino acid they can create a different protein or cut off protein production prematurely. SNPs account for 90% of all genetic variation in humans.

Figure 4: Laboratories prevented from performing diagnostic tests due to gene patents
Survey results from Mildred K. Cho et al., "Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services," *Journal of Molecular Diagnostics* 5.1 (2003): 3-8.

Disease	Gene(s)	# of labs
Breast & Ovarian Cancer	BRCA1/2	9
Alzheimer's Disease	APOE	9
Muscular Dystrophy	Dystrophin	5
Canavan's Disease	ASPA	4
Hemochromatosis	HFE	4
Spinocerebellar Ataxia	SCA	4

Figure 5: Visual representation of whole exome sequencing (see footnote on p. 50)
Source: GenXPro©: Products and Services: Exome Sequencing
http://www.genxpro.info/products_and_services/Exome_Sequencing/

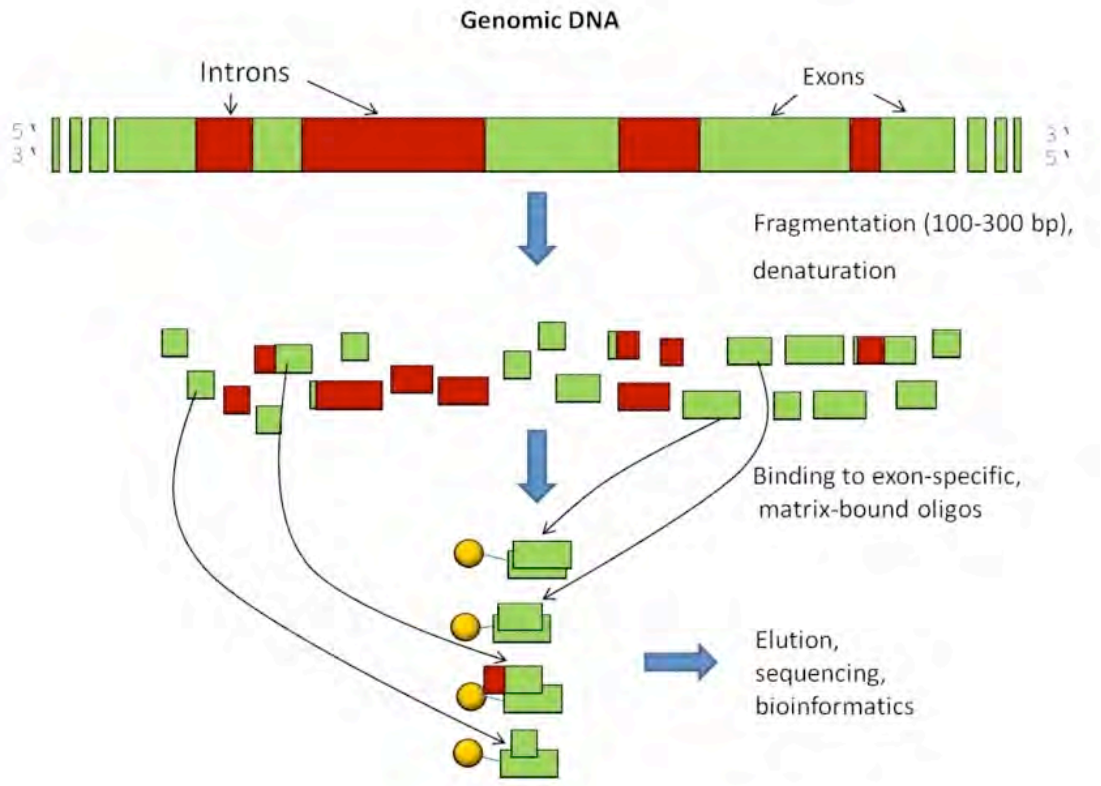
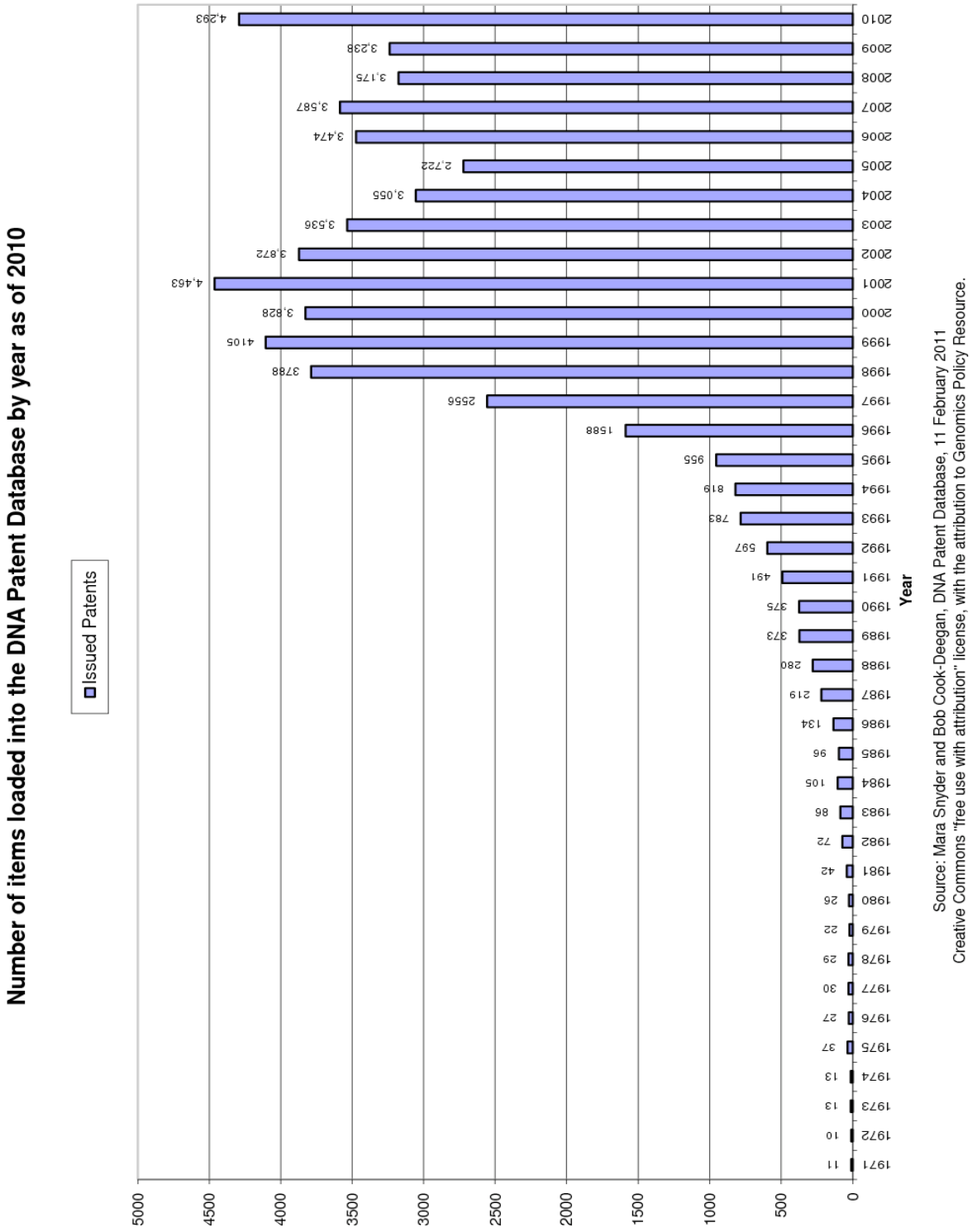


Figure 6: Rise in number of DNA patents issued, 1971 – 2010
Source: Dr. Robert Cook-Deegan, Capitol Hill Briefing on Gene Patents, 15 Sept 2011
http://ondemand.duke.edu/video/28953/capitol-hill-briefing-on-gene-



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