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## Myriad Genetics: In the eye of the policy storm

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### Abstract

From the late 1980s, a storm surrounding the wisdom, ethics, and economics of human gene patents has been brewing. The various winds of concern in this storm touched on the impact of gene patents on basic and clinical research, on health care delivery, and on the ability of public health care systems to provide equal access when faced with costly patented genetic diagnostic tests. Myriad Genetics, Inc., along with its subsidiary, Myriad Genetic Laboratories, Inc., a small Utah-based biotechnology company, found itself unwittingly in the eye of this storm after a series of decisions it made regarding the commercialization of a hereditary breast cancer diagnostic test. This case study examines the background to Myriad's decisions, the context in which these decisions were made and the policy, research and business response to them.

### Keywords

patents; intellectual property; genetic testing; breast cancer; ovarian cancer; BRCA1; BRCA2; Myriad Genetics

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From the late 1980s, a storm surrounding the wisdom, ethics, and economics of human gene patents has been brewing. The various winds of concern in this storm touched on the impact of gene patents on the basic and clinical research, health care delivery, and ability of public health care systems to provide equal access when faced with costly patented genetic diagnostic tests. Myriad Genetics, Inc., and its subsidiary, Myriad Genetic Laboratories, Inc. (together, “Myriad”), a small Utah-based biotechnology company, found itself unwittingly in the eye of this storm after a series of decisions it made regarding the commercialization of a hereditary breast cancer diagnostic test. This case study examines the background to Myriad's decisions, the context in which these decisions were made, and the policy, research, and business responses to them.

The very idea of granting patents on human genes has been controversial since they were first granted in the 1980s. A patent is a legal monopoly that the state grants to an inventor, preventing others from using, making, selling, or importing an invention for a set period of

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time. Academic articles and expert reports throughout the 1980s and, particularly, the 1990s raised two primary concerns regarding gene patents: whether it is appropriate to grant commercial rights over components of the human body and whether patents on human genes would stifle research. This controversy is well illustrated by the debate in Europe surrounding the Directive on the Protection of Biotechnological Inventions,<sup>1</sup> a piece of legislation proposed by the European Commission to recognize patent rights over all forms of biotechnology. Although some parliamentarians initially objected to the commercialization of human and animal life, the European Parliament eventually passed the legislation.<sup>2-4</sup> The debate then shifted to individual European countries, and although many initially resisted the Directive, by 2007, all had transposed it into national law.

As these debates proceeded, public health care administrators struggled with how best to integrate costly genetic testing while allowing for continued equal access to publicly funded health care. These administrators aimed to control increasing costs while providing the best and most cost-effective health care.

Given this general environment, it is no surprise that debate intensified when one of the first patented genetic tests, for breast and ovarian cancer, went on the market. It is perhaps because of the high profile of breast cancer that this test, patented by Myriad, struck a chord among politicians and the public. One in nine women is expected to develop breast cancer during her lifetime, and 1 in 27 will die of it.<sup>5</sup> Of all cases of breast cancer, the estimates of affected women who are carriers of a mutated allele dominantly transmitted and associated with a high risk of breast cancer ranges between 5% and 10%.<sup>6,7</sup> Estimates of breast cancer cases occurring in *BRCA1* or *BRCA2* mutation carriers vary from between 3% and 10%.<sup>8</sup> Women with hereditary breast cancer can undertake prophylactic treatment, making the availability of genetic tests for hereditary breast cancer important for individuals at risk.

Scientists at institutions around the world discovered and sequenced a series of genes linked to breast and ovarian cancer in the early 1990s. Mutations in these genes prevent the body from producing tumor suppressing proteins, which in turn increases an individual's risk of contracting breast or ovarian cancer. Individuals with these mutations have a cumulative lifetime risk of ~40–85% of developing breast cancer and ~16–40% chance of developing ovarian cancer,<sup>9</sup> compared with 12.7%<sup>10</sup> and 1.4%<sup>11</sup> risk for the general population of developing breast or ovarian cancer, respectively. With this knowledge, laboratories developed diagnostic tests for these mutations, which opened up the possibility of preventive management for breast and ovarian cancer, including prophylactic surgery (often, a mastectomy) and the use of tamoxifen.

At this point, Myriad entered the scene with its own diagnostic test for breast and ovarian cancer using state-of-the-art laboratories. Although many scientists were involved in the initial stages of research, it was Myriad that obtained patents over the sequenced *BRCA1* gene, associated mutations, and associated diagnostic test. Myriad also received a patent over the sequenced *BRCA2* gene and associated mutations. Given public concern over breast cancer, Myriad may have expected their test to be greeted with excitement. However, as a result of having pursued patents on the genes, Myriad ran into great resistance from the scientific and medical communities. Furthermore, Myriad's perceived business model clashed with the way in which health care administrators in the public sector made decisions about the provision of health care and conflicted with established practices about administering existing testing for breast and ovarian cancer. Instead of resolving these clashes through dialogue, actors from the various communities severed links, misunderstood one another, and distrusted one another's motives.

Much has been written about concerns with gene patents in general and how Myriad's decision may or may not have impeded research and access. However, this case study presents a more in-depth understanding of the interaction between Myriad's patents and business strategy and the policy response to that strategy. We present the business, health research, and health administration context in which Myriad made its decisions and the way that different actors, in different countries, responded to those decisions. In particular, we focus on the way that institutional structures and roles shaped the debate and outcomes, all with the goal of providing insight to the policy community on how laws, institutions, and practices interact to shape effective policies for emerging technologies.

This case study highlights the important relationships within intellectual property (IP) systems—consisting of the laws, business, and governmental practices and the institutions that manage IP—which need to be considered in understanding the effect and effectiveness of IP on various socioeconomic outcomes. The case study was developed through an examination of existing literature, discussions at a workshop involving some of the primary actors involved in the conflict surrounding Myriad and through oral and written comments on drafts of the case study (see Appendix for list of participants). By drawing on this literature and ensuring that the views of individuals involved in the conflict are fairly reflected, we present as neutral an account as we can manage. There was no attempt to reach consensus among all actors at the workshop; each actor had his or her own interpretation of the events. Nevertheless, the workshop's participants agreed on the principal events and motivations of the parties, as well as on some of the key reasons that the breast cancer genetic test became so controversial. To respect the confidentiality of the individuals providing interviews or who participated in the workshop, we do not provide direct citation to the interviews and workshop statements. Rather, unless otherwise indicated, statements as to the events and perceptions of actors involved with the Myriad controversy are derived from the literature, documents obtained by the authors, workshop discussions, and interviews. Only where interviewees or participants have specifically agreed to be quoted, have we done so.

Part I of the study sets out a chronology of the events that led to the sequencing of the genes eventually patented by Myriad. It examines the state of science at the time and chronicles the competition between the various scientific groups racing to identify and sequence the genes and mutations for inherited breast cancer susceptibility.

Part II continues the discussion by presenting the story of Myriad, starting with its early days as a startup, and outlining its research strategy, business model, and licensing strategy in the United States, Canada, Europe, Australia, and Japan.

Part III outlines the national and international levels of the policy context in which Myriad commercialized the breast and ovarian genetic test and the resulting policy responses that Myriad faced in various countries. Responses ranged from ignoring the patents in Canada, to the launch of an opposition procedure within the European Patent Office (EPO), to more localized reactions within smaller scientific and medical communities.

The study concludes in Part IV with a discussion of the lessons to be learned from Myriad's story. We pay special attention to the way in which laws, institutions, and practices interact to form IP systems, the lack of empirical data to form policy, and the role of politics and ideology in influencing the successful introduction of a technology nationally and internationally.

## PART I

### In the beginning ...

For the past few decades, several teams of scientists have used a diverse set of techniques to identify the various genes associated with diseases. For example, researchers linked muscular dystrophy to the X chromosome because of the sex-linked pattern of inheritance of the disease. Other teams observed the occurrence of disease within families to identify inherited mutations that led to disease.

Scientists estimate that between 5% and 10% of breast cancers are hereditary.<sup>7</sup> So far, researchers have identified >2000 mutations in these genes. Some of these mutations exist at birth, and others are caused by environmental factors. The sizes of the mutations vary widely from single nucleotide mutations to large-scale rearrangements or deletions within the gene. In the absence of a candidate gene, researchers use linkage studies to localize the gene (its locus) on the chromosome. Researchers then sequence the DNA that makes up the gene. Additional sequencing allows them to identify the “normal” variation of the gene and the disease-causing mutations of the gene. The latter is done by examining the gene sequence in individual members of families with a high incidence of breast or ovarian cancer. Although different types of genes associated with breast cancer have been discovered, in this case study, we focus on *BRCA1* (located on chromosome 17) and *BRCA2* (located on chromosome 13).

Competition among the seven major research teams working to locate and identify *BRCA1* and *BRCA2* was vicious. In the United States, the two main competitors were Mary Claire King's group (including Francis Collins, Anne Bowcock, and initially Barbara Webber) and Mark Skolnick's group (including David Goldgar). Andrew Futreal and Roger Wiseman from the National Institutes of Environmental Health Sciences also worked with Mark Skolnick on *BRCA1* research. In the United Kingdom, the main group involved in research, particularly *BRCA2* research, surrounded Michael Stratton, Bruce Ponder, and Richard Wooster. With respect to *BRCA2* research, Andrew Futreal also collaborated with this group. In addition, researchers in France (Gilbert Lenoir and Dominique Stoppa-Lyonnet), Japan (Yusuke Nakamura), and Canada (Stephen Narod working alongside Gilbert Lenoir and Jacques Simard working alongside Myriad), all participated in the mapping of the genes. At various times, these groups collaborated: some collaborations succeeded, others failed. For example, Mark Skolnick and Mary Claire King attempted to combine efforts to identify the gene, but their collaboration ended after a disagreement on how to conduct the research.<sup>12</sup> Despite fierce competition, researchers formed the international Breast Cancer Linkage Consortium (BCLC) in 1988 to bring together research groups from the United Kingdom, United States, Canada, France, Belgium, and The Netherlands, among others, to compile later stage research on the gene and to speed up the pace of identifying relevant mutations.<sup>13</sup>

In 1990, a group of US researchers lead by Mary Claire King at the University of California at Berkeley announced at the American Society of Human Genetics Meeting that they had located a breast cancer gene (*BRCA1*) on chromosome 17 through a technique called linkage analysis.<sup>14</sup> This provided the first evidence of the potential existence of genes for hereditary forms of breast cancer.<sup>15</sup> The team eventually patented the markers used to locate the gene, which were subsequently licensed to OncorMed, a US company.<sup>16</sup>

After King's announcement, Gilbert Lenoir and Steven Narod published an article confirming King's results and, additionally, linked the region to hereditary forms of ovarian cancer.<sup>17</sup> The next stage was to identify the gene through sequencing. Competition intensified as teams came closer to finding the gene on chromosome 17. At this time, the

BCLC began collecting information on 214 families, which showed that *BRCA1* was particularly associated with families in which both breast and ovarian cancer occurred frequently. This study also provided conclusive evidence of the existence of other breast cancer genes, as only 45% of breast cancer in families with a high incidence of hereditary breast cancer could be explained by *BRCA1* alone. Members of the Consortium subsequently compiled their research to provide a composite map of the *BRCA1* region to help in the identification of mutations. In 1993, the BCLC published a series of articles in the *American Journal of Human Genetics*.<sup>18</sup>

At the same time, a group of scientists (including two from the National Institute of Environmental Health Sciences in the United States) led by Marc Skolnick at the University of Utah's Centre for Genetic Epidemiology were also working to identify the gene. Much of their work relied on a database of an extensive pedigree of Mormon families that Skolnick had begun developing in the 1970s.<sup>19</sup> This database contained information on 200,000 Mormon family groups and most of the 1.6 million descendants of the initial 10,000 Utah settlers.<sup>19</sup> When Skolnick linked the database to the Utah Cancer registry, the database contained 40,000 cross-linked entries that spurred much of Myriad's future research.

In 1991, Skolnick's group formed Myriad as a spin-off from the Centre for Genetic Epidemiology with the aim of obtaining the funding needed to complete the research. Myriad secured funding from Eli Lilly and Co., a US-based pharmaceutical company. The National Institutes of Health (NIH) contributed \$5 million to the University of Utah research team.<sup>20</sup> Then in 1993, Myriad raised \$10 million in a private stock offering, \$1 million was equity from the pharmaceutical giant Eli Lilly and Co. Eli Lilly also provided another \$1.8 million over 3 years to search for the genes associated with hereditary breast cancer in return for licensing privileges for diagnostic kits and therapeutic products on *BRCA1*. Myriad did not at that time hold any patents, often considered as essential<sup>21</sup> to attracting money from private investors to biotechnology companies. Nevertheless, Myriad convinced Eli Lilly to invest based on Skolnick's privileged access to and knowledge of the Mormon database. The scientific clout that came along with one of Skolnick's partners, Walter Gilbert, the winner of the 1990 Nobel Prize in Chemistry, likely influenced Eli Lilly as well. Although control of the Mormon database always remained with the University of Utah, Skolnick was best positioned to use it, giving Myriad the inside track in the race to sequence *BRCA1*. In return for the funding, Myriad gave Eli Lilly the rights to develop any future therapeutics involving *BRCA1*. Essentially, Myriad was setting the stage for a winning cocktail: leading personalities, cutting-edge research, and an excellent opportunity for commercialization with a strong potential for patent protection. Because large pharmaceutical companies anticipated that genetics would produce many new therapeutic products, Eli Lilly believed it was investing in research that might lead to a future development of blockbuster drugs.

## **PART II—ENTER MYRIAD GENETICS, INC., EXCLUSIVE PROVIDER OF *BRCA* TESTING**

### **Business model in the United States**

The Myriad team first published its results about *BRCA1* in *Science*<sup>22</sup> on October 7, 1994. This was shortly after Myriad had filed a patent application covering the gene and its mutations on August 12, 1994, along with its coassignees the University of Utah and the United States Department of Human Health and Services (added to the application after a dispute with Myriad). Myriad filed several revisions to the original application (called continuance or continuation applications) during the next 12 months, updating the sequence, the last of which was filed on June 7, 1995. On December 2, 1997, the United States Patent and Trademark Office (USPTO23) granted Myriad a patent that covered 47 separate



mutations in the *BRCA1* gene (US 5,693,47323). The team of inventors included two scientists from each of Myriad, le Centre de recherché du CHUL, Quebec, Canada, and the Cancer Institute in Tokyo, Japan. The other parties granted Myriad the sole right to control both research and commercial uses of the *BRCA1* gene.

Subsequently, the USPTO granted five additional patents to Myriad covering the *BRCA1* gene and associated diagnostic tests (US 5,709,999; US 5,747,282; US 5,710,001; US 5,753,441; and US 6,162,89723). On June 7, 1995, Myriad filed two more patent applications, covering methods of detecting *BRCA1* mutations and the entire sequence of the *BRCA1* gene and tools used in their work. These two patents were granted on January 20, 1998, and May 5, 1998, respectively. It was the last patent that gave Myriad the greatest control over *BRCA1*, as it covered all uses of the *BRCA1* gene.

Meanwhile, OncorMed, another US-based biotechnology startup company, had also filed patents over *BRCA1*. By using the markers that they licensed from King, OncorMed obtained what it believed to be the most common sequence (allele) to be found in the majority of the population without mutations. OncorMed was granted a patent a few months before Myriad, on August 5, 1997, which claimed the consensus sequence. Myriad and OncorMed subsequently both filed infringement suits against each other. As will be discussed below, however, Myriad eventually acquired OncorMed's patents, settling those suits.<sup>16</sup>

Both the identification of the *BRCA1* gene and the knowledge that there had to be other genes related to hereditary breast cancer precipitated the discovery of *BRCA2*. A team of researchers led by David Goldgar from the University of Utah and a United Kingdom team led by Michael Stratton at the Institute for Cancer Research and the Wellcome Trust's Sanger Centre located another region linked to hereditary breast cancer on chromosome 13 containing the *BRCA2* gene. Michael Stratton's group announced the existence of *BRCA2* in an article coauthored by 31 researchers from the multinational team, published in *Science* on September 30, 1994.<sup>24</sup>

The next step was the work of actually sequencing the *BRCA2* gene. The United Kingdom group published an article in *Nature* in December 1995, coauthored by 40 researchers from 6 countries, which contained the gene's sequence.<sup>25</sup> The charity that funded the research, the Cancer Research Campaign, filed a patent application covering the gene with the United Kingdom patent office. Meanwhile, the day before Stratton's article was published, Myriad announced that it too had isolated and sequenced the gene, had deposited the entire sequence into Gen-Bank—a database containing gene sequences—and filed for a patent in the United States. Researchers, including Mark Skolnick from Myriad, eventually published its article setting out its sequencing of *BRCA2* in a March 1996 issue of *Nature Genetics*.<sup>26</sup> In this article, the researchers claimed that Stratton's article had only “reported a partial sequence and six mutations,” whereas its team had supplied the complete sequence.<sup>26</sup> Myriad filed a patent application claiming *BRCA2* DNA, mutations, and diagnosis on April 29, 1996, and for a patent over the method of detecting *BRCA2* mutations and antibodies on March 20, 1998. The USPTO granted these patents on November 17, 1998 (US 5,837,49223) and September 26, 2000 (US 6,124,10423), respectively.

Once Myriad had its patents (nine in total) on the *BRCA1* and *BRCA2* genes, it gained control over the use of diagnostic tests based on those genes. To make use of this advantage, Myriad opened a US\$30-million laboratory in late 1996. It began marketing three principal diagnostic tests: (1) the Comprehensive BRACAnalysis, which involved full sequence testing of the *BRCA1* and *BRCA2* genes (offered at the time at US\$2400), (2) the Single Site BRACAnalysis test (offered at US\$395.00), and (3) the Multisite three BRACAnalysis,

three mutation *BRCA1/BRCA2* analysis, which identified mutations that were particularly prominent in the Ashkenazi Jewish population.

Armed with patents in the United States over the breast cancer genes, mutations of those genes, and diagnostic tests, Myriad began marketing its tests in the United States. Its goal was to be a leading biopharmaceutical diagnostic company that linked gene discovery to therapeutics. Because diagnostic products and services could be put on the market relatively quickly—not having to undergo clinical trials in the United States—Myriad's diagnostics business was designed to generate the funds necessary to engage in drug discovery and clinical trials. In 2008, Myriad posted quarterly revenues from its diagnostic services at \$59 million, representing a 55% increase in product revenues from the first to third quarter of fiscal 1997. Myriad believes that its increased sales, marketing, and educational efforts, including its direct-to-consumer advertising campaign for BRACAnalysis® in the Northeast region, have resulted in increased demand for its products.<sup>27</sup>

Myriad recognized that, to be successful in the diagnostics business, it needed to build a strong network of health care providers, laboratories, and insurers, which would put Myriad high on the list for anyone thinking about genetic diagnostic services. Using the *BRCA1* and *BRCA2* patents, Myriad would build a reputation for quality genetic testing. This reputation could then be leveraged to cover other genes as these were discovered. Anyone entering into the genetics diagnostics market would think first of licensing their test to Myriad, which would ensure a solid revenue flow to Myriad.

With this in mind, in the United States, Myriad put together a group of laboratories, health insurers (e.g., Blue Cross/Blue Shield), sales and distribution teams, physicians, and a communication team to promote its tests. For example, in 2000, Myriad signed an agreement to provide its BRACAnalysis breast and ovarian cancer susceptibility test to Kaiser Permanente patients.<sup>28</sup>

Myriad only offered testing services through physicians. To that end, Myriad initially advertised its services only to physicians and clinicians. Myriad counted on genetic counselors to screen potential test subjects; however, it soon realized that there was an insufficient number of these counselors available to meet population needs. In response, Myriad sponsored training for physicians about the test. Myriad employed >20 genetic counselors to educate physicians on how to identify patients who would benefit from the test. Training encouraged physicians to refer such patients into centers that provided testing services or participated in research studies.

Myriad's diagnostic testing model relied on interested patients to present themselves to a physician who would counsel the patient on whether breast cancer testing was appropriate. Although no genetic counseling was formally required by Myriad, the health care provider was responsible for ensuring that the patient signed an informed consent form (the requirements of which were left up to the individual health care provider, although Myriad did send a sample form with the test kit). The health care provider then sent the patient's blood sample directly to Myriad for full sequencing (called proband testing, referring to the first family member identified with a mutation—whose sequence becomes the reference sequence against which other family members are compared).

Myriad anticipated that for every woman whose test revealed a mutation, 10 of her relatives would want to be tested for that same mutation. Instead of having to undertake the full sequencing of both *BRCA1* and *BRCA2* genes, these relatives could simply ask to test their DNA against the previously identified mutation in their family member, at about one-tenth the cost. Myriad was willing to license out this follow-up testing to local laboratories. On the assumption of 10 relatives being tested for particular mutations (at one-tenth the cost) for

every positive proband test, Myriad assumed that it would split revenues evenly with its licensees. By the late 1990s, Myriad had licensed 13 laboratories in the US to conduct this type of single mutation testing.

By the time Myriad introduced its test in the late 1990s, other laboratories had already been performing *BRCA1* and *BRCA2* tests using other methods. Once Myriad obtained its patents, especially the gene patent issued in May 1998, it attempted to eliminate BRCA testing at competing laboratories by sending cease-and-desist letters. Myriad sent letters to the Genetics and IVF Institute (GIVF) and the University of Pennsylvania's Genetic Diagnostic Laboratory (GDL) in 1998. GIVF acquiesced to Myriad's demand to stop testing but GDL initially refused to do so, claiming that a "research exemption" covered its activities.<sup>29</sup> Although the status of a research exemption in US law is unclear, GDL's position was that, because it provided its testing services for researchers working under protocols within the National Cancer Institute's (NCI) Cancer Genetics Network, it was not infringing on Myriad's patent. Myriad disagreed with GDL's position, arguing that because the actual research did not take place at the GDL, the GDL was providing a commercial service. In response to these disagreements and to set the stage for research on *BRCA1* and *BRCA2*,<sup>30</sup> Myriad entered into a Memorandum of Understanding (MOU) with the NCI to provide at cost or below cost testing to the NCI and any researcher working under a NCI-funded project. (Myriad had similarly offered to provide NIH researchers with at cost testing given that the NIH was a co-owner of some of the relevant patents). The MOU defined research testing services as "part of the grant supported research of an investigator, and not in performance of a technical service for the grant supported research of another (as a core facility, for example)" (MOU between Myriad Genetics Laboratories and the NCI). Research testing services are further defined as paid for by grant funds and not by the patient or by insurance. So long as the patients were part of the research protocol, they would be provided with the testing results. Under this definition, GDL was not providing research testing services and, thus, fell outside the scope of permitted activity.

To summarize, Myriad's competitive advantage in the United States resides in its network of health care professionals, service providers, and insurers. The company attempted to position itself to be the laboratory that people thought of when they wanted to conduct genetic testing. Their patent rights served to secure this network and ensure a stable stream of income to be reinvested in the development of other tests and therapeutics.

To date, Myriad has yet to make a profit despite revenues from its diagnostics business. Profitability would require the development of new products, especially therapeutic products, which offer a higher financial return.

### **Myriad's international business model**

Myriad attempted to replicate internationally what it viewed as a successful business model in the United States. Myriad sought patent rights internationally using the applications submitted to the USPTO to give it priority over other would-be inventors. The company then deployed a traditional international commercialization model: it attempted to identify a single licensee in each country or region that would market the tests within that territory. The licensee would obtain an exclusive license, so neither Myriad nor anyone else would be permitted to market the test in the territory. As it did within the United States, Myriad would provide the proband testing at its Utah laboratory and leave it to its local licensees to provide the less expensive single-mutation tests. In most of Myriad's agreements, defense of the patents was left to Myriad.

The Canadian Intellectual Property Office (CIPO) granted Myriad three patents based on a patent application the company filed in 1995. Two patents covering *BRCA1* and mutations



of *BRCA1* were granted on October 10, 2000 (patent numbers 2,196,797 and 2,196,79031). On April 3, 2001, Myriad was granted a patent on the diagnostic test (patent number 2,196,79531). CIPO also granted Myriad a patent on *BRCA2* on April 3, 2001 (patent number 2,239,73331). On January 10, 2001, the EPO granted Myriad its first European patent (EP 699,75432) covering any methods of diagnosing a predisposition for breast and ovarian cancer using the normal sequence of the *BRCA1* gene. The EPO then issued a second patent relating to the mutated *BRCA1* gene (34 mutations) on May 23, 2001 (EP 705,90332), and on November 28, 2001, the EPO issued Myriad a third patent relating to the *BRCA1* gene itself (EP 705,90232). Finally, on January 8, 2003, the EPO granted Myriad a patent claiming the *BRCA2* gene (EP 785,21632). Myriad also obtained patents in Australia (patent numbers 686,004 and 691,95833), New Zealand (patent number 326,52534), and Japan.

Myriad's marketing strategy in Canada began by the announcement that, on March 9, 2000, it had awarded MDS Laboratories (MDS), a private company, the exclusive right to market the BRCA tests in Canada.<sup>35</sup> Myriad would provide proband sequencing and leave it to MDS to arrange for individual mutation testing within its "network of physicians and hospitals."<sup>36</sup> In Europe, in October 1998, Myriad invited a group of researchers to visit its Salt Lake City laboratories, discussed the issue of patents, and offered them a license. As each country within Europe has a separate health care and laboratory system, Myriad engaged in country by country negotiations.

On March 8, 2000, Myriad announced a strategic alliance with Rosgen, Ltd., for BRCA testing in the United Kingdom and Ireland. The agreement held that Rosgen would send patient samples to Myriad in Salt Lake City for proband testing (the Comprehensive BRCAAnalysis<sup>®</sup> full-sequence breast and ovarian cancer test) and would also establish a service in the United Kingdom to provide single-mutation screening tests. Under the arrangements, Rosgen had the ability to decide whether and how to enforce Myriad's patents in the United Kingdom and Ireland. Rosgen then negotiated an agreement with the United Kingdom's Department of Health that would allow the national health authority, the National Health Service (NHS), to perform the testing. The agreement stated that not only could the NHS provide testing services without having to pay but also that it could offer an unlimited number of tests, that Rosgen would share mutation data with the NHS, and that the NHS could ask Rosgen to provide testing services at a discounted price.<sup>37,38</sup> As Myriad was licensing its test to Rosgen, the Cancer Research Campaign, which held another patent covering parts of the *BRCA2* gene, licensed its patent to OncorMed but with the stipulation that the NHS could continue to provide testing services for free.

Rosgen soon went bankrupt, ending the agreement with the NHS. Myriad and the NHS did not negotiate a replacement agreement.<sup>37,38</sup> However, Myriad found another United Kingdom licensee, Lab21, with whom they signed a license agreement for the BRCA test in December 2005.<sup>39</sup>

Myriad licensed Bioscentia in Switzerland, Germany, and Austria to market its test for proband testing and to provide the follow-on testing to family members for single mutations. When it became illegal in France to send blood samples out of the country, Myriad claimed that it would be willing to allow local laboratories to perform proband sequencing. However, because no laboratory in France was ever licensed to perform the testing, the offer never came to pass.

In Australia, the situation was different as Myriad was forced to license the BRCA test to Genetic Technologies, Inc. (GTG) because GTG was pursuing Myriad for patent infringement. In exchange, Myriad received a nonexclusive license to GTG's patent over

noncoding DNA, so that it could continue BRCA testing elsewhere.<sup>35</sup> Although GTG initially permitted provincial health authorities to take nonexclusive licenses for BRCA testing, as of July 2008, it has announced that it will now enforce its patents.<sup>35-40</sup>

Although Myriad preferred to license the BRCA tests on its standard model, it showed some flexibility with respect to Japan. Because authorities required clinical trials to demonstrate that the BRCA test was effective for the Japanese population, Myriad's Japanese licensee faced significant costs in entering the market. To compensate for this, Myriad permitted its licensee, Falco Biosystems, Ltd., to conduct proband and single-mutation testing after an initial period in which Myriad did all the testing and a subsequent period in which it did only proband testing.

Although there were certain exceptions, Myriad's preferred business model was to conduct all proband sequence analysis at its Utah laboratory and to license out single-mutation sequencing. Myriad's ultimate goal was to recoup the investment it made in its Salt Lake City laboratories and to use testing revenue to fund future research. Armed with its patent rights, Myriad anticipated taking firm control of the Canadian and European markets, as it had done in the United States. What it failed to realize was that it had entered into a storm about the patenting of biotechnology, the ways in which to regulate genetic testing, the role of private companies in determining which health services are on offer within public health systems, and how to provide access to genetic testing. Those miscalculations would thwart Myriad's success outside the United States.

### **PART III—THE EYE OF THE POLICY STORM**

Although Myriad's commercialization strategy may have worked well for another type of good, the company did not take into account the policy realities surrounding the delivery of health care, particularly in countries with public health systems.

In the 1990s, policymakers were led to believe that, largely because of “genohype,”<sup>41-43</sup> a plethora of new genetic and genomic technologies were on the verge of entering the market. For those policymakers in public health care systems, the first concern was how to integrate these new technologies—in terms of quality, cost, human resources, and effectiveness—into public health care systems. Myriad was one of the first companies to propose a genetic diagnostic test with broader health relevance, and it did so with a novel commercialization strategy. Although public health care administrators had experience with kit-based tests—whether genetic or otherwise—they were not familiar with a business model that required them to give up control over the performance. In addition, many researchers and clinical geneticists opposed gene patenting in general and felt a degree of hostility toward Myriad because of the way the scientific race had proceeded. This they communicated to policymakers.

Myriad introduced its licensing strategy into this clinical and policy context. It said it did so fully aware of the difficulties it faced. Others, based on their perceptions of Myriad's behavior in entering Canada, Europe, and Australia, saw little indication that Myriad understood the policy environment in those countries. We examine, in this Part, the clash between Myriad's commercialization strategy and the community norms of scientists and clinicians, patient groups, and policymakers.

#### **Clash with scientific community norms**

Starting in the 1980s, biotechnology researchers increasingly applied for patents over their early stage research. Legal scholars and the social science community explored the possibility that this rise in patenting could hinder research because of the inability of

scientists to obtain the right to use all necessary inventions (the anticommons problem)<sup>44</sup> or to afford access to critical technology (blocking patents).

Social science research that identified the potential risks of gene patents amplified the concerns of key members of the science community. In 2001, Isaac Rabino<sup>45</sup> published results of a survey of human geneticists on a variety of issues including patenting, academic secrecy, duplication of efforts and commercialization. His research suggested that geneticists were optimistic about the positive health benefits that human genetics could offer but were concerned about the impact that patenting genes may have on future research. This was true even among industry scientists. In two surveys, Cho et al.<sup>46</sup> and Merz et al.<sup>47</sup> also examined the impact of gene patents on research and the clinical delivery of genetic testing services in the United States. The authors concluded that, “although patents may have provided incentives to conduct the basic research underlying genetic tests, the reported inhibition of clinical testing and research does not bode well for our ability to fully and efficiently use the results of the Human Genome Project and related work.”<sup>46</sup> In addition, Walsh et al.<sup>48</sup> used survey data to examine the effects of research tool patents and licensing on biomedical innovation and concluded that most scientists found ways around these patents, often by simply ignoring them. Joseph Straus<sup>49</sup> (in Germany) and Nicol and Nielsen<sup>50</sup> (in Australia) undertook similar studies and reached similar conclusions.

Myriad entered the scene in what the scientific and clinical communities considered an aggressive manner. One example of this is the short amount of time it took Myriad to send its cease-and-desist letter to the University of Pennsylvania's GDL after Myriad obtained its major patent. GDL ensured that this letter received significant media attention, with the accompanying message that Myriad was attempting to impede basic scientific research. It is worth noting that GDL did not complain about its own university's role in the BRCA patents. After all, the University of Pennsylvania was a co-owner of the patent over *BRCA2* and had licensed its use to Myriad. In any event, Myriad disagreed with the GDL's assessment and stated that it fully supported the use of its inventions, without license or payment, by researchers actually carrying out their own research projects. As noted earlier, Myriad took the position, enshrined in its agreement with the NCI that by supplying testing services to outside researchers, GDL was not conducting its own research and, thus, needed to obtain a license.

Although, on several occasions, Myriad representatives confirmed during media interviews<sup>51</sup> that the company had no intention of enforcing its patents against scientists conducting research on their own behalf, the company did not broadly publicize this (however, its spokespeople did state in newspaper interviews that Myriad would not prevent scientific researchers from using the genes). Instead, the GDL story, and general discussion in the scientific community, left researchers with the impression that Myriad would enforce its patents against them if they pursued research on the genes. Even though news that Myriad was willing to provide a half-price testing service to those conducting research testing with funding from the NCI was widely disseminated, little was said of Myriad's willingness to permit researchers to do their own sequencing of *BRCA1* and *BRCA2*. There are precedents of companies providing public assurances in respect of research, although in the software industry. Red Hat, for example, posts “Our Promise” online which states: “to the extent any party exercises a Patent Right with respect to Open Source/Free Software which reads on any claim of any patent held by Red Hat, Red Hat agrees to refrain from enforcing the infringed patent against such party for such exercise.”<sup>52</sup> This enables users to act in accordance with the promise, but it also constrains Red Hat's ability to enforce its patent. Similarly, Myriad could have defined some uses as research and publicly assured researchers that it would not enforce against such use. However, once such a statement is made public, it does have legal implications.

To the large majority of researchers who had not been closely following Myriad's public statements, it seemed that Myriad was willing to block scientific research to turn a profit. In reaction, a number of scientists expressed concern about contributing their own research results on *BRCA1* and *BRCA2* to public databases for fear of providing Myriad with evidence of patent infringement. In fact, one researcher at the University of Alberta was advised not to contribute new mutations to databases for this very reason. Following on these fears, King, Stoppa-Lyonnet and others spoke out against Myriad's patents, arguing that Myriad's aggressive stand would prevent researchers from developing improved *BRCA1* and *BRCA2* tests, assessing the quality of Myriad's test, and developing treatments for breast and ovarian cancer.<sup>53-55</sup>

Myriad staunchly denies that it ever blocked research use of *BRCA1* or *BRCA2*. In fact, Myriad states that it did not even require researchers to sign a license to use these genes for research purposes. "Myriad has never required a license for research. Its position has consistently been 'proresearch' from the beginning. Since research performed on *BRCA1* and *BRCA2* could only confirm and expand the clinical utility of testing, it would have been counter productive to science or to Myriad's commercial development to require researchers to obtain a license" (W. Rusconi, Director of International Marketing, Myriad Laboratories, personal communication, 2006). To support its position, Myriad points to the large number of articles published about BRCA. (A search of PubMed for articles containing *BRCA1* or *BRCA2* reveals 6785 articles. Note that this number includes articles on ethics and clinical care.)

Of concern to both Stoppa-Lyonnet and King was the fact that, at that time, Myriad's test did not catch all mutations in the *BRCA1* and *BRCA2* genes, in particular, large-scale changes in the genes (called large-scale rearrangements such as deletions of gene segments or partial duplication of the gene). The first article reporting such large-scale gene rearrangements was published in 1999.<sup>56</sup> In 2001, Stoppa-Lyonnet and coworkers<sup>57</sup> published an article reporting the identification of a deletion in a family previously studied by Myriad. Subsequently King and her coauthors<sup>58</sup> studied 300 particularly high-risk women who, despite having four or more cases of breast cancer in their families, had received a negative test result using Myriad's BRACAnalysis. The authors used various testing techniques beyond those used by Myriad to find that 35 of these women— or almost 12%— did have mutations in the *BRCA1* or *BRCA2* genes despite the initial negative result. Because of this, King argued that better tests needed to be developed. She argued that, however, because Myriad held patents over the genes and the genetic tests, it could prevent others from developing more comprehensive or accurate tests. By the time, King had published her article in 2006; however, her critique had lost some of its force. Myriad states that it had been working on large-scale rearrangements since 1999 and, in 2002, introduced analyses for the most significant of these into the BRACAnalysis test. By the summer of 2006, it had introduced them all (G. Critchfield, President, Myriad Laboratories, personal communication, 2006).

Even before 2002, Myriad readily acknowledged that its early test did not catch all large-scale rearrangements. In fact, Myriad states that, through physicians, it would inform patients who were at risk of having such a rearrangement of other laboratories providing a test that might catch them. These laboratories provided individualized testing and so could catch the rearrangements while Myriad worked at developing the high throughput rearrangement panel that it introduced in 2002. Although these other laboratories may have been technically infringing on Myriad's patent, Myriad states that it did not and had no intention of preventing these laboratories from providing this individualized testing.

Stoppa-Lyonnet and others also raised a more general concern about the implications of exclusive licensing on the training of new laboratory professionals. If only the patent holder could perform genetic tests, Stoppa-Lyonnet worried, it would be difficult to train the next generation of geneticists to perform proband testing. In the long term, this would undermine the ability of laboratories to incorporate the new advances in genetics and genomics.

Fueled by these concerns, several European research institutions launched opposition procedures—a mechanism through which individuals, institutions, or governments may challenge the decision of the EPO to grant a patent based on the criteria for patentability—against all of Myriad's patents granted by the EPO. The Institut Curie launched the opposition against Myriad's various patents together with the Assistance Publique-Hopitaux de Paris, the Institut Gustave Roussy, the Belgian Human Genetics Society, and German, Dutch, Czech, Austrian, Swiss, British, and Finish genetic societies and patient associations. Although this unofficial consortium challenged the patent before the EPO based on the criteria set out in the European Patent Convention—that the inventions lacked novelty, were not inventive, had no industrial application, or were not properly described—they also raised two policy concerns in the media. First, they argued that Myriad's patents prevented other groups from developing other *BRCA1* and *BRCA2* tests that would capture more mutations than did Myriad's test. Second, they argued that Myriad's business model did not adequately ensure that women would obtain genetic counseling and follow-up care. This is because the procedure for obtaining the test was divorced from the overall health system.

Oppositions were generally successful in limiting Myriad's patents (assigned to the University of Utah around the time the opposition procedures were launched). On May 18, 2004, an opposition division of the EPO revoked Myriad's patent on the diagnostic test (EP 699 754).<sup>59</sup> In January 2005, an opposition division limited Myriad's patent over mutations of *BRCA1* (EP 705 903) to specific mutations.<sup>60</sup> Appeals from these two decisions were heard and decisions rendered in November 2008. First, instead of revoking EP 699 754, the Technical Board of Appeal restricted the patent to certain mutations of the *BRCA1* gene and to diagnostic methods for their identification.<sup>61</sup> With respect to EP 705 903, the Technical Board of Appeal expanded the opposition division's amendments to cover methods for identifying mutation 185delAG, a deletion of two nucleotides.<sup>62</sup>

With respect to the patent over *BRCA1* itself, the opposition division maintained the patent, in amended form, in January 2005.<sup>63</sup> On September 27, 2007, the Technical Board of Appeal upheld the opposition division's decision.<sup>64,65</sup> Finally, in 2005, an opposition division of the EPO also ruled that Myriad's patent over *BRCA2* in amended form—limited to the detection of the 6174delT mutation in people of Ashkenazi descent—was valid.<sup>66</sup> Although the opposition division only focused on technical matters, as opposed to policy arguments, the scope of Myriad's patents have nonetheless been significantly reduced.

The Institut Curie raised an additional concern about Myriad's business model: that Myriad was using its patents to force patients to send their tissues to Myriad, allowing Myriad to collect annotated DNA samples that would give it an unfair advantage over potential competitors in discovering cures. According to the Institut Curie, Myriad could effectively block the creation of any other database by threatening legal action against any other researcher who conducted research on the *BRCA1* and *BRCA2* genes. This would provide the company with the only viable database containing breast and ovarian cancer data, thus giving Myriad a large advantage in conducting further work in developing medicines to treat these cancers.

Myriad states that it has not and has never intended to build a private mutation database. The company's researchers have extensively contributed new mutations they discover to the



Breast Cancer Information Core mutation database.<sup>67</sup> The Breast Cancer Core Information group meets once a year to discuss new mutations and to decide what constitutes a mutation. Myriad states that its own interests are served when other researchers contribute mutations to the database because the knowledge produced improves the accuracy and value of Myriad's tests.

### Clash with the clinical community

Clinicians articulated similar concerns about Myriad's commercialization strategy. First, they worried that Myriad was making the test available to any person who wanted it, even if there was little clinical justification for the test (e.g., if such people were not from a high-risk family). Second, they opposed efforts by Myriad at direct-to-consumer advertising, arguing that this artificially increased demand for the test and drew in many “worried well” who were not truly at high genetic risk from *BRCA1* or *BRCA2* mutations.

**Myriad's target audience**—Genetic testing allows patients at a high risk of contracting a particular disease to preemptively take action—through measures such as diet, exercise, medications, and surgery—to prevent that disease from occurring. In the case of breast cancer, diet and exercise are risk factors, but relatively weak ones, and the main clinical decision concerns preemptive removal of both breasts and/or ovaries and the use of tamoxifen<sup>68</sup> to manage the risk. Moreover, genetic testing indicates the probability rather than the certainty of having a disease, and the results of the tests can be difficult not only for the average patient but also for the average doctor to interpret. For example, a negative result does not mean that the patient will not contract the disease. It only means that the patient is not at a higher risk than average of contracting the disease. Similarly, a positive result does not necessarily mean that the patient will contract the disease; it simply means the patient is more likely to get the disease than the average person. Tests say little about the age at which the patient may contract the disease—20 or 70 years old, for example.<sup>69,70</sup> In response, several US medical specialty societies (e.g., American Society of Clinical Oncologists, Society of Gynecological Oncologists, American Society of Breast Surgeons, American College of Medical Genetics, American Medical Association, American College of Obstetrics and Gynecology, and others) have published guidelines and educational materials for their respective professional members to assist them in identifying and counseling patients for hereditary cancer testing.

The psychological impact of BRCA diagnostic testing is evident when one looks at the results of a study by Lynch et al.<sup>71</sup> The study asked women (290 positive mutations, 370 negative mutations) from 84 hereditary breast and ovarian cancer families with known deleterious *BRCA* mutations to participate in an evaluation regarding cancer prevention recommendations before and after *BRCA* mutation disclosure. Based on a questionnaire, the study concluded that before BRCA testing, 23.0% of these women underwent prophylactic bilateral mastectomy, oophorectomy, or both; of these, 53% were subsequently found to be mutation negative. After mutation disclosure, 52.9% of mutation carriers and 0% of noncarriers underwent prophylactic surgeries. Psychologically, a significantly higher percentage of carriers, regardless of their cancer status, felt guilt, compared with noncarriers without cancer, about passing a mutation to their children, worried about developing additional cancer or their children developing cancer, and were concerned about health insurance discrimination.

The key insight from the study is that in truly high-risk families, the genetic test can be quite valuable, as it reduces the number of women who have their breasts removed who do not have *BRCA1* or *BRCA2* mutations, a clinically significant outcome. However, one can also infer from this study that misunderstanding genetic test results can lead not only to poor

medical decisions but also to psychological harm. For example, it could lead to false reassurance among women testing negative and cause distress among women testing positive on whether to seek prophylactic treatment (e.g., mastectomy). Even properly understood tests can lead to harmful psychological consequences. Those carrying the gene may have feelings of fear, anxiety, and guilt for having passed down the gene to offspring.

In addition to the psychological concern, there is a risk that those who test positive may face insurance discrimination, whereas women who would otherwise choose not to be tested will be forced to do so if they want insurance coverage.<sup>72</sup> This fear is held both among patients<sup>73</sup> and physicians and clinicians.<sup>74</sup> Such concerns may even be a reason for patients to refuse genetic testing.<sup>75</sup>

Because of clinician concerns about Myriad's broad marketing strategy, the psychological effects of testing, and the potential discrimination from testing, clinician groups have developed strict protocols regarding who is eligible for the *BRCA1/BRCA2* tests. Generally, the protocols target individuals with a significant family history of breast or ovarian cancer. Before Myriad cloned *BRCA1* and *BRCA2*, genetic testing was generally offered within academic medical centers and, so, was only available to families participating in research studies under the scrutiny of ethics committees. Even those private companies providing testing services at the time limited their availability. For example, OncorMed only provided testing to those who were defined as "high risk" according to personal/family history and who were enrolled in a research protocol, either through a university or through OncorMed itself.<sup>29</sup> Under the terms of its license from the Cancer Research Campaign, OncorMed agreed to administer the genetic counseling guidelines that Stratton's research team had developed, which only called for testing in a narrow set of circumstances. The GIVF also offered testing as an integrated service (both counseling and laboratory analysis) although GIVF's experience was limited as it only tested for three mutations.

In Canada and Europe, laboratories also offered an integrated counseling and testing service. Patients were seen at clinics where they received genetic counseling. A blood sample was then sent to a laboratory affiliated with the center that would analyze the results. Patients then received follow-up care. In the United Kingdom, diagnostic testing was administered through the government-funded NHS, and it was the NHS regional genetic clinics that conducted BRCA testing.<sup>38</sup> Through this system, patients learned about the testing through primary care physicians, oncologists, or surgeons. Individuals then made an appointment at the clinic offering the service. These clinics followed the Clinical Molecular Genetic Society's guidelines to ensure that only those individuals with a strong family history of cancer were tested. Because each regional center had administrative autonomy, there were some differences in treatment between centers. However, the test was offered on a fairly restricted basis, and counseling was integrated into the health services provided. Recently, the United Kingdom adopted a harmonized national strategy that maintained integrated services and regulated access.<sup>38</sup>

Similarly, before Myriad's entrance into the field, advertising for the test was limited. Cho et al.<sup>76</sup> conducted a study in 1999, which revealed that only 11% of practitioners reported learning of the *BRCA1* and *BRCA2* test through lay media, whereas 54% learned about them through academic journals and 47% through conferences.

Myriad did not directly provide testing services to patients. Rather, it worked through referring physicians who would be responsible for screening patients, providing pretest and posttest services and test interpretation. For Myriad, BRCA testing was a discrete service; for the United Kingdom NHS and other systems of care, BRCA testing was just one element of a broader array of health services.

To the clinical community, it appeared as if Myriad was only interested in selling testing services to as large an audience as possible without the types of controls recommended by professional clinical associations. Myriad did not agree with these fears. Its primary focus was on providing high-quality, rapid, full-sequence testing for *BRCA1* and *BRCA2*, and not direct patient care. Nevertheless, Myriad recognized that genetic counseling was an important component of the entire testing process. Initially, Myriad relied on genetic counselors (and helped train them) to provide this service. After it noticed that, however, the number of genetic counselors being trained in the United States was not only insufficient to meet demands but also in decline, Myriad sought to train physicians to provide counseling. Myriad did so both by preparing its own material and by financially supporting an effort by the American Medical Association to prepare physician guides, written by representatives from the major medical societies, on how to assess patient risk for hereditary cancer syndromes. There is little data available on genetic counseling; so, it is difficult to assess the impact of training and physician guides on the quality of counseling. Myriad states that, however, its own internal data support the conclusion that physicians are as effective at screening patients as are genetic counselors.

Myriad's own educational materials<sup>77</sup> aimed to inform physicians about the appropriate use of genetic tests. These materials incorporated guidelines from professional organizations responsible for genetic testing, such as the American Society of Clinical Oncology (ASCO), the American Society of Human Genetics, the American Medical Association, and the National Comprehensive Cancer Network. In 1996, the ASCO published guidelines on when an individual should be tested<sup>78,79</sup>:

ASCO recommends that cancer predisposition testing be offered only when:

1. the person has a strong family history of cancer or very early age of onset of disease;
2. the test can be adequately interpreted; and
3. the results will influence the medical management of the patient or family member.

Myriad developed standards that it viewed as being in line with those of the ASCO. In its resource for physicians, "A Clinical Resource for Health Care Professionals," Myriad listed the following criteria to be used in identifying patients who might benefit from testing:

1. a family history that includes two or more individuals on the same side of the family—such as a mother, sister, daughter, aunt, or cousin—with premenopausal breast cancer or ovarian cancer at any age,
2. a diagnosis of premenopausal breast cancer and any relative with premenopausal breast cancer or ovarian cancer at any age,
3. a diagnosis of ovarian cancer and any relative with breast cancer or ovarian cancer at any age, or
4. a relative with a known *BRCA1* or *BRCA2* mutation.<sup>77</sup>

This, according to Myriad, resulted in testing women with a 10% or greater chance of having a known cancer causing mutation.

Myriad suggested that physicians follow a three-step process before collecting and sending a sample to Myriad: (1) obtain a medical and family history to determine whether the patient is an appropriate candidate for BRACAnalysis testing, (2) provide the patient with pretest education and counseling including a referral to the Genetic Counseling Resource Directory through which patients can obtain counseling services for a fee, and (3) obtain the patient's

written informed consent for the test.<sup>77</sup> The sample informed consent form that Myriad provides to physicians states as follows:

Myriad Genetics Laboratories makes patient education materials about *BRCA1* and *BRCA2* tests available to all physicians who contact it about testing. If you have not read this material, please ask your doctor for a copy and read it. Do not decide to be tested or sign this consent form until you have read the material and had the opportunity to have your questions answered to your satisfaction by your physician or other health care professionals. Persons specially trained in genetic counseling are available for you to talk to about these tests, but costs associated with this counseling may not be covered by your health insurance plan.<sup>77</sup>

This warning seems to have had an effect. According to one study of women who had *BRCA1/BRCA2* testing between August 1998 and July 2000—excluding women being treated at academic centers—82% of patients tested claimed that they had discussed or reviewed the consent form with a health care provider, on average, for 30 minutes.<sup>80</sup>

**Direct-to-consumer advertising**—Clinicians' concerns only increased when Myriad experimented with direct-to-consumer advertising.<sup>81</sup> The fear was that Myriad was reaching far too large an audience with its messages, encouraging women to be tested—with all the psychological harms noted earlier—who were actually at low risk.

Myriad launched a pilot direct-to-consumer advertising campaign in 2002 in Denver and Atlanta. Myriad conducted market research with the help of physicians to help ensure that the advertisement presented factually correct information, did not scare women, and reached the target audience of at-risk women. The company then ran a pilot television commercial, advertised in various magazines such as *Prevention*, *People*, *Atlanta Monthly*, *Colorado Life*, and *Time* and in regional newspapers. As Myriad recognized that the demand for the test would far outweigh the number of clinical geneticists available, it prepared online materials and sponsored a Continuing Medical Education program for physicians before and after the launch of the advertising. The commercials, however, never aired nationwide because Myriad realized that there were too few trained genetic counselors to be able to deal with all the women who visited a health care professional following the advertisements. Without sufficient genetic counseling, the backlog was so long that many of these women gave up before they could visit a counselor. Rather than expand the advertisements, Myriad decided to sponsor the training of more counselors and, later, more physicians on genetic testing. By 2007, Myriad used the same information campaign in New York, Connecticut, Rhode Island, and Massachusetts to determine whether the bottleneck had been eliminated.

Although only 15 for every 10,000 women seeing the advertisement would actually have a mutation in *BRCA1* or *BRCA2*,<sup>82</sup> there is no evidence that women at low risk took steps to be tested. In fact, a study conducted by Kaiser Permanente<sup>83</sup>—a private health care provider in the United States—concluded that the advertisements worked in targeting interest among those women who were at a higher risk of having a mutation. According to the study, among those women who completed a questionnaire (largely white women above the age of 45 years), the advertisements seemed to have had the effect of simply increasing patient awareness about the test and reducing confusion. The study found that although the advertisements led to an increased demand for genetic counseling, this did not translate into an increased percentage of women for whom counseling was inappropriate or to an increased demand on physicians to provide referrals.<sup>83</sup>

## Patient concerns

Patients and patient groups had their own concerns over the introduction of Myriad's genetic tests for susceptibility to breast and ovarian cancer. Specifically, they were concerned that Myriad could violate patient privacy by building a database of genetic mutations containing private health information and that Myriad's practice of offering genetic tests to particular ethnic groups could give rise to discrimination.<sup>84</sup>

Myriad's position was that it was not building a private genetic mutations database and thus patients had nothing to fear. For patients in the United States, test results are only reported to doctors and not directly to insurers or the government. For individuals in health plans that cover more than 50 people, insurers and health plans cannot exclude individuals based on genetic information. On the other hand, individuals not covered by such plans (e.g., employees of small businesses or those seeking individual health insurance) may be obliged by an insurer to reveal the results of any genetic test to obtain insurance coverage. (This would be precluded under the Genetic Information Nondiscrimination Act recently passed in the US House and Senate.) For patients outside the United States, working through one of Myriad's partners, Myriad never receives information that could identify the patient. Instead, Myriad receives the sample under a unique code. Only the intermediary in the patient's home country possesses identification information.

## Health care administrator concerns

Although there was active debate within the research, clinical, and, to a lesser degree, patient communities about Myriad's test, it was not until health care policymakers entered the debate that Myriad encountered serious difficulties.<sup>85</sup> These policymakers approached Myriad with a more general concern over how best to integrate new genetic and genomic services into health care systems, particularly those that are publicly funded. Given the differences in health care systems, the debate among policymakers took on different hues in different regions. Here, we discuss the debates in the United States, Canada, Europe, Australia, and Japan and their spillover to the broader international arena.

**United States**—Even before the introduction of Myriad's breast and ovarian susceptibility test in the late 1990s, the US government had struggled with issues relating to genetic testing, particularly over quality control. Although certain government committees examined the impact of gene patents and patented diagnostic tests on health care, no legislative changes were made. Myriad encountered little opposition from the government over its commercialization strategy and was not impeded in the United States as it was in other countries.

In the 1970s and 1980s, genetic testing developed as genes associated with sickle cell anemia, cystic fibrosis, and Huntington disease were discovered. Although, initially, most tests were offered through hospitals, testing eventually expanded to private clinics (e.g., GIVF) and commercial services (e.g., Athena Diagnostics, Abbott, Roche Diagnostics, and Genzyme Genetics).

The National Research Council addressed emerging practices in genetic testing in its 1975 report, *Genetic Screening: Programs, Principles, and Research*.<sup>86</sup> The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research further examined the scientific, medical, legal, and ethical challenges raised by genetic testing in its 1983 report, *Screening and Counseling for Genetic Conditions*.<sup>87</sup> The Commission supported genetic testing as long as patient confidentiality, autonomy, equity, and well being were respected and that the tests provided patients with useful knowledge.



By the early 1990s, the number of genetic tests performed grew so significantly that national advisory committees began to examine them. In 1994, an Institute of Medicine committee recommended that genetic testing be brought under the Food and Drug Administration and that strict guidelines for genetic counseling be developed.<sup>88</sup> At the recommendation of another committee, the Task Force on Genetic Testing,<sup>89</sup> the government formed the Secretary's Advisory Committee on Genetic Testing. Both of these committees similarly recommended Food and Drug Administration regulation of genetic tests. Nevertheless, none of these efforts led to any regulation.

Although government and expert committees addressed quality control, little thought was given to the intersection of gene patenting and genetic tests. The Department of Commerce strongly supported the patenting of genes with little opposition from the executive branch. In fact, the Bayh-Dole Act P.L. 96-517, Patent and Trademark Act Amendments, 1980, aimed at encouraging universities to patent research, including biotechnology research, to foster commercialization.

The first real opposition within government came from two bills introduced by Representative Lynn Rivers. Rivers was inspired to introduce this legislation by the growing controversy surrounding Myriad's patents on the *BRCA1* and *BRCA2* genes and diagnostic test.<sup>90</sup> The first bill, the Genomics Research and Diagnostic Accessibility Act of 2002, H.R. 3967 (107th), would have amended US patent law to specifically permit physicians to conduct genetic diagnosis, prognosis, and predictive testing without having to obtain permission from a gene patent holder. The Bill also called for those who had used federal money to conduct their research to publicly disclose all DNA sequences within 30 days of filing a patent. Industry strongly opposed the Bill,<sup>91</sup> and it never progressed. The second bill, the Genomic Science and Technology Innovation Act of 2002, H.R. 3966 (107th), called on the Director of the Office of Science and Technology Policy to conduct a study examining whether scientists and clinicians had sufficient access to research information to conduct their research. This Bill also never passed.

Another push to reform the patent system came later and was a direct result of the Myriad controversy. Researchers became increasingly concerned that too many research outputs were being patented, slowing down research. This emerged as a central concern of a 2004 report by the United States National Research Council of the National Academies entitled, *A Patent System for the 21st century*.<sup>92</sup> This was followed by the introduction of legislation on June 8, 2005,<sup>93</sup> in Congress that proposed to overhaul the patent system. This legislation, at least in its initial form, would have made it easier for individuals and companies to submit evidence to prevent the issuance of a patent and allow individuals to more easily fight an issued patent. It would also have made it more difficult for a patent holder to stop others from using the invention until the courts had had a chance to look at the matter by limiting the availability of preliminary injunctions, adopting a first-to-file rule (as opposed to the current first-to-invent rule) and the requirement that all applications be published after 18 months (starting from the priority date) and a reinvigoration of the duty of candour. The status of these reforms is currently uncertain.

On the policy front, the NIH, the federal government agency that has funded part of virtually every major US biomedical research project at some stage, responded by drafting nonbinding guidelines on when grant recipients ought to apply for a patent over a genomic invention and the manner in which those recipients are to grant licenses over their inventions.<sup>94,95</sup> The guidelines clearly favor broad research and commercial access to gene patents as the following example illustrates:

Whenever possible, nonexclusive licensing should be pursued as a best practice. A nonexclusive licensing approach favors and facilitates making broad enabling

technologies and research uses of inventions widely available and accessible to the scientific community. When a genomic invention represents a component part or background to a commercial development, nonexclusive freedom-to-operate licensing may provide an appropriate and sufficient complement to existing exclusive IP rights. In those cases where exclusive licensing is necessary to encourage research and development by private partners, best practices dictate that exclusive licenses should be appropriately tailored to ensure expeditious development of as many aspects of the technology as possible. Specific indications, fields of use, and territories should be limited to be commensurate with the abilities and commitment of licensees to bring the technology to market expeditiously.<sup>95</sup>

As part of this initiative, the NIH also sponsored several studies to provide an empirical understanding of the scope and impact of university gene patents. For example, Pressman et al.<sup>96</sup> conducted an empirical study to determine the patenting and licensing practices of universities.

More recently, the Secretary's Advisory Committee on Genetics, Health, and Society, which advises the Secretary of Health and Human Services on a broad range of ethical, legal, clinical, and social issues arising from the development and use of genetic and genomic technologies, issued a report on February 10, 2010, based on substantial evidence, that found that gene patents were not an important incentive to develop and make available genetic tests.<sup>97</sup> The Committee concluded that, while gene patents should be held valid, the provision of diagnostic genetic testing should benefit from the same exemption from patent infringement as does the provision of other medical care.<sup>97</sup> This committee is also involved in examining other issues related to genetic tests including insurance discrimination, reimbursement, and effects of direct-to-consumer marketing, all issues that Myriad faced in the United States.

On March 29, 2010, the District Court for the Southern District of New York in *Association for Molecular Pathology et al. v United States Patent and Trademark Office et al.* (March 29, 2010) (09 Civ. 4515) invalidated seven of Myriad's US patents relating to the *BRCA1* and *BRCA2* genes and associated genetic tests. The basis of the decision was that Myriad's claims to isolated human genes are unpatentable products of nature and that the diagnostic testing claims cannot be patented because they are mere mental processes. We will discuss both these arguments in Part V, but it is extremely likely that the United States Court of Appeals for the Federal Circuit will overturn the District Court on the issue of patenting human genes. The question of whether the diagnostic test claims are valid is less clear.

A recent statement on patent licensing by many of the largest university licensing offices, since endorsed by the Association of University Technology Managers, devotes a section of its "nine points to consider" statement to genetic diagnostics:

Unlike most research tools or manufacturing methods, diagnostic tests often must go through the regulatory approval process and, so, may warrant exclusive licensing when the costs of test development, approval, or diffusion require substantial investment of capital. Nevertheless, licensing of diagnostic tests based on broadly applicable genomics or proteomics methods should strive to preserve sufficient flexibility to permit testing for multiple indications (i.e., not an exclusive licensee's single disease of interest) perhaps through multiple field-restricted or nonexclusive licenses. Exclusive licensing of a single gene for a diagnostic may be counterproductive in multigene pathology where only a panel of genes can yield an adequate diagnosis, unless the licensee has access to the other genes of the panel ... [when] no alternative testing strategy is available for a given indication, consideration should be given to means of ensuring reasonable access for patients

and shielding individual health care providers from the risk of suit for patent infringement. As with any medical technology, licenses should not hinder clinical research, professional education and training, use by public health authorities, independent validation of test results or quality verification and/or control.<sup>98</sup>

Despite these efforts, given the private nature of health care insurance in the United States and the preference of limited government regulation, the US government did little to limit Myriad's ability to commercialize tests in accordance with the company's commercialization strategy. The same cannot be said of other governments, especially those with public health care systems.

**International concerns**—Outside the United States, Myriad sought to find an intermediary in each region—in Europe, Canada, and Japan—with which it could enter into a licensing agreement. As was the case with its US licensees, Myriad wanted to reserve proband testing for itself at its Salt Lake City facility but was willing to permit local licensees to conduct follow-on testing. Recall that, in the late 1990s, Myriad believed that this would roughly split revenue between itself and its licensee. Myriad approached a mixture of private and public sector actors to act as its local licensee depending on what it knew of each country and the organization of its health care system. Myriad's choice of partner, particularly in Canada, led to difficulty. As we will later discuss, the situation in Australia was slightly different in that GTG was pursuing Myriad for patent infringement, thus forcing Myriad to enter into an agreement.

In internationalizing its US commercialization strategy, Myriad failed to account for important policy debates occurring within national health departments and research institutions. In particular, the international policy community was struggling with how to ensure the appropriate introduction of new genetic technologies into health care systems and whether and to what extent these technologies should be patented. The overarching question facing policymakers, particularly those in publicly funded health care systems, was how to administer new genetic tests to both ensure access for those who needed them while ensuring universal coverage.

Myriad walked into this policy debate largely unaware that it was going on and with little knowledge or, according to press reports,<sup>99</sup> sympathy for public health care systems. In so doing, Myriad placed itself squarely in the eye of a policy storm.

**The Canadian story:** In Canada, jurisdiction over patents and health care is split not only between the federal and provincial governments but also between different federal departments. The Canadian federal government possesses specific powers to enact and administer patent law and implicit power over health and industrial policy—through its ability to spend money—whereas provincial governments actually manage and pay for the public health care system. At the federal level, Industry Canada is in charge of the Patent Act (R.S.C., 1985, c. P-4) (the Patent Act) and of industrial policy regarding biotechnology, while, at the provincial level, ministries of health are in charge of spending approximately half of provincial budgets on health care services. There is also a Federal ministry, Health Canada, mandated with national harmonization of health policy, through its administration of the Canada Health Act (R.S.C., 1985, c. C-6), as well as several health agencies such as the Public Health Agency of Canada.

Myriad applied for patent protection on not only the *BRCA1* and *BRCA2* genes themselves but also all diagnostic procedures using them. Although it may not have expected to obtain such broad protection over the diagnostic field, the CIPO granted its claims. There seems to

have been some sense that the validity of the Canadian patents was uncertain given their breadth. Nevertheless, Myriad took the patents as they came.

Before Myriad's arrival in Canada, provincial government policymakers responsible for their respective provincial health care systems were studying the new genetic technologies and their promises. In the late 1990s, press reports suggested that genetic tests would soon be available for a large number of significant diseases, that new gene-based therapies were around the corner, and that genetic tests could be used to better determine which medication would work best on which patient.<sup>100,101</sup> Policymakers were discussing how best to introduce these technologies into the health care system on a cost-effective basis and with appropriate controls and regulations.

Some provinces offered genetic tests for *BRCA1* and *BRCA2* on a research basis. For example, the Hereditary Cancer Program at the British Columbia Cancer Agency and provincial government laboratories in several other provinces—Alberta, Manitoba, Ontario, and Quebec—offered tests to a limited number of patients.<sup>20</sup> These laboratories selected patients who had a strong family history of multiple cases of cancer, who had an early age of onset for the disease, or who belonged to ethnic groups with high rates of breast and ovarian cancer. All of these institutions provided not only testing but also genetic counseling, follow-up monitoring, and, where available, treatment. Testing services already existed, and policymakers had started to examine the implications of new genetic technologies. From their point of view, Myriad and its business strategy were disrupting a system, not just introducing a new test.

For example, in Ontario, Canada's largest province with the largest health care budget, testing was available through Cancer Care Ontario's research protocol to those who met strict high-risk criteria to determine the utility of the tests.<sup>102</sup> Under this protocol, physicians and genetic counselors collected detailed medical and family histories. Where these histories pointed to a risk of hereditary breast or ovarian cancer, the patient was given a protein truncation test (PTT) at independent laboratories. Unlike a genetic test that pinpointed the patient's particular mutation, PTT simply identified whether the patient produced full-length proteins from the *BRCA1* and *BRCA2* genes. Although a patient who did not produce full-length proteins definitely had a genetic problem, patients producing full-length proteins might still harbor a harmful genetic mutation that the PTT test would not identify. The physician and genetic counselor would use both the collected histories and the results of the PTT to determine whether the patient should undergo a full genetic test for *BRCA1* and *BRCA2*. Where the patient failed to produce full proteins under the PTT or where the patient's medical or family history pointed to a high risk (even if the patient produced full-length proteins), the patient would be offered the DNA-based test. At least one study indicated that the use of multiple factors, including PTT, provided the most cost-effective form of diagnosis.<sup>103</sup> The test would again be conducted at the independent laboratories. After the test, the physician or genetic counselor would meet with the patient to discuss the patient's risk of contracting breast and ovarian cancer and possible therapies and lifestyle changes the patient might wish to contemplate.

MDS, the only Canadian-based private laboratory that provided services across the country, approached Myriad to be its Canadian licensee. MDS had operated in the United States and, in particular, Utah and, so, was working in the same circles as was Myriad. MDS provided a suite of diagnostic and other testing services in Canada, primarily through the public health care system. The majority of MDS's revenues derived from payments made by provincial health care systems, particularly that of Ontario. Nevertheless, MDS identified the introduction of new technologies into the Canadian health care system as a strategic goal. In particular, as no breast and ovarian cancer genetic testing was available through the public

health system in Ontario until April 2000, MDS saw an opportunity to enter into the genetic testing market.<sup>104</sup> MDS's normal practice had been to provide diagnostic services that were directly reimbursed by the public health care system. This was a role that the private sector had long provided. However, by the end of the 1990s, private sector participation in Canadian health care became complex and symbolically potent.

The core of the Canadian public health system—physician and hospital services—is publicly financed and managed through the provinces but is generally privately delivered. The Canada Health Act (R.S., 1985, c.C-6), which governs the role of the federal government in financing health care, requires that the federal government transfer funds to the provinces in which certain rules are maintained that, notably, accessibility be maintained for all Canadians and through a ban on private financing.<sup>105</sup> This restriction means that it has historically been impossible to pay out-of-pocket or through private insurance for speedier access to medically necessary physician or hospital services. As evidenced in the Supreme Court of Canada case, *Chaouilli-Zeliotis v Government of Canada* (2005) 1 S.C.R. 791, there is great debate over one form of privatization—that is, the use of private funds to gain access to medically necessary physician or hospital services.<sup>106</sup> Even within this sector, however, there have been intense debates about other forms of privatization—notably, contracting out and the increased use of for-profit providers. For the most part, however, this type of privatization has proceeded, and private delivery of many publicly funded services (e.g., laboratory, cleaning, and food) is quite common. Beyond the “core” basket of public health services—for home care, long-term care, dentistry, optometry, chiropractic services, and so on—the extent of public delivery varies considerably across provinces, and to a corresponding degree, the role of the private sector is evident in both private financing and private delivery. Debates about “privatization” in Canada often confuse the different forms of privatization<sup>107</sup> that are possible but are nonetheless symbolically powerful.<sup>108</sup>

As a result of cutbacks through the 1990s, MDS believed that governments were slow to approve the introduction of new tests under provincial health plans. MDS thought it could fill this gap by providing new tests directly to individual patients outside the health systems on a private basis. MDS saw itself as supplementing the core public health care system, rather than competing against it, as it was providing services that the public systems did not cover. This was a critical distinction, as MDS in no way wished to enter into a confrontational relationship with public health care administrators. In furtherance of its goal, MDS developed partnerships with hospitals and regional health centers to provide testing services.

Myriad and MDS entered into a 3-year agreement in 2000 under which MDS would be responsible for marketing the test in Canada and shipping samples to Myriad for sequencing in the United States. At that time, MDS did not have the expertise to conduct the tests in Canada. The parties nevertheless agreed that, at some time in the future, Myriad would assist MDS in developing the expertise to conduct follow-on mutation testing in Canada. However, this never came to pass because Myriad's test led to so much controversy.

There was at least one point on which the expectations of Myriad and MDS diverged. Myriad planned on concentrating its activities on the US market, leaving MDS to develop the Canadian market. In particular, Myriad wanted MDS to approach provincial governments to negotiate the introduction of Myriad's test. MDS was lukewarm to this idea. MDS provided a variety of health services to Canadian provincial governments and did not want to jeopardize any of its existing relationships by too strongly pushing the Myriad test in Canada, particularly because the Myriad test represented only a small fraction of its business with provincial governments. In particular, MDS did not want to take a strong position against Ontario, its largest customer. Instead, MDS saw its role as an advisor to Myriad and



expected Myriad to approach provincial governments directly. In fact, once the controversy fully erupted, MDS backed away from the test. This lack of clarity between Myriad and MDS may have contributed later to a lack of decisive leadership in addressing the policy crisis that emerged.

Soon after their agreement and still in 2000, MDS and Myriad together approached provincial government officials in charge of diagnostic laboratories to sell their services. Ontario had experience buying test kits—the materials and process necessary for the provincial laboratories to themselves administer the test—and particular diagnostic services, but it had not before confronted a vendor that prescribed the form and method of a diagnostic service. Because Myriad wanted to provide testing services instead of diagnostic kits, the Ontario officials that Myriad and MDS approached decided to ask the policy unit of the province's Ministry of Health and Long-Term Care for guidance. These officials soon realized that Myriad's commercialization model—of requiring patient samples to be collected, sent outside the country, and analyzed using a methodology determined by Myriad and not health care authorities—represented not only a significantly higher cost (~three times the cost of the test already in use in Ontario) but also, more importantly, a challenge to the way the province provided services. Among these challenges was the province's ability to determine how to provide the tests to that part of the population at risk of contracting breast or ovarian cancer, so that each patient received appropriate counseling before and after the test and to ensure that tests were provided only when a treatment was available.

Given their preliminary work on genetic technologies, the policy branch in Ontario realized that whatever agreement it entered into with Myriad would set the pattern for future genetic services and related technologies purchased by the province. They believed that a slew of other tests would soon be introduced and, collectively, these new tests threatened the province's ability to provide efficient and integrated genetic testing if not properly managed.

By late 2000, to formulate what it viewed as an appropriate response to Myriad's offer, the Ontario Health Ministry's policy unit consulted with scientists and laboratory directors, both within and outside Canada, about what to do. At this point, the policy unit heard some of the negative stories circulating about Myriad within the international scientific community. The policy unit also heard that Myriad had entered European countries and Australia with the same commercialization model as it was proposing in Canada and that the company had encountered the same health system resistance. Based on these stories, provincial officials began to believe that Myriad might present a significant policy problem.

Because of the significance of its concerns, the policy unit worked well into the spring of 2001 on how to handle genetic testing services. In the meantime, the province continued administering the BRCA tests itself. By the spring of 2001, MDS and Myriad became frustrated at having received no response months after having approached the provincial governments. Because the companies were negotiating not with the policy unit, which was considering the issue, but with the laboratory branch of Ontario's Ministry of Health, MDS and Myriad had no idea of the policy unit's concerns or why there was a delay in the response. Instead, the companies discussed whether and how to escalate the issue to obtain a response.

MDS, still concerned with its relationship with provincial health ministries, wanted to take no action that these ministries would perceive as aggressive. MDS believed that Myriad had been patient in its relationship with the provincial governments and, thus, thought that Myriad probably had no alternative but to threaten the provincial authorities with an infringement action unless these authorities agreed to enter into an agreement with Myriad

through MDS. Nevertheless, MDS did not want to take responsibility for this action and left the decision to Myriad. Myriad viewed the situation differently. As Myriad saw MDS as leading the Canadian strategy, it took MDS's suggestion of threatening legal action as a request to do so. Therefore, in the spring of 2001, it sent cease-and-desist letters through its lawyers to four provinces administering the tests: Quebec, Ontario, Alberta, and British Columbia. The letter to Ontario dated May 30, 2001, stated that "by funding, directing or contracting with others to perform genetic testing services...the Ontario Ministry of Health is infringing and inducing others to infringe the above-listed patents" (letter on file with the authors). The letter continued by asking Ontario to give a written undertaking that it would direct "all laboratories under its jurisdiction to cease performing genetic testing services" covered by Myriad's patents and that Ontario would only contract with MDS for these services. In a follow-up letter dated June 8, 2001, Myriad's lawyers asked for full compliance by Ontario by June 18, 2001.

To government officials, who understand that 6 months is not long in which to develop policy, Myriad's actions showed bad faith. The letters quickly raised the issue to the political level. Then Ontario Health Minister, Tony Clement, responded to Myriad's letter on August 31, 2001 (letter on file with the authors). He stated that, "it is the government's position that predictive breast and ovarian cancer tests should be available to women who require them." He also stated that it was the government's position "that payment to hospitals for the purpose of providing these services does not constitute infringement of any valid claim of the patent" and that services provided by Ontario hospitals "do not constitute infringement of any valid claim of the patent." This letter addressed two concerns raised by Myriad's cease-and-desist letter. Although Myriad claimed that by funding a laboratory that Ontario knew to be infringing a patent, Ontario was itself responsible for infringement, this argument was not strong. Second, Ontario was opening up the question of the validity of Myriad's Canadian patents. Given that most of Myriad's patents were (later) struck down in Europe, Myriad's patent position in Canada was uncertain despite differences in patent law between Canada and Europe.

In a press statement, Clement stated in the summer of 2001 that "monopoly pricing of a whole new category of diagnostics" threatened publicly funded health care and equitable coverage. Then Premier of Ontario, Mike Harris, brought the issue of gene patents to the annual Premiers Conference in August 2001 where he echoed his Health Minister's concerns over gene patents and affordable health care. Harris stated that the province would continue to provide the genetic tests through its own system of laboratories.<sup>109</sup>

In response to his letter of August 31, 2001, the Presidents of Myriad Genetic Laboratories and MDS wrote a joint letter to Clement dated September 7, 2001. In it, they expressed surprise that Ontario would "continue to provide funding to laboratories that are directly infringing" Myriad's patents (letter on file with the authors). They nevertheless called for a meeting with Clement to resolve the problem amicably. In mid- to late November 2001, senior representatives of Myriad and MDS met with the Minister in his offices where they presented him with a package of letters. Two of these letters, addressed directly to Clement, were threatening. The first, by then US Ambassador to Canada, Paul Cellucci, dated November 16, 2001, indicated that the US government was considering trade sanctions against Canada under Section 301 of the Trade Act of 1974 (letter on file with the authors). This US statute had required the US government, at the behest of a corporation, to impose unilateral trade sanctions for failure of a country to comply with US IP rules. However, by the date the letter was written, the relevant section of US law had been ruled illegal under international trade law. The second letter, also dated November 16, 2001, was written by US Senator Orin Hatch, the senior senator from Utah (letter on file with the authors). In it, Hatch stated that he had urged the US Trade Representative, Robert Zoellick, who

administers the US Trade Act, to make Ontario's failure to comply with Myriad's patents “a top priority.” In addition to these letters, Myriad included letters from various US and Canadian scientists criticizing the use of the PTT to determine whether a patient had a hereditary predisposition to breast and ovarian cancer, as PTT would miss at least 600 mutations in *BRCA1* and *BRCA2* (letter on file with the authors). In writing these letters, the scientists apparently did not understand that Ontario did not rely on PPT to make definitive diagnoses, but only used it as a supplement to the patient's medical and family histories in determining whether the patient would be a good candidate for full sequencing. Myriad was also able to convince the Biotechnology Industry Organization (BIO) to threaten to move its annual meeting, scheduled to be held in Toronto in June 2002, out of the country if Ontario did not respect Myriad's patents. However, ultimately, BIO did not support Myriad, and did hold its annual meeting in Toronto.<sup>110</sup>

Far from helping to resolve the dispute, Myriad's tactic of presenting the letters to Clement only seemed to have hardened the government's position. Given the political context—which included not only concerns over US intervention in Canadian affairs but also, more importantly, over a private actor determining which health services Ontario was to provide to its residents—Clement simply could not realistically be seen as giving into a US patent holder and a for-profit health provider. With time, it became clear that Clement took the position that the entire issue of gene patents should be solved at the federal, not provincial level. His public statements and the report that his Ministry eventually prepared expressed his view that the federal government needed to revise the Patent Act to provide provinces with greater freedom to operate in the diagnostics field. This position obviously had the advantage of moving the political controversy off of his shoulders and onto those of the federal government. In addition, one could surmise that Clement was likely displeased with the fact that Myriad and MDS sprung the letters on him at the meeting. In the result, these letters did little to convince him that they were serious about negotiating their way out of the impasse. From the Ministry's perspective, these were hardball tactics that undermined the credibility of a claim to be seeking an amicable agreement.

Myriad's strategy did win it media exposure, but this was almost entirely negative.<sup>41</sup> Newspaper editorials, pundits, and professional health organizations competed in criticizing Myriad and what they viewed as its bullying tactics. They also condemned what they saw as the incursion of the private sector into the health care system. This was not completely accurate, however. Private providers, such as MDS, had been licensed for years by provincial health authorities to provide tests to the public health care system. In one sense, Myriad and MDS were proposing to do no more than this. In another sense, the fact that the companies were dictating which tests to provide and where the tests were to be conducted represented an important change in the provision of health services. The controversy also served to bring to light an emerging policy of incremental privatization that had not borne much scrutiny. The commentators did not address this point. As the controversy mounted, MDS altered its position and was willing to license provincial health centers to directly provide the tests that those centers wanted. By the time this happened, however, the controversy was so intense that no compromise was possible.

In August 2001, Ontario Premier Mike Harris raised the issue of gene patenting at the Annual Premier's conference.<sup>111</sup> Subsequently, Clement organized a roundtable discussion in Toronto in December 2001 on genetic testing, at which experts on genetic testing and patents presented their views to an audience of policymakers and industry actors, including MDS. By drawing on that roundtable discussion and its own research, the Ministry of Health and Long-Term Care issued a report<sup>112</sup> in January 2002 that set out a multistrategy to deal with how provincial health care systems ought to adapt to the introduction of new gene-based technologies. The first and a main focus of the report was the call to reform Canada's

health technology assessment process to better assess the quality and efficacy of new technologies on a harmonized basis across the country. Second, the report suggested that the federal government examine ways to reduce any negative impact that gene patents may have on research and on the administration of the patent system. This, Ontario suggested, could be accomplished in any number of ways ranging from a change in patent office practice to making gene patents harder to obtain by increasing the application of patent criteria (as had been done in the United States), to the manner in which the Competition Bureau interpreted competition legislation, and to the introduction of the right of provinces to use an invention—on payment of a reasonable fee—even without the agreement of the patent holder (as was done in France [L. 613-16 Code de la Propriété intellectuelle, as amended in 2004]). Ontario did not suggest invoking the general compulsory licensing provisions of the Patent Act to permit it to provide testing in Ontario without Myriad's consent. Although it was clear that Ontario could have invoked the section—as it permitted the government to use a patented invention for “public noncommercial use” including the provision of health services—it decided that this would have been too drastic. Although fighting over the scope and validity of a particular patent was one thing, threatening to use a blanket provision such as s. 19 of the Patent Act would have sent the wrong message to industry about the government's faith in the patent system as a whole.

At the next First Minister's Conference after the issuance of the Ontario report, held in February 2002, all provincial leaders agreed to support the approach set out in the Ontario report. Surprisingly, given the Canadian political context, the government of Quebec, then led by a separatist party, agreed to support the report including its call for a national technology assessment process.<sup>113</sup> As a result, the provincial health ministries, together with Health Canada—the federal department responsible for setting national health policy—established an intergovernmental committee (Federal/Provincial/Territorial Coordinating Committee on Genetics and Health) to develop a national technology assessment process and to coordinate positions over changes to the patent system. By presenting a common enemy, Myriad appeared to have unified often fractious constituencies.

Although Ontario was preparing its report, most of the other provinces continued to provide testing services. There were two exceptions. First, although continuing to screen two populations (French Canadians and Ashkenazi Jews) for the specific mutations that are most common to those groups, Quebec sent the remaining blood samples directly to Myriad for sequencing.<sup>20</sup> Second, British Columbia initially not only decided to comply with Myriad's demand to stop testing but also decided that it would no longer reimburse patients for the tests, leaving women in British Columbia who wanted the test to pay for it themselves. When this solution proved unworkable, the province developed a “work around solution” that involved sending patient samples to Ontario for sequencing. Still later, in February 2003, British Columbia again reversed its position when its Minister of Health Services authorized the resumption of in-house BRCA testing.<sup>20</sup> Eventually, British Columbia Health Minister Colin Hansen wrote to the federal government, urging it to review the Patent Act. Myriad responded to provincial actions by indicating that Canadians should be very concerned that their governments would selectively decide which patents to respect.

During this period, the federal government unit responsible for the Patent Act remained silent. Industry Canada's Patent Policy Directorate neither questioned Myriad's patents nor seriously addressed concerns over gene patents in general. Industry Canada asked Ontario to provide it with concrete evidence that gene patents were deterring research, that Ontario could not obtain a compulsory license to use Myriad's invention under the Patent Act, and that Canada's Competition Act (R.S.C, 1985, c. C-34) did not provide Ontario with a remedy. Without strong evidence, the Directorate stated, it would not intervene.

In contrast, Health Canada seemingly became sympathetic to the provinces' concerns over Myriad's genetic testing. For example, the department joined the intergovernmental committee looking at issues relating to genetic tests discussed earlier. Another branch of Industry Canada, the Life Science Branch, responsible for general industrial policy—but not patents—relating to health and agricultural biotechnology, was open to discussions with the provinces.

During the course of 2002, Ontario, on its own behalf and that of the other provinces, together with officials from Health Canada met with the Patent Policy Directorate at Industry Canada to resolve the Myriad patent problem. Although Ontario and Health Canada worked well together, there was a high level of frustration by Ontario and Health Canada officials with their counterparts in the Patent Policy Directorate and vice versa. Although personal interactions were strained, the fundamental tension revolved around the Patent Policy Directorate's insistence on clear evidence of an actual crisis that required intervention. On the other hand, Ontario and Health Canada took the position that although there existed no incontrovertible evidence of a problem—and that collecting such evidence was either impossible or would take many years—there was enough concern to prompt a policy response. In particular, Ontario and Health Canada feared that if nothing were done to address the problem of broad patents being granted over genes, health research and the provision of health services to Canadians would be at risk.

The adversarial tone of the debate between the provinces and the federal government continued. According to Myriad, during a teleconference with two of its senior officers and MDS management in the fall of 2003, officials from Industry Canada—although likely not the Patent Policy Directorate—seemingly encouraged Myriad to bring infringement actions against the provinces. At an earlier point, Industry Canada officials had suggested that the provinces consider the possibility of seeking a compulsory license to Myriad's invention. It is not clear why Industry Canada took these inconsistent positions or even how seriously its officials intended the suggestion that Myriad sue the provinces. The effect of these conversations was, however, not only to escalate the conflict between Myriad and the provinces but also to seemingly put the Canadian federal government on the same side as a US private company against Canadian provincial governments.

By the spring of 2003, Ontario had bigger health concerns than gene patents. In the winter of 2003, Toronto suffered an outbreak of severe acute respiratory syndrome (SARS) that in a matter of days became the intense focus of health policy analysts. All of Ontario's few members of the health policy unit were redeployed to address the SARS crisis. The unit's senior policy person devoted virtually all of his time over the next few years to SARS while the other officers tried to cope with not only SARS but also other policy issues. Political interest also declined after the Ontario provincial election in fall of 2003. The reigning party, Mike Harris's Conservative government, was replaced by a Liberal government that did not place a high priority on the gene patent debate.

The media seemingly also lost interest in the subject. Not only did SARS make headline news but also the US invasion of Iraq drew off whatever remaining interest remained in gene patents. Both the media and politicians had bigger worries than how Ontario would deal with Myriad's patents. Moreover, Myriad never took enforcement action, so the energy behind the public spectacle dissipated. Changes in staffing within the Patent Policy Directorate and Health Canada introduced new figures and reduced tensions.

Ontario officials nevertheless continued to pursue the file, although with less intensity. In the winter of 2004, Ontario made arguments to the Supreme Court of Canada in a case<sup>114</sup> dealing with biotechnology patents, encouraging the Court to keep in mind the effects of its



decision on the health system. This intervention was not very successful as the majority of the Court did not address Ontario's concerns in its judgment.

After being at loggerheads over the gene patent issue for years, officials from the Patent Policy Directorate and Health Canada finally agreed, in the fall of 2004, to ask an independent governmental body, the Canadian Biotechnology Advisory Committee (CBAC),<sup>115</sup> to consult with Canadians on what policies Canada ought to adopt with respect to gene patents.

The Canadian federal government established CBAC in 1999 to investigate cross-cutting issues related to biotechnology in Canada. CBAC had previously studied such issues as the labeling of genetically modified foods, stem cell research, and, in the patent field, the patenting of animals and plants. Composed of independent experts, CBAC reported to the federal Biotechnology Ministerial Coordinating Committee consisting of the Federal Ministers of Industry, Agriculture and Agri-food, Health, Environment, Fisheries and Oceans, Natural Resources and International Trade. Even though CBAC had prepared several reports, the federal government has ignored virtually all of the Committee's recommendations. For example, although CBAC released a report entitled *Patenting of Higher Life Forms and Related Issues*<sup>116</sup> in June 2002, the federal government has yet to officially respond. The CBAC has since been disbanded and its work transferred to the Science, Technology, and Innovation Council.

Despite CBAC's poor record of being taken seriously by the government and presumably because they had no other way of resolving their ongoing dispute—or in the hopes of unloading what had turned into a fruitless debate—Industry Canada and Health Canada jointly asked CBAC to report back to them on the interaction between human gene patenting, health research, and development and the provision of health services within a public health system. CBAC established an expert group to advise it on what to recommend to the government. The group consisted of industry representatives, patent lawyers, federal and provincial government representatives, and bioethicists. The expert group held a series of consultative meetings across Canada and reported back to CBAC in the fall of 2005.<sup>117</sup> It concluded that Canada should introduce a narrow research exception and an opposition procedure into its patent law. It also recommended that the CIPO should scrutinize patent applications more carefully and that guidelines be developed with respect to the licensing of genetic inventions.

Drawing on the expert group's recommendations, but making substantial modifications to them, CBAC released its own report<sup>118</sup> in March 2006. In particular, although CBAC accepted some of the expert group's recommendations, it softened some of the pro-patent statements that the expert group made and added recommendations designed to address the concerns of provincial health care administrators. For example, CBAC rejected the expert group's conclusion that any statutory research exception be limited in scope, preferring a broader exception that included noncommercial activity to use an invention to improve on it. The Committee also rejected the expert group's conclusion that no changes were necessary to Canada's compulsory licensing provisions to deal with health needs. CBAC instead recommended that the Patent Act be amended to provide the public health care system with a mechanism through which to use health-related inventions. Contrary to the conclusions of the expert group, CBAC also recommended changes to the abuse of patents provision in the Patent Act and suggested that high prices be considered as a factor in determining whether patent rights have been reasonably exercised under both the compulsory licensing and abuse provisions of the Patent Act.

At the end of this long debate, Myriad decided to give up on the Canadian market. From Myriad's point of view, the provincial governments' failure to respond to their calls meant they were unwilling to negotiate. Given the relatively small size of the Canadian market and given that its customers would be the provincial governments, Myriad decided to devote its limited resources to further building its US market.

Meanwhile, despite >7 years of discussions and policy debates, Canada has not altered its original position of ignoring not only Myriad's patents but also the general issue of the interaction between the human gene patents and the public health care system. There are no indications from the Patent Policy Directorate that this situation is likely to change in the foreseeable future.

For its part, although having preferred a more concrete change to patent practice in Canada, provincial policy officials are generally satisfied with the outcome. Ontario and the other provinces have sent a clear signal that Myriad's proposed commercialization strategy will not work in Canada. Time will tell if Ontario's message has really been received. A recent controversy over the *JAK2* gene, which was licensed on an exclusive basis to a Canadian company, Warnex, led some in the clinical genetics community to worry that they were facing a repeat of the Myriad problem. Canadian hospital laboratories have, for a number of years, provided genetic tests for mutations in this gene. They worried that Warnex would prevent them from doing so despite the fact that no patent had yet issued. In any event, faced with the controversy and the intervention of one of the authors of this report, Warnex and its French licensor reformulated their deal to sell kits to Canadian public laboratories rather than assert exclusivity over the test. This should dissipate the concern over *JAK2*, but the very existence of this controversy may indicate that Ontario's message has not fully come across.

**The European story:** Just as Myriad entered a policy storm in Canada, it suffered rough sailing in Europe, where it found a storm made all that more intense because of the residue of previous scientific rivalry over the discovery of *BRCA1*. Just as in Canada, Myriad did not understand the European policy context in which it attempted to license its test. Rather than escalating the problem as it had in Canada, however, Myriad withheld additional investments in the European market, at least pending a final decision on its European patents. At the same time, various research institutions, professional organizations and nongovernmental organizations successfully challenged Myriad's patents through the opposition procedure discussed earlier.

Gene patents had been a controversial issue in Europe for at least a decade before Myriad's entry into the European market. In July 1998, the European Union (EU) enacted Directive 98/44 on the Legal Protection of Biotechnological Inventions. The Directive was a compromise between those favoring broad patent protection over new genetic technologies and those concerned over the sanctity of life, particularly human life.<sup>119</sup> Given this context, the Directive contains some confusing and even contradictory statements about human gene patents.<sup>2</sup> However, the bottom line of the Directive is that all countries belonging to the EU (then 15 and now 27) had to pass legislation allowing patents to be granted over human gene sequences and associated processes. Despite the passage of the Directive, some countries continued to debate the ethics of patenting genes and the impact of gene patents on research and innovation. Only four EU countries—Denmark, Finland, United Kingdom, and Ireland—passed the required legislation by the Directive's deadline of July 2000. The other countries moved slowly in transposing the Directive with the last of the original 15 EU countries, Luxembourg, to do so only in April 2006, 6 years beyond the original deadline.

The debate over the wisdom and manner of patenting genes took on a different tone in the different EU countries with political opposition coming from both the left and the right. On the left, the Netherlands was so opposed to the Directive that it made an unsuccessful bid to the European Court of Justice to invalidate it.<sup>2</sup> Germany faced opposition by the Green Party that formed part of the governing coalition.<sup>120</sup> In Austria, it was a right wing member of the governing coalition that made it initially impossible to pass transposing legislation.<sup>2</sup>

France provides a particularly interesting example of European debates. In 1994, France had passed a bioethics law that essentially prevented the French patent office from granting patents over human genes to respect the sanctity of the human body (Law No. 94-654 of July 29, 1994, J.O., July 30, 1994, p. 11,062; D.S.L. 1994, 29, 411.) Despite this, France had initially backed the Directive although implementation was met with protest.<sup>120,2</sup> France finally transposed the Directive into French law in 2004.<sup>2</sup> The French scientific community was ill-disposed toward Myriad because several French laboratories had participated in the race to sequence *BRCA1* and harbored ill feelings toward Skolnick.

Myriad first approached the European market by inviting researchers and geneticists to visit its laboratories in Salt Lake City at the end of October 1998. Its goal was to license its patents and provide services directly to those European researchers and laboratories already expert in *BRCA1* and *BRCA2* testing. In pursuing this goal, Myriad targeted public sector laboratories rather than those in the private sector. As part of this strategy, Myriad approached one of the leading French researchers on *BRCA1*, Dominique Stoppa-Lyonnet of the Institut Curie, about the possibility of having the Institut Curie become the French licensee of Myriad's patents. Stoppa-Lyonnet, who had been part of the French research team in competition with Skolnick and who had developed her own test at the Institut Curie, did not respond to Myriad's offer, neither did the other researchers nor the laboratories that Myriad approached.

At the time that the EPO awarded Myriad its patents, the French Government, in particular, the French Ministry of Health, undertook to examine the situation of diagnostic testing in France. The tone of the government's consultations was largely set by Stoppa-Lyonnet who was one of the country's lead breast cancer researchers and a vocal critic of Myriad and its patents. She and the Institut Curie opposed Myriad's patents for two reasons. First, a French study had indicated that *BRCA1/BRCA2* genetic testing was less cost-effective for health care systems than a stepped and multifactorial analysis of individual patients.<sup>102</sup> Stoppa-Lyonnet was of the opinion that Myriad would insist on its preferred protocol of full-sequence proband testing and would not permit other tests such as PTT that would allow for most cost-effective diagnosis. Second, the Institut Curie was concerned that Myriad's patents would prevent the Institut Curie from putting into practice its own genetic diagnostic test, which it argued, was better than that provided by Myriad, especially because it identified large-scale rearrangements which, at the time (pre-2002), Myriad's test did not find.

Based on the government's consultations, which notably did not involve Myriad, the French Ministry of Health and the Ministry of Research developed a joint strategy. The essence of this strategy was to strengthen the hand of French clinics in negotiating a deal with Myriad under which all genetic testing could be performed in France using French methodologies. At the same time, the government did not want to show general opposition to patenting human genes, despite the 1994 bioethics law.

The strategy was to have those clinics affected by the patent, but not the government itself, commence an opposition procedure at the EPO. An opposition procedure is an administrative means to challenge a patent through a tribunal at the EPO. An opposition procedure must be launched within 9 months after the patent is granted. It is a step short of

infringement litigation and is initiated not by the patent holder but by those raising questions about the validity of the patent. Through an opposition, the administrative tribunal can uphold, invalidate, or modify an issued patent. Under European patent practice, the launching of an opposition by those directly affected by a patent was a way of weakening the position of the patent holder enough to make the patent holder start to negotiate a license. The two ministries decided to offer public support for the opposition of the Institut Curie and two other clinics that wanted to provide *BRCA1/BRCA2* diagnostic tests.<sup>122,123</sup> The ministries did not, however, actually participate in the opposition which, to the French, was designed to demonstrate that the French government did not oppose the principle of gene patenting. The intended signal was that Myriad should negotiate with French clinics, so that the clinics could perform *BRCA1/BRCA2* genetic tests in a manner that integrated diagnostic and clinical care in France.

The Institut Curie launched the opposition against the first of Myriad's patents on September 6, 2001. On October 9, 2001, the Assistance Publique-Hôpitaux de Paris, the authority administering Parisian hospitals, and the Institut Gustave Roussy, another clinical laboratory, joined the Institut Curie's opposition.<sup>124</sup> Once launched, other groups joined in, fomented by ongoing ethical debates about the wisdom of gene patents, opposition to the Directive and continuing resentment within the scientific community against Myriad. The opposition proceeding also drew regional support, as groups from the Netherlands and Belgium joined in the opposition, including individuals, research institutes, and associations of human geneticists.<sup>125</sup>

According to Myriad, the French Minister of Health called a meeting with Myriad 1 week after the filing of the opposition proceedings. At this meeting, Myriad offered to license public laboratories in France to conduct genetic testing. The French government does not have authority, however, to direct French laboratories, each of which was independent. The Minister, therefore, responded to Myriad's suggestion by providing the company with a list of French laboratories to contact directly. From its perspective, there was nothing else the government could do. In June 2002, the Socialist government fell in national elections and was replaced by a new Gaullist government. Myriad received no further word from the French government and interpreted this as an unwillingness to negotiate. It is unclear what follow-up, if any, there was on the meeting with Myriad after the change of government.

Meanwhile, the new French government worked on expanding its compulsory license regime to cover diagnostic tests. Until 2004, French law provided that the French government could issue a compulsory license where public health was at stake over any medical product or procedure, provided that prior negotiation failed to meet public health concerns. What was missing from the legislation was the ability to issue such licenses over diagnostic tests. In the mid-1990s, this had caused a number of problems for the French government in negotiation with various companies over these tests, although none of these negotiations came within the public's view.

After the problems in the 1990s, work advanced on amending the Code de la propriété intellectuelle to include diagnostic procedures. The controversy over Myriad's patents in 2001 added urgency to the need to revise the Code. With an amendment to the compulsory license provisions, the government would have been able to issue a license to French laboratories wishing to provide the test. In 2004, France reopened its Code de la propriété intellectuelle to extend its compulsory licensing provision to include diagnostic procedures (LOI no 613-16 as amended in 2004).

At the same time, to meet its obligations under the Directive, France amended its bioethics law to permit the patenting of genes. It did so in a manner that left much uncertainty. The

amendments did not remove the blanket prohibition on patenting human genes; it merely added a section that would permit the patenting of human genes for specific uses. It is unclear how these provisions will eventually be reconciled. Through this maneuver, the French government was able to claim that it complied with European law while at the same time resisting broad human gene patents. The amendments to the bioethics law also prohibited the export of blood samples (LOI no. 2004-800 du 6 août 2004 relative à la bioéthique, J.O no 182 du 7 août 2004 page 14040, art. 8 modifying article L. 1221-12 of the code de la santé publique), thus making it impossible for Myriad to insist that any testing be done in its Salt Lake City facilities.

As in France, Germany's coalition government faced difficulty with the Directive. The largest coalition partner, the Socialist Party, wanted to jump-start Germany's biotechnology sector and, therefore, supported the Directive. The coalition government's junior partner, the Green Party, opposed the Directive but was willing to consider accepting it if the majority could demonstrate an international consensus that biotechnology patents were necessary for innovation and that concerns over the negative effect of patents on the delivery of health care services and researcher access to innovation were unfounded. As we discuss below, the government asked the Organization for Economic Cooperation and Development (OECD) to gather this evidence. It did so by bringing together patent experts and government and industry representatives to discuss these issues. With a supportive report<sup>126</sup> from the OECD, Germany passed legislation<sup>127</sup> in February 2005 that, as in France, provided that human genes could only be patented for the specific function disclosed in the patent application.

In the United Kingdom, the situation was complicated by the fact that the Cancer Research Campaign also held patents over *BRCA2* and hostility between United Kingdom scientists and Myriad's Mark Skolnick were particularly strong. As previously discussed, Myriad initially negotiated a license with Rosgen, but Rosgen subsequently went bankrupt. Although Myriad began discussions with the NHS over licensing the test, these discussions proved fruitless (for a discussion of the situation in the United Kingdom<sup>38</sup>). Nevertheless, it entered into a license agreement with Lab21 with respect to private health services in the United Kingdom. Meanwhile the NHS continues to provide BRCA testing without payment to Myriad.

**The Australian story:** As in Canada and the United Kingdom, Myriad's commercialization strategy presented concerns for Australia's public health care system but with an important difference. In October 2002, Myriad entered the Australian market through a somewhat forced partnership with GTG, Australia's largest DNA testing laboratory. At the time, GTG was pursuing Myriad for patent infringement. To settle, Myriad gave GTG an exclusive license over BRCA testing. In return, Myriad received a broad, nonexclusive, and international license to use GTG's patents that cover "junk DNA"—regions of DNA that do not code for proteins—and associated methods of using junk DNA in human therapeutics and diagnostics.<sup>128</sup> In addition, Myriad agreed to pay an upfront fee of \$1 million for the nonexclusive license and also annual license fees.<sup>128</sup> Myriad needed this license to provide full genetic testing services and in its work developing new medications. Although it did not, at the time, lay out what it would do with Myriad's patents, in reality, it would never have to enforce Myriad's patents as its junk DNA patents encompassed and covered an even broader territory.<sup>129</sup>

As in other countries, Australian laboratories were already providing BRCA testing before Myriad obtained its Australian patents. These laboratories were, for the most part, attached to public hospitals or universities. These were supplemented by a few private genetic testing or pathology laboratories and government laboratories. As in Canada, the federal and territorial governments shared responsibility for funding, providing, and regulating health



care. Unlike Canada, Australia possessed a centralized system to assess genetic tests before they are offered to patients.<sup>130</sup> Essentially, only testing that is performed at accredited laboratories (accredited through a centralized agency) will be covered by the government. GTG was one such accredited laboratory.

The Australian government increasingly became interested in the social effects of new genetic technologies in the late 1990s and early 2000s. In February 2001, the Attorney-General and Minister of Health jointly asked the Australian Law Reform Commission (ALRC) to examine the privacy, discrimination, and other ethical issues related to the collection of genetic information and samples.<sup>131</sup> The ALRC conducts inquiries—known as references—into areas of law reform at the request of the Attorney-General of Australia. The ALRC reported back to the Australian Parliament in May 2003, recommending (1) the tightening of discrimination laws, (2) the harmonization of privacy laws, and (3) the establishment of a Human Genetics Commission of Australia to provide technical and strategic advice on emerging human genetics issues.<sup>132</sup>

In the course of conducting its enquiry into discrimination and privacy related to genetic information, the ALRC noted that patents over human genes required further investigation. Because the patent issue fell outside of its 2001 mandate, it suggested to the government that it commission a second study, specifically on human gene patents.<sup>133</sup> The government did this in December 2002.

Myriad's patents lay, once again, at the center of this policy debate. Myriad had obtained its key Australian patents in 1998 (AU 686,004, AU 691,958, and AU 691,331). It was Myriad's October 2002 agreement with GTG, however, that raised concerns and drew policymaker attention in Australia.<sup>134</sup> The policy community became even more worried when GTG decided, in March 2003, to assert its patents over junk DNA against universities, public laboratories, and private sector.<sup>134</sup> GTG was, in effect, threatening public laboratories that without a license, they would no longer be able to conduct genetic tests for diseases such as cystic fibrosis, Duchene muscular dystrophy, Friedreich's ataxia, and fragile X syndrome.<sup>134</sup> GTG's November 2003 announcement<sup>136</sup> that it was suing US-based Applera (and two other companies) in patent infringement for providing cystic fibrosis testing only heightened these concerns. The controversy over gene patents became so vehement that GTG announced that it would not enforce the *BRCA1* and *BRCA2* patents it had licensed from Myriad in Australia or New Zealand, going so far as to call it “a gift from GTG to the people of Australia and New Zealand.”<sup>137</sup> When this did not calm concerns, GTG drafted an open letter to the medical and scientific communities, in July 2003, reiterating its position that it was not and had never intended to enforce the Myriad patents.<sup>138</sup> The tone of the letter showed how frustrated GTG was with the criticism leveled against it:

It is interesting that many of the most vocal anti-GTG exponents themselves have lucrative patents and/or hold directorships or consultancies to Australian and global pharmaceutical and biotech companies. All of these individuals work for or have worked for academic institutions who are themselves enthusiastic patentors.<sup>138</sup>

As much of the criticism against GTG centered on its insistence that universities and research laboratories obtain licenses in relation to its junk DNA patents to conduct research, GTG changed its initial policy and provided research licenses to noncommercial organizations for a nominal one-time fee, covering all noncommercial applications for the life of the patent.<sup>139</sup>

However, on July 11, 2008, in a highly controversial move, GTG announced that it will start enforcing the BRCA patents in Australia and New Zealand.<sup>40</sup> This has sparked fears that the

cost of the test will significantly increase.<sup>140</sup> Only time will tell what the impact of this decision will be.

**The Japanese story:** Myriad's experience in Japan differed significantly from its experience in the other countries discussed. This is due in large part to the fact that few of the genetic tests that are used on European populations are relevant to the Japanese population. Further, Japan regulates genetic testing far more than do other countries. For example, the Japan Society of Human Genetics established special examinations for clinical geneticists in 1994. Japan also requires genetic testing to undergo clinical trials on Japanese populations before being put on the market, leading to significant extra costs.<sup>141</sup> Given these costs and the relatively small market for *BRCA1* and *BRCA2* testing in Japan, Myriad decided that it would exclusively license all of its rights to Falco Biosystems, Ltd., which would perform all testing within Japan.

**The international arena**—Given the controversy that accompanied the award of Myriad's patents in many different countries, it is not surprising that this soon affected international debates on human gene patenting. Although neither Myriad nor its patents seem to be the initial cause of any specific thread of international negotiation about gene patents, Myriad's practices had the effect of heightening debate and spurring countries to action.<sup>142</sup>

At approximately the same time that the NIH provided a forum for developing guidelines within the United States on gene patents, the OECD also began to look at the question of human gene patents. The OECD was a natural choice to bring experts together. The organization comprised like-minded (with respect to IP policy at least), politically stable countries with developed economies that generally share a belief in the value of markets. Its mandate includes economic and social issues from macroeconomics to trade, education, development, and science and innovation.<sup>143</sup> It works through dialogue and consensus and crosses ordinary departmental boundaries (such as research, industry, health, and environment). The OECD not only conducts its own research but also often sponsors expert workshops to investigate various cross-departmental questions touching on subjects as diverse as corporate governance and science and technology policy. All of these factors led the German government at the turn of this century to believe that the OECD could provide it with the reassurance it needed to transpose the European Directive into German law.

Between the time that Germany asked the OECD Secretariat to work on the project in early 2001 and the actual holding of an expert workshop on human gene patents and health care in January 2002 in Berlin, as we have seen, Myriad's patents had made front page news in several of the participating countries. Although these patents had not been the original reason for holding the workshop, they and access to genetic testing more generally emerged as the central concern. After the workshop, the OECD Secretariat prepared a report in which it reviewed the data presented at the workshop and identified possible policy responses to address negative effects of human gene patents on health research and the provision of health services.<sup>144</sup> The report suggested that the IP system, as applied to genetic inventions, functions largely as intended—stimulating innovation and the disclosure of information—and found that the existing, limited evidence did not suggest any systemic breakdown in the licensing of these inventions. That is, the report concluded that research and innovation continued despite or because of the availability of human gene patents. However, the report also concluded that gene patents might cause problems in specific areas, including clinical genetic testing, as illustrated by Myriad's business strategy, although the report stated that the reasons for this were unclear. Because of the potential for problems, the report suggested that more work be done in several areas including whether research exceptions—under which researchers can use inventions without infringing a patent—or alternative licensing arrangements, such as patent pools and clearinghouses, or licensing guidelines could be used

to address those concerns. Based on this report, the Working Party on Biotechnology—consisting of representatives from OECD Member Countries—instructed the OECD Secretariat to develop guidelines on licensing genetic inventions, which were first released for public comment in 2005 and were approved by the OECD Council in 2006.

The guidelines<sup>145</sup> set out principles and best practices on how those in business, research, and health systems should think about license agreements covering genetic inventions. The guidelines deal with five subjects: general licensing practices; health care and genetic inventions; research freedom; commercial development; and competition. Overall, they seek to promote genetic research and innovation while maintaining access to health care. Given the different legal systems and practices existing within the OECD Member Countries, the guidelines present the principles and practices at a general level. It was left to individual Member Countries to implement the guidelines in a way that takes into account their particular needs, circumstances, and legal system.

Although Myriad had been contacted by the OECD Secretariat in the summer of 2003 to participate, it did not take up this offer. Instead large pharmaceutical companies and BIO, the US BIO (of which Myriad was not a member), participated in the meetings. Governments wanted to ensure that universities and companies would not license gene patents in such a way as to prevent research or access to new genetic technologies while industry wanted to avoid a legislative response to concerns over gene patents. All were content to treat Myriad as a rogue actor that needed reigning in.

Although the controversy surrounding Myriad did not start the process of policy formation at the international level, Myriad, its patents, and business strategy had a major impact on the debates surrounding the creation and approval of the OECD guidelines. Myriad became an easy example of what could go wrong if patent holders did not act responsibly. Even industry groups shunned Myriad's practices, arguing that Myriad did not represent the bulk of companies working in the biotechnology field. With BIO being selected as the US industry representative group, and because Myriad was not a member of BIO, the process left out the actor responsible for what was often cited as the most problematic case of patent practices bearing on genetic diagnostics.

Perhaps surprisingly, given how Myriad was portrayed as the outlier, once it had reviewed the contents of the OECD guidelines, Myriad was not only in agreement with them but also took the position that it was and had always been in compliance with them. Myriad had, after all, supported research freedom and access to information and stated that it was prepared to license its patents out broadly.

## PART IV—LESSONS LEARNED

The media, government reports, academic literature, and even Michael Crichton's book *Next*, all portray Myriad as a greedy, self-absorbed, unconcerned, and inflexible company. Although differing on how best to address Myriad's actions—by changing patent law, altering licensing practices, creating research exemptions, or creating compulsory licensing authority—the public record provides a strong condemnation of the company. The facts as set out in this report suggest, however, that this view may be unfair. Myriad is certainly guilty of many mistakes: it failed to fully understand and perhaps even respect the nature of public health care; it allowed hostile attitudes to persist in the scientific community without seriously attempting to correct the public record; and it too quickly attributed hostile motivations to those working in government. However, Myriad was caught up in a debate inspired and sustained by much broader concerns than those relating to it alone including, general hostility to human gene patents, concern about the sustainability of public health systems, and anxiety at the apparent demise of “open science.” Myriad became a lightning

rod for these debates: a necessary foil for an already assembled opposition. At least three kinds of problems play prominent roles in our analysis: (1) communication failures; (2) institutional failures; and (3) lack of trust. We deal with each in turn.

### Communication failures

Much of the policy storm surrounding Myriad and its genetic test stemmed from Myriad's failure to communicate its position clearly, if indeed its position was clear and stable to itself. At least according to early public statements to the media, the research it supported and its statements today, it would seem that Myriad was ready to accept that scientists could freely conduct noncommercial research and that the company was flexible about the way it would go about licensing. Myriad did not inform itself sufficiently about the policy concerns of governments and health system administrators, particularly in Canada, leading to its misinterpretation of government signals (most notably, silence). Further, the negative comments about the Canadian public health care system bred suspicion and conveyed a sense of Myriad's inflexibility. Although Myriad may have been responsible—perhaps out of naïveté or poor decision making and a conviction that its test should be welcomed as the gold standard worldwide—for many of the communication failures, it was not alone. The Ontario Ministry of Health neglected to adequately inform both Myriad and MDS about the reasons for the delay in its response. Perhaps Myriad and MDS would have been more willing to wait for a response had they known what was going on behind closed government doors.

Outsiders view Myriad as a secretive company. There are several factors that lead to this conclusion. First, Myriad has done little to explain its side of the events leading to its submission of a patent claim over *BRCA2* just before Stratton's publication of an article in *Science* announcing the sequencing of the gene. Second, Myriad made no serious attempt to address the accusations of researchers that the company is hostile to academic research. Third, Myriad did nothing to make clear that it was prepared to alter its commercialization strategy to suit local concerns.

Myriad's first communication error was in failing to explain its role in the sequencing of *BRCA1* and *BRCA2* and its claim of victory in the patent race. It seems possible that Myriad's goal was to avoid placing focus on the controversy by remaining silent. Alternatively, the company may have assumed that its patent position would carry the day, rendering the controversy and conflict as mere annoyances. This strategy worked, for the most part, in the United States. It failed miserably, however, in other jurisdictions primarily because of failure to appreciate the power and importance of decision pathways in health care systems, particularly those regarding price, coverage, and reimbursement.

Scientists suspected that Myriad was being secretive because of how the discoveries were announced and the chronology of patent applications. Myriad's filing a patent on the eve of Stratton's important scientific publication appears to be too coincidental to be an accident; however, Myriad insisted it had no inside information about the publication. This led to hostility within the scientific community. Myriad's failure to communicate to address criticism not only led the scientific and clinical communities to treat the company with suspicion but also led those communities to carry their complaints about Myriad into the policy debate.

A second area of poor communication was in Myriad's interaction with the research community. According to Myriad, it had a very open attitude toward noncommercial research, one that other companies would do well to emulate, at least in the name of furthering academic research. Myriad stated that anyone conducting noncommercial research, which it defined broadly, could do so without even having to contact Myriad or

obtain a license. To Myriad, noncommercial research was any research conducted by a researcher under a research protocol. As long as the actual use of the genetic test was conducted within the same organization as was doing the research—that it was not outsourced to another organization—Myriad required no approval or license. In addition, Myriad contributed all of its mutation data to public databases even before knowing whether it could obtain patent protection. That is, Myriad was both open to others conducting research and contributed to that research effort by openly sharing its data.

Instead of advertising its openness to research, however, Myriad acquiesced in letting others believe that the company threatened ongoing research. From the outside, at least, one can only view that as a significant strategic error. Myriad's reputation for hampering research was one of the most important factors in mobilizing the international reaction against Myriad. Given this, Myriad's relative silence on the issue is surprising. We return to possible reasons for Myriad's silence below.

Myriad's third communication failure was in not being transparent in relation to its commercialization strategy. Myriad's approach was to adopt the same commercialization strategy for its genetic tests as other companies would with respect to health services and products generally. That is, it adopted the strategy of finding a single licensee in each country, which would take over responsibility for marketing the test locally. In doing so, Myriad initially had little idea about the health care systems that it would be affecting. In Canada, it selected a private sector actor in an era of heightened public concern over the privatization of health services. It did better in Europe, particularly in the United Kingdom, after quickly encountering resistance. It nevertheless attempted to convince the French government to license its patents, after Stoppa-Lyonnet failed to respond, even though the government had no direct authority over laboratories. In other places, it approached researchers themselves rather than their institutions. If it ever made it to the right decision makers, Myriad laid out its strategy of licensing marketing rights to the local licensee, keeping the right to conduct proband testing to it and allowing the licensee to conduct follow-up single-mutation testing of the *BRCA1/BRCA2* genes. Discussions never moved beyond this, leaving the impression that its proposition was take it or leave it.

Even in Ontario, where discussions had been substantive, Myriad only presented its basic licensing strategy and did not make clear that it was willing to accept a different approach, at least not until it was too late in November 2001. In fact, Myriad had licensed all uses of the *BRCA1/BRCA2* genes to its local licensees in both Japan and Australia, but did not, in the early stages, suggest that it was prepared to do so in Ontario. If it had, Ontario may have been able to meet its goal of integrating the testing services within its health system through negotiation rather than confrontation. By the time that Myriad did suggest flexibility, Ontario could not back down.

The impact of this failure was to leave policymakers with the impression that Myriad was unwilling to meet their needs in administering a public health care system. Myriad did nothing to dispel the concern that its licensing strategy would prevent policymakers from deciding which tests were to be provided to which populations in which sequence. Although Myriad's test may have been the gold standard, many policymakers felt that it was more efficient to offer other tests first, before proceeding, with a more limited number of patients, to full-sequence testing. Through its direct-to-consumer advertising in the United States, Myriad further alienated policymakers. Instead of contributing to solving a problem—ensuring that those women in need of treatment received it early, efficiently, and in a cost effective manner—Myriad left the impression with policymakers that the company was creating an artificial demand for its services. This demand would not only eat up public



health care funds but also overload the health care system with women who demanded the test but would receive no real benefit from it.

This impression was further exacerbated by Myriad's other failures, namely, communication to the research and clinical communities. When policymakers sought out information about Myriad's test and the ability to integrate that test within their health care systems, they first turned to experts in the research, clinical care, and academic policy research communities. Those communities were, by and large, hostile to Myriad's business strategy, and the experts freely conveyed their misgivings about Myriad, leading policymakers further away from compromise.

There is no clear answer to the question as to why Myriad was so reticent to communicate its positions on research and licensing flexibility. Myriad clearly believed that—and most clinicians support it in this—its test was the most accurate available. When others identified, from time to time, a failing in Myriad's test, the company responded by not only improving its test—the large-scale deletion panel being one example—but also referring patients who could benefit from another laboratory's test to those laboratories, regardless of its patents. Perhaps Myriad's confidence in its own test blinded it to the need to properly communicate its motivations. It also too easily attributed ill-will to those who did not adopt its test, an issue to which we will return in our discussion of trust.

Communication involves not only conveying information but also understanding the context in which one will or will not be understood. Myriad made several mistakes in this area. For example, Myriad misinterpreted what the French government intended to convey when it decided to only support, but not participate in, the opposition launched by the Institut Curie and others against Myriad's European patents. In fact, the French decision was laden with meaning: under European patent practice, it meant that the French government was neither opposed to gene patents in general nor the patenting of *BRCA1/BRCA2* in the abstract. By supporting an independent entity—the Institut Curie is not, after all, a state-run institution—in the opposition process, the French government was at most challenging the EPO's analysis of whether Myriad had submitted a valid patent claim.

More significantly, however, the launching of opposition procedures by a private actor—such as the Institut Curie—is, within European patent practice, a strong signal that the actor wishes to negotiate a license with the patent holder. By putting the patent under the shadow of an opposition proceeding, the challenger hopes to push the patent holder to negotiate on better terms. Myriad missed this signal, likely because of its ignorance of European patent practice. It was a costly error. Instead of negotiating a settlement in France—and, hence, the opposition—that could have brought it revenue, overall it lost the oppositions and some of the power of its patents. Myriad may have missed this message not only because of ignorance about the European opposition practice but also because of the confrontational tone of many of the Institut Curie's public statements about Myriad and its patents, which was a carryover from the acrimonious scientific priority race.

Although Myriad may have engaged in the most serious and far-reaching communication failures, it was not the only actor responsible for not communicating clearly. Researchers, particularly in Europe, never responded to Myriad's request to license its patents, even to tell it why they refused to do so. Perhaps no license could have smoothed over the differences between the formerly competing research teams, but no effort was made by the research community to do so.

Industry did no better in communicating. According to Myriad, industry organizations, such as BIO, made no serious attempt to talk to the company about its position. True, Myriad was not a member of the organization but given that the entire diagnostics industry, if not the

entire biomedical industry, faced criticism over their patents, BIO could have done more. Myriad, for its part, appeared to prefer to rely on a political connection to Senator Hatch rather than to engage in other political actions such as joining BIO. Although Myriad claims that the cost of joining BIO was the reason for the decision not to join, they did have enough funds to engage in legal battles with provinces.

### Institutional failures

Although communication failures can, in large part, be blamed on naiveté and perhaps even arrogance on the part of Myriad, institutional failures illustrate the inability of existing IP policymaking institutions to adequately address the ideas, knowledge, and information that now constitute the foundations of all developed world economies and increasingly also that of developing nations. The institutional failure is particularly apparent in Canada where not only did federal and provincial governments battle over which was responsible for addressing the problem but also competing federal government departments (Industry Canada and Health Canada) and even units within the same department entered into long battles over jurisdiction.

Responsibility over patents in Canada is split between Industry Canada's Patent Policy Directorate, which proposes legislation and regulations, and the CIPO, which administers the patent system but, until recently, had no explicit policy function.

The Patent Policy Directorate was under pressure in the early 2000s to revise Canada's patent system to deal with biotechnology. In 2002, the CBAC had recommended, for example, several changes to the Patent Act and the Supreme Court of Canada had invited the government to respond to the challenges posed by biotechnology patents the same year (*Harvard College v Canada [Commissioner of Patent] 2002 SCC 76 [Harvard College]*). Concurrently, the pharmaceutical industry continued to complain about Canada not providing them with sufficient patent incentives. One of the things that this industry wanted was term extensions on patent rights to compensate them for the time it takes to determine whether new pharmaceutical products are safe. A second complaint was that Canada did not sufficiently stop generic companies from relying on the health and safety data submitted by pharmaceutical companies to the federal government. Patent reform does not, however, win votes. With a departing Prime Minister, an election and two successive minority governments, there was no will at the federal level to open up the question of patent reform.

In these circumstances, the Patent Policy Directorate's reaction to provincial complaints was to deny that any problem existed. Instead of responding substantively to provincial government concerns, the Directorate asked for ever more and clearer evidence that Canada was facing a crisis because of its patent laws. This information not only did not exist—in Canada or elsewhere—but also was difficult if not impossible to collect. Thus, the Directorate's position can best be understood as an attempt to throw the issue back to the provinces by making unattainable evidentiary requests, rather than to confront the need for patent reform.

The result of the positions taken by the provinces and by the Directorate was a standoff. Bureaucrats from the federal and provincial governments met but could not even agree on the nature and extent of the problem, let alone responsibility and strategies to address it. Because neither faction had sufficient jurisdiction over all aspects of the Myriad controversy—health care administration, funding, and patent law—and both had political reasons to avoid a resolution, nothing was done. The tension only dissipated when provincial governments, particularly Ontario, became distracted by the bigger problem of the SARS outbreak and Canadians turned their attention to the war in Iraq.

Within the federal government itself, there were other institutional failures. Health Canada has jurisdiction over the federal government's health policy, including funding, research, and international relations with respect to health. As noted above, Industry Canada has jurisdiction over patent law. Early in the dispute, Health Canada sided with the provincial governments and called for patent reform. The Patent Policy Directorate not only rejected Health Canada's position but also resisted any attempt by the department to involve itself in addressing the controversy. This frustrated Health Canada officials greatly as they were worried about the effect of patents on both the provision of health care and on biomedical research. Instead of working to bring together the perspectives of health and industrial policy, the two departments worked at counter purposes.

There were even contradictory policies within Industry Canada. The Patent Policy Directorate had jurisdiction over patent law, whereas other units had jurisdiction over the life sciences. These other units seem to have wanted Industry Canada to take a more conciliatory role in the Myriad dispute to settle the problem rather than to encourage the provinces to invoke a compulsory license. The Life Sciences Branch was concerned that, for example, the dispute would lead investors outside the country to think that Canada was hostile to patents or to biotechnology in general. From that perspective, the best solution to the problem was to address the provinces' concerns without encouraging legal action. The CIPO remained on the sidelines. Unlike the Patent Policy Directorate, CIPO had, at the time, no explicit jurisdiction in patent policy and, hence, stayed out of the debate.

The duration and intensity of the controversy over Myriad's patents in Canada resulted in part from institutional failure. The Patent Policy Directorate's decision to avoid making a decision rather than engaging the provinces in finding a solution heightened tensions and prolonged the controversy. The Directorate guarded its jurisdiction jealously, missing opportunities to work with Health Canada (and perhaps CIPO) to find strategies to address provincial concerns.

If the Directorate had seen its role as a facilitator of a practical solution rather than as a guardian of the integrity of Canada's patent laws, the dispute might have been much shorter. For example, the Directorate could have explored the possibility of introducing a statutory research exception in Canada. The Ontario government had called for this as had the CBAC. Myriad states that it would have been in favor of such an exception as it represented the company's practice. Health Canada and the Life Science Branch would likely each have welcomed the initiative. It was also in line with the patent laws of most other nations. Even the US Supreme Court created what can only be considered a very broad exception for health-related research a couple of years later (see *Merck KGaA, v Integra Lifesciences I, Ltd.* [2005] 125 S.Ct. 2372). Although not solving all of the issues that Ontario and the provinces had raised, the introduction of a statutory research exception would have provided common ground between Myriad and the provinces, which could have provided a foundation on which to negotiate a more general resolution.

It would be wrong, however, to place too much blame on the Directorate itself. It was caught in a no-win position. It possessed only the blunt instrument of patent law to address the Myriad problem. It had no power to revise administrative practices (these rested with CIPO), change research practices (these lay with research granting councils), set health policy (this rested with Health Canada and the provinces), or other mechanisms short of legislative reform to achieve its goals. If the Directorate had shown itself open to changing patent law, it would have faced significant political difficulties including calls from the pharmaceutical industry to address their concerns and an absence of support from politicians who saw no political advantage in patent reform.

Part of the problem may well have been the split in competence between the Patent Policy Directorate and CIPO. CIPO had the ability to develop “softer” tools of patent reform, such as the standards to apply in evaluating a patent claim, the development of guidelines on patenting and licensing of inventions, and the education about the patent system. Even CIPO's lack of jurisdiction over patent law itself—this was reserved to the Directorate—could have permitted CIPO to act as conciliator. At the time of the dispute with Myriad, however, CIPO did not possess a strategy unit, so, the Directorate claimed exclusive competence in this area. This has recently changed, with CIPO having established such a unit. This institutional change may open the way for more subtle and effective methods of resolving disputes analogous to the controversies about Myriad's patents.

### Lack of trust

The communications and institutional failures are themselves symptoms of a more fundamental problem: the lack of trust among the principal actors. Things started well with King and Skolnick's collaboration. The research community successfully formed the BCLC. However, these efforts were relatively short-lived with scientific—rather than purely commercial—competition undermining cooperation and eventually leading to accusations of unethical practices and distrust. This distrust spread quickly to policy communities trying to grapple with the impact of new genetic technologies. From these seeds of distrust, the communication and institutional problems failures extended, amplified, and entrenched suspicion.

The failure to trust is a recurring theme in disputes over biomedicine and biotechnology more generally.<sup>41</sup> Consumer distrust of agrobiotechnology companies, particularly Monsanto, over genetically modified plants, and community organization distrust of pharmaceutical company promises to assist in ensuring access to medicines in developing countries are other prominent examples of this. Distrust is sometimes so strong that it overcomes traditional political barriers. For example, it led to the creation of an alliance between the religious right and elements of the political left to oppose technologies as varied as embryonic stem cell research and gene patenting.

It was in this atmosphere of distrust that Myriad patented and then attempted to enforce its patents over the *BRCA1/BRCA2* genes. Public opinion quickly soured against Myriad, perhaps propelled by negative media coverage of the company and its practices.<sup>41</sup> Rather than confronting this distrust, Myriad let negative public opinion fester and contaminate virtually every aspect of the debate.

Consider, for example, Myriad's position over the right of others to conduct research on the *BRCA1/BRCA2* genes. Myriad maintains that its position has always been that it welcomed research with the aim of facilitating the discovery of new mutations and to develop better methods of detecting mutations. This informal research exception extends, according to Myriad, to anyone working under a valid research protocol. On the other hand, Myriad does not include within this exception those in the private or public sector who only provide sequencing services to others as part of a research protocol or otherwise. Analyzed in the context of the spectrum of research exceptions that exist around the world, Myriad's is a generous approach. This is not to say that Myriad did not benefit from its approach as additional mutation information increases the value of Myriad's genetic testing services and new methods help the company to improve its own test, as illustrated by its development of a large-scale deletion panel.

Despite Myriad's intentions regarding the research exception, it seems that all relevant actors—researchers, clinical laboratory directors, commentators, and policymakers—uniformly assumed that Myriad would actively pursue any researcher who worked on the *BRCA1/*

*BRCA2* genes. This led to some researchers withholding mutation information from public databases out of fear that any contribution would open them up to a patent infringement lawsuit by the company. Instead of more research being done on the two genes, some researchers either stopped working on them or at least stopped contributing their results to public databases. This was taken as proof that Myriad's practices blocked research and indeed it did block at least dissemination of results.<sup>46</sup>

Distrust of Myriad is only half of the story, however. Myriad soon came to distrust the intentions of the policymakers with which it was dealing. For example, Myriad assumed both in Canada and in France that the lack of policymaker response to the company's requests to sell services was a rejection of Myriad's patents rather than merely deliberation at a slower pace. Myriad's issuance of cease-and-desist letters to Canadian provincial governments was a remarkably poor decision in retrospect. Before it sent out those letters, there was little knowledge of or interest in Myriad's Canadian patents. Those Canadian researchers who had been involved with the race to sequence *BRCA1* were on the Myriad team and not on the opposing teams. There had been no significant news coverage of Myriad or its patents in Canada.<sup>41</sup> Therefore, at the time that Myriad sent out its letters, none of the policymakers, the public, or the Canadian researchers had specific negative views of the company. Despite what both Myriad and MDS viewed as the slow pace of negotiations—exacerbated by Ontario's failure to communicate that its policy branch was trying to come to grips with the entire issue of genetic testing—there was no substantive reason to presume any hostility. Nevertheless, Myriad and MDS fired a shot. They assumed the worst that Ontario would not respect its patents, and thereby raised the stakes by sending out the cease-and-desist letters. In doing so, Myriad ironically found proof of its assumption. Now facing significant public opinion against Myriad—because of news coverage, latent hostilities to biotechnology patenting in general, and government cutbacks to the public health care system—most provincial governments felt that they had little choice but to fight Myriad's patents.

It is not clear whether one can characterize the relationship between the health departments—provincial and federal—and the Patent Policy Directorate as one based on lack of trust rather than simply being tense and secretive. Whatever the case, there was little evidence of cooperation. Although a lack of jurisdiction may explain some of the failures, there also appears to be a lack of willingness to act in this case.

The three failures—communication, institutional, and trust—go far in explaining why Myriad and its patents, out of all health biotechnology companies and their patents, continue to be singled out and vilified. Without these failures, one can venture to say, Myriad may have encountered some rough water, but it would not have encountered the policy storm that it did. Nevertheless, these failures were likely not enough, by themselves, to have caused the storm. They acted against a more fundamental problem that we investigate next: a clash of world views between the public health care systems and the private sector.

## PART V—ANALYSIS

### Law versus practice

In reading those policymaker statements,<sup>50,109,146,147</sup> government reports<sup>148,149</sup> (see also *Lane Fox v Kensington and Knightsbridge Electric Lighting Co.* [1892] 9 RPC 413, 416, cited with approval in *National Research Development Corp v Commissioner of Patents* [1959] 102 CLR 252, 263) and academic articles<sup>125,150-152</sup> that are critical of Myriad, one is left with the impression that the fundamental problem is one of failure to comply with law. As forcefully as these arguments are made, they not only mischaracterize the law but



also miss a more fundamental tension: that is, between commercialization practices and the administration of public health care systems.

**Legal arguments**—Policymakers, clinicians, and commentators converged on three legal arguments against Myriad's patents and business practices. These were as follows: (a) human genes cannot be patented because they are “discoveries” and not “inventions,”<sup>125</sup> (b) Myriad's business practices violated competition (antitrust) laws by preventing other actors from entering the market for diagnostic tests related to breast and ovarian cancer,<sup>153</sup> and (c) Myriad's practice of requiring patient samples to be sent to the United States violated the privacy laws of the EU and Canada.<sup>43</sup>

Despite the energy put into these arguments, they are mis-characterizations of patent law, competition law, and privacy law. Patents on genes have been issued for years in the United States, Europe, Canada, Japan, Australia, and other jurisdictions. Myriad's business practices are not in violation of current competition laws. And, it is not clear whether there was a privacy violation. Indeed, until French law was changed to proscribe sending DNA abroad, it is not clear that there was any legal problem with Myriad's practices. That is, Myriad acted within its formal legal rights. We provide a more detailed analysis of this argument in the Legal Analysis Supplement to this case study<sup>154</sup> and a summary below. However, what this case so strikingly points out is that a focus on legal rights is misleading because when legal rights conflicted with business and governmental norms and with institutional structures, it was the set of the legal rights that were of least significance.

Despite the recent ruling by the District Court for the Southern District of New York in *Association for Molecular Pathology et al. v United States Patent and Trademark Office et al.* (March 29, 2010) 09 Civ. 4515), human genes are patentable subject matter in all countries in which disputes over Myriad's genes arose. According to the patent laws of these countries, human genes purified and isolated or put in a nonnatural state (for example, isolated in a test tube or inserted into a species different from its natural host) and artificial genes can be patented (see <http://www.cipp.mcgill.ca/en/resources/world/> for charts summarizing patent laws in Canada, United States, France, United Kingdom, Australia, and Japan). Patent law considers an “invention” to be anything that is in an altered form (from its natural state) because of human intervention. This technical definition of invention differs from the more common definition of invention that focuses on originality. For the purposes of patent law, an invention need not be original in the sense that the thing owes its existence solely to the inventor. Instead, an inventor needs to only show that the thing did not exist in the exact way the inventor described it (that is, it is placed in a different context), that the inventor exercised a degree of creativity, and that the invention as described is useful. On this understanding, although a human gene in an isolated state may not be an invention in ordinary parlance, it is an invention under the accepted principles of patent law. It is for this reason that the District Court decision in *Association for Molecular Pathology et al. v United States Patent and Trademark Office et al.* will almost certainly be overturned.

With respect to competition (antitrust) law, although Myriad used its patents to exclude competitors from providing sequencing services, this is an accepted use of a patent. Indeed, excluding competitors is the very purpose of a patent. The competition laws of the United States<sup>155</sup> and Canada<sup>156</sup> do not require a review of the actual way in which a company deploys its patents except where that company has market power—meaning it has effective control over the market for, in our case, diagnostic services—and that it is trying to use its patent to obtain benefits beyond the scope of its patents, for example, forcing purchasers to buy other products or services. As we understand competition law today, Myriad neither possesses market power nor is engaging in practices that stretch its patent rights beyond the scope set out in its patent claims.

Although US privacy law provides less protection to individuals against private actors than do the laws of Europe or of Canada, there is nothing to forbid a Canadian or European patient (with the exception of France [LOI no 2004-800 du 6 août 2004 relative à la bioéthique, J.O. no 182 du 7 août 2004 page 14040, art. 8 modifying article L. 1221-12 of the code de la santé publique]) from consenting to have her blood sample sent to and examined in the United States. In sending a sample to Myriad, the patient accepts the lower level of legal protection offered in the United States. In addition, Myriad's own internal privacy policy only permits disclosure of health information to the patient's doctor and researchers who have obtained ethics approval for accreditation and oversight of its operations or as required by law.<sup>157</sup>

Simply because human genes can be patented and because Myriad's practices conform to law does not necessarily mean that all of Myriad's patents are valid, however. Patent claims can always be attacked on the basis that the patent office wrongly applied the criteria set out in patent law (utility or industrial application, novelty, enabling disclosure, and nonobviousness or “inventive step”). In fact, as previously discussed, in Europe, the Institut Curie and others have, to date, successfully argued that Myriad's patents are, for the most part, invalid.

Whatever the eventual validity of Myriad's patents turns out to be, we can conclude that the law is clear—as clear as it ever is—that the Myriad dispute is not one concerning compliance with law. The problem lies elsewhere: in the realm of a clash between business and health policy practice. We turn to this now.

**Clash of norms and practices**—Myriad pursued a fairly traditional commercialization strategy. As noted earlier, this strategy involved finding domestic distributors monitored directly by Myriad and identifying exclusive distributors in other countries that would be responsible for marketing and selling the product internationally while ensuring compliance with national laws. What this approach missed, however, was the fact that a genetic test for breast cancer is unlike other products and that, especially outside the United States, there is no “traditional” market for health services.

By the late 1990s, breast cancer had become a highly charged political issue and BRCA genetic testing was pulled into a debate. Women overwhelmingly suffer from the disease—it is the second leading cause of cancer deaths in the United States for women. Breast cancer diagnosis and treatment raised gender and equity issues in the United States and elsewhere.<sup>158-162</sup> Breast cancer had an engaged constituency that was becoming highly effective in US politics. The introduction of a new diagnostic test was significant not only for its health implications but also for its effect on fairness and gender equality. In this climate, few patients or policymakers would consider such a test as just another product; rather, they would have seen it as raising important questions of availability and accessibility, two issues rendered problematic by Myriad's business model.

Further, the BRCA test itself is different from many other diagnostic tests. First, most women suffering from breast cancer do not have a known genetic predisposition for the disease: as previously noted, hereditary breast cancer makes up only 5–10% of breast cancer cases. Therefore, a negative test result (i.e., no mutation in the *BRCA1/BRCA2* test) does not mean a woman will not contract breast cancer; rather, it means that she has the average (i.e., the same as the general population) risk rather than a high risk of eventually suffering from the illness. On the other hand, a positive test result does not mean that the person tested will develop breast (or ovarian) cancer, but only that she is at higher risk. Because of this complexity, a patient requires substantial counseling to fully understand the meaning of test results. Second, the test itself is more complex than most kits that one can buy in a

pharmacy. To identify a mutation, a blood sample must be sent to a laboratory that follows a complex laboratory procedure. Because of the complexity of the *BRCA1/BRCA2* genes, this procedure may not find all mutations, as the Myriad test did not before 2002 for large-scale deletions. Further, some test results will come back “inconclusive” because a sequence variant is identified, but its clinical significance is unknown.

Beyond the particularities of the test itself as a product, the market for the test was anything but traditional outside the United States. Outside the United States, the purchasers of the test were not, for the most part, individual patients but publicly administered health systems. What the administrators of those systems needed (cost-efficient interventions) and what Myriad was offering (the gold standard diagnostic) differed significantly.

Myriad offered a defined genetic testing service rather than an integrated suite of related services that included interpretation and clinical decision making in addition to genetic testing. Health systems that incorporated genetic services generally also included these other features. Although Myriad did engage in training genetic counselors and physicians, it did so to ensure receptivity and marketing of its tests, rather than as one of its core services. Myriad was, at bottom, in the business of sending sample-gathering kits to health professionals who would then take responsibility for collecting the samples and ensuring that patients received adequate genetic counseling. Myriad sequenced the genes and identified mutations. Myriad returned reports to the health professional, who took responsibility for ensuring that the patient understood the meaning of test results.

This approach may have fit in with the largely private health care system in the United States under which health management organizations or other providers act as gatekeepers to individuals accessing health services. Health plans and payers would ensure that the individual patient was in sufficient need of the service to justify reimbursement.

Public health care administrators contend, however, with a number of questions about when and how best to introduce genetic testing services. For example, it may not make sense to cover the costs of a test that provides no information with respect to disease treatment or prevention, even if individuals may wish to know the test result. Similarly, it may not make sense to provide the test to the entire population when only a few could, actually, benefit. Health administrators engage in some form of triage in their decision making to ensure that only those who benefit get an expensive test.

Private systems such as those that exist in the United States (which is really a mixture of public and private systems given the importance of Medicare and Medicaid) work on a different logic. In these systems, those individuals fortunate enough to be able to afford it purchase private insurance to cover health care costs such as doctor visits, surgery, and so on. If an individual does not have insurance but is not poor or old enough to qualify for Medicare or Medicaid, he or she would have to pay directly for the health service. In the United States, this system is further mediated by so-called health maintenance organizations (HMOs). HMOs bring together a number of individuals, each of whom makes monthly payments. The HMO enters into contracts with preferred health care providers and bargains for a list of services and cost of services offered to its members. Some HMOs, such as Kaiser Permanente, run their own hospitals and clinical networks and employ in-house physicians. The government's role is limited to paying for Medicare and Medicaid and certain nonprofit hospitals available to help those who cannot afford insurance.<sup>162</sup> Consequently, government health administrators under a private system are not faced with the same kind of decisions as to how to roll out which medical procedures when. Insurance companies or HMOs will choose to either cover a procedure or not and if they do not, then a person wishing to obtain the service must pay out of pocket.<sup>164</sup>

Myriad's tests posed two problems for public health system administrators. First, the cost of the tests was high: several thousand dollars. For example, France estimated that complying with Myriad's European patents would result in an additional cost of Cdn\$7.6 million to hospital budgets.<sup>165</sup> In Canada, BRCA testing was originally available through public health care institutions (such as the Hereditary Cancer Program at the British Columbia Cancer Agency) at a cost of \$1200. In contrast, MDS Laboratory Services, the exclusive provider of Myriad's test in Canada, marketed it at Cdn\$3800.<sup>166</sup>

Nevertheless, the actual cost of Myriad's test was not the real problem for policymakers. A few million here or there in large health care budgets was not about to bankrupt any public health care system. The worry was the precedent that would be set: Myriad's BRCA test represented just the first of a new wave of genetic tests expected to hit the market that, collectively, could dramatically increase health care costs.<sup>164</sup> Consequently, what health administrators sought was a way to control costs by establishing criteria to decide whether a test brought value—economically and socially—rather than simply providing information that might inform the patient but would not change health outcomes. Other efficiency measures included the ability to offer a less precise (and less expensive) initial test and only provide the more precise (and more expensive) test in cases of high risk.

Because Myriad insisted that its methodology was the gold standard for breast cancer genetic testing, it did not permit any other test to be used (except in those few cases in which it admitted that another test was more appropriate). Health administrators faced a take-it-or-leave-it situation: purchase Myriad's test or not. What these administrators were looking for was quite different. They were looking to find the most effective overall combination of tests and counseling to detect and treat breast cancer. More specifically, they were looking for ways to help identify those patients who would most benefit from expensive proband testing by deploying a variety of screening procedures that used, but was not based only on, other testing methodologies.

In short, the dispute represented a clash between the way Myriad structured its commercialisation efforts and the public health administrators' need for flexibility in introducing and implementing suites of health care services. Operating within the framework of their respective roles and responsibilities, both were sensible but held fundamentally incompatible understandings of what was optimal. This at least exacerbated, if not caused, many of the communication and trust failures.

The dispute between Myriad and policymakers was not the only one, however. Myriad's business strategy also clashed with the scientific community's attitudes about gene patents and genetic testing. Although scientists do not speak with one voice by any means, there is a strong feeling among many that genes are not inventions.<sup>167</sup> That is, they consider that the discovery of the existence of a gene and the determination of its biological function are basic scientific facts and not the application of general scientific knowledge to develop particular products. Thus, some scientists believe that gene patents run contrary to the scientific ethos. Obviously, not all scientists agree, as many do seek and obtain gene patents. However, even among those who have patented human genes, there is a strong belief that the genes should be readily available,<sup>168</sup> and the discovery of a gene is not sufficient without knowing what it does and how it might be made useful. For example, Michael Stratton and his sponsor, the Cancer Research Campaign, which patented the *BRCA2* gene in the United Kingdom, only licensed the gene to OncorMed after having made OncorMed promise to permit other researchers to make use of the gene and to not enforce the patent against the NHS.

Beyond simple resistance to the idea of patents over genes, many scientists take the position that the sequencing of human genes is the last step in a long history of scientific effort.<sup>169</sup>

The person who isolated, sequenced, and even identified the biological function of a gene was simply the last person in a long line of researchers. Conferring all exclusive property rights on the person who runs the last leg of a race is unfair to others in the relay. In the language of Andrew Read, Chair of the British Society for Human Genetics, the patent system grants a prize to the person who put the last brick on the wall rather than to everyone who contributed to the wall's construction.<sup>170</sup> Thus, a patent vastly over-rewards the efforts of the researcher who makes a particular kind of discovery. Other scientists are not opposed to patenting per se but believe that all basic discoveries ought to be made easily accessible to all researchers.

Given the views just outlined, many scientists believed that, through the award of patents, Myriad obtained too much credit for what it had added to the store of scientific knowledge. Sir Walter Bodmer, one of the United Kingdom scientists involved, stated that Myriad claimed far more than it actually had contributed. Many British scientists and geneticists felt the patents were unfair in this sense.<sup>171</sup>

### Lessons learned

One lesson we can draw from Myriad and its difficulties is the sheer complexity of the IP system. Although a patent right may provide an inventor with the legal right to exclude others from using an invention, a range of laws (e.g., competition law and privacy law), business practices, and institutions affect whether and how a patent holder can actually exercise that legal right.

On paper—that is, according to the strict dictates of patent law—Myriad could effectively block anyone, including governments and other researchers (at least in those countries without research exemptions), from providing genetic tests for breast and ovarian cancer in those countries where it still maintains valid patents and has not given up such rights through license agreements. Myriad's US patent claims were very broad in scope; they covered a wide range of activities including virtually any genetic test on *BRCA1/BRCA2*. However, the reality was quite different. Although Myriad did succeed in using its patents to close other commercial laboratories in the United States, it did not try to prevent other researchers from pursuing their research even in a clinical setting, it did not sue provincial governments in Canada for patent infringement, and it did not construct a private database of mutations that only it could use. Why it did not is an interesting question. A large part of the answer to that question may be that existing practices and institutions would not have supported more aggressive enforcement of the patents.

**Practices**—Common business practice pushed Myriad not to sue researchers for infringement for two reasons. First, standard business practice is to allow researchers to conduct research without fearing enforcement against infringement. As Walsh et al.<sup>48</sup> note, industry and academic researchers often develop “working solutions” for basic material such as genes—including a tolerance for technically infringing uses of inventions without payment—which allow basic research to move forward. The biotechnology industry group, BIO, noted the importance of permitting researchers to use inventions without licenses in a letter to House of Representatives member Lynn Rivers about her proposed Genomic Research and Diagnostic Accessibility Act of 2002: “The fact of the matter is that academic researchers who are not engaged in research for commercial use are not affected by the existence of a patent. Biotech companies do not sue researchers who are conducting research for purely academic purposes.”<sup>172</sup> Although there was a dispute between Myriad and the University of Pennsylvania's GDL, this was a question of how one defines research in deciding whether to enforce a patent. As noted earlier, GDL was providing testing on an outsourced basis for other research laboratories and charging a fee for this service. Thus,



Myriad considered its activities to fall outside of a reasonable research exception. Second, it was not generally in Myriad's interests to prevent researchers from conducting their research: the more mutations that these researchers identify for *BRCA1/BRCA2*, the more mutations Myriad could test for and the more licensing opportunities would present themselves.

Good business practice also militated against Myriad enforcing its patents against those Canadian provinces that provided their own *BRCA1/BRCA2* tests. First, Myriad is a small company with limited resources and few political ties in Canada. Further, given the relatively small size of the Canadian market, the capital and human resources that Myriad would have been required to invest to sue the governments and the possible rewards of winning were simply not worth the costs of bringing an infringement action. Second, if Myriad had commenced legal proceedings in Canada against the provinces, it risked a court ruling that its Canadian patents were invalid. Third, Myriad's Canadian licensee, MDS, had much to lose if Myriad sued the provincial governments. MDS's largest customers were the provincial health care systems. The *BRCA1/BRCA2* test represented only a small part of MDS's business. Thus, victory in the BRCA case might be a pyrrhic one if it led to alienation of the company's principal customers. Fourth, although Myriad suffered from bad press over its cease-and-desist letters, the public's negative perception of the company would have been far worse if it had actually sued the provincial governments.

How biotechnology research is funded also has a significant impact on how a technology is brought to market. Public funding agencies normally attach conditions—some binding, others mere guidelines—to their funding to ensure access to research results and to ensure availability of the technology to as many people as possible. As noted earlier, the NIH encourages researchers to patent human genes only when patents are needed to encourage investment in development beyond the gene discovery stage. Under these guidelines, a case could be made against patenting the *BRCA1/BRCA2* genes as many clinical laboratories had already developed genetic tests without a patent and others were poised to do so. The more recent example of the patents over the *JAK2* gene would also seem to fall within the ambit of these guidelines.

On the other hand, private investors, wanting to ensure that the companies in which they invest will be profitable, encourage those companies to patent whatever inventions they can. When pharmaceutical (or, for that matter, biotechnology) companies invest in a company such as Myriad, they look for three things: probability of success, proprietary position, and expected market size. To assure its investors of the second of these three things, Myriad would have wanted to protect its research lead through patents. This is presumably what Eli Lilly sought when it invested in Myriad's breast cancer research.

As previously discussed, Mark Skolnick originally conducted his research at the University of Utah through public funding. Once Myriad was spun out of the university, it relied on a combination of public and private funding. Thus, it lived under both the imperative to share and the requirement to patent. With few resources internally, the company followed a traditional commercialization strategy: one that turned out not to balance these opposing imperatives sufficiently to keep the company out of trouble.

**Institutions**—Institutional structures clearly influenced the outcome of the dispute over Myriad's patents. The way that governments responded to the Myriad controversy depended, in a significant way, on the allocation of responsibilities among departments and agencies. Because each country has a different institutional structure, the debate over Myriad and gene patents in general, followed different routes. Furthermore, responsibility for different aspects of the controversy—health and industrial policy, administration of the patent system,

research policy, and so on—are normally distributed among several departments and agencies, and so managing a coherent government response is not easy. This is certainly true of national debates in most countries.

In Canada, the split of jurisdiction between the federal and provincial governments, with the federal government setting patent policy and the provincial governments providing health services, produced a fragmented policy response to the Myriad situation. It also led to a failure to arrive at a solution that fully met the needs of either the health care system or the biotechnology industry.

The further division of responsibility between Health Canada and Industry Canada did little to help the situation. Although each department represented the interests of its “client” constituency, the two departments were unable to develop a joint policy that responded to Canada's broader interests. The inability of the departments to resolve their disagreements over policy is best illustrated by the fact that, in the end, the only thing they could agree upon was to send the issue to CBAC to resolve. In light of CBAC's previous lack of success in influencing policy, referring the question of gene patents in general, and implicitly the Myriad case in particular, to CBAC signals a level of desperation at Health Canada and Industry Canada at being able, themselves, to overcome policy differences. Perhaps there was hope that CBAC's recommendations would actually be acted on this time, but this could only have been a vain aspiration.

European governments also suffered from split jurisdiction, albeit of a different kind. National governments, the EU and the EPO, all competed for jurisdiction over patent law in general and for dealing with the Myriad controversy in particular. The EU had tried to exercise jurisdiction in two contradictory ways. First, in 1998, the EU passed a Directive requiring all of its Member States to implement laws enabling the patenting of human genes. Only in 2006 did the last of the Member States implement the Directive, and even then, France and Germany enacted legislation that fell short of the Directive's mandate. Human genes cannot be patented in France, in defiance of article 5 of the Directive, whereas in Germany, human genes can only be patented for the particular functions disclosed in the application and not for all uses. Second, the European Parliament contradicted itself by supporting the EU Directive, whereas at the same time calling on the EPO to not grant patents over human genes as the EPO had with respect to Myriad.<sup>173,174</sup>

Although much of European patent policy is set at the supranational, EU level, national governments administer health care systems. They are faced with not only concern about the costs of genetic tests—such as *BRCA1* and *BRCA2*—but also patient and researcher concern over exporting blood samples to the United States where privacy laws are less strict than in Europe. These national governments also face the same kind of split in jurisdiction that exists in Canada between health and industrial policy that make development of a coherent response difficult. France and the United Kingdom have been, perhaps, the only two countries to overcome this difficulty, although with opposite results. France passed compulsory licensing legislation, which permitted the government to give permission to use a patented diagnostic procedure—such as genetic testing—without consent of the patent holder. This provision is not so much designed to actually be invoked as to provide the government with a stronger bargaining position when trying to persuade patent holders to agree to more reasonable license terms. The United Kingdom decided, in contrast, to use soft-law measures, such as guidelines, to encourage companies to license the genes they patented in a nonexclusive manner.

The fact that controversies over gene patents are highly technical—both scientifically and legally—complicates public involvement in policymaking. The legislature, being the part of

government most responsive to public opinion and least expert on scientific issues, had little ability to enter the gene patent debate in a consistent and helpful manner. The few times they did, they arrived at contradictory statements such as the European Parliament both supporting and denouncing gene patents. In Canada, the federal Parliament's Standing Committee on Health did no better, wrongly stating<sup>175</sup> that Canada did not grant patents on genes while condemning the practice.

At the international level, the OECD's structure made it an attractive interlocutor for several reasons. First, in comparison with other international governmental organizations with relevant expertise—such as the World Health Organisation or the World Intellectual Property Organisation—the OECD is and is perceived to be a much more nimble organization, able to handle smaller, short-term projects and larger ones as well. This is partly because its membership is smaller and more homogeneous—it does not include low income countries—and OECD works on member-financed rather than top-down projects. Second, the OECD normally works through so-called “soft law,” meaning that it would issue recommendations and guidelines that would not be binding in the way that a new treaty would be. Third, the OECD had built expertise on issues related to biotechnology, including genetics research and its relationship to human health and health care. Fourth, the OECD had more credibility with industry than many other international governmental organizations. This was an advantage to governments wishing to continue to encourage investment in the biotechnology sector while addressing health care concerns.

**The need for empirical evidence**—Part of the reason that governments have been unable to develop coherent policies with respect to gene patents and health care is the lack of institutional mechanisms to gather necessary knowledge about the effect of patents on biotechnological innovation, research practices and the delivery of health services. Although theories abound about how patent law encourages or discourages innovation, we actually have little empirical data on how the patent system actually works and even less on how patents affect health care specifically. Studies on the functioning of the patent system in particular countries, or in regions, are few at best and, overall, more qualitative than quantitative.<sup>142,176</sup> These studies are effective at pointing out areas of concern but are limited in their ability to provide the information required to answer policy questions.

The evidence that exists suggests that most basic research, including the discovery of new genes, tests, and other genetic technologies, would have occurred in the absence of patent rights. The evidence is less clear on whether anyone would have done the work of perfecting those technologies and placing them on the market without patents. The case of Myriad points strongly to fact that genetic tests would have been available in the absence of patents.<sup>46</sup> However, the question is less clear with respect to therapeutic products. There are few examples of these being commercialized without IP, but it is unclear whether this is because nobody has tried to do so or whether IP is, in fact, essential to the effort. The evidence is similarly unclear about how much patents on existing technology place roadblocks in the way of new research and of access to technology. Whether patents turn out to be an overall positive or negative force is unknown. Nevertheless, most economists would presume that patents have an overall positive function, although much research could still have been put into use without them.<sup>176</sup>

If the general question over the incentive effect of patents is unclear, the specific workings of the patent system with respect to genetic technologies are even murkier. Given that genes have a great variety of applications—from diagnostic tests to new treatment options to anthropology—one would expect higher level of patents blocking research than in other fields. This has not, however, been documented with good empirical data. It is extremely difficult to know whether particular aspects of patent law—such as how patent offices

interpret the criteria of novelty, inventive step, and industrial application and the scope of research exceptions or of the interaction between patent and competition law—have much influence on overall innovation levels and access to technology. Even countries as similar as the United States, Europe, Canada, and Japan differ in the particularities of the rules they apply to gene patents, with some countries being more generous in certain areas but less so in others.

Given that research and innovation exist within complex environments involving universities, public and private funding of research, different health care systems, and education systems, it is highly unlikely that we will ever have a clear answer to the question of how patents actually work to increase or decrease research, commercialization, and access. Therefore, premising policy action on decisive evidence is a futile quest and, indeed, may simply be a cover for ideology, inertia, or political weakness.

Further, the bulk of what is known about the patent system comes from opinion evidence from industry representatives,<sup>48-50</sup> clinicians,<sup>46,47,50</sup> or others. Although such evidence provides important insights into motivations and practices, it must be, nevertheless, approached with caution for a variety of reasons.<sup>177</sup> First, it is based on the interviewee's beliefs about the patent system. It is often framed by those beliefs without explicit attention to the implicit assumptions or the economics behind them. Interviewing 20 expert sailors or cartographers 600 years ago would have led to the conclusion that most experts believed the Earth to be flat, not that the world was indeed flat. Similarly, 20 people believing that the patent system increases innovation (or decreases innovation) does not demonstrate that the patent system has this effect. It simply demonstrates that people believe it. Given the state of evidence, no strong conclusion can be drawn for or against the patent system in general.

Opinion is also granular: questions are usually posed at a relatively high level of generality because most respondents are not expert in patent law and, thus, cannot be expected to fully appreciate the law's subtleties. Given this, one simply cannot draw the conclusion that because a large majority of industry representatives or of researchers believes that the patent system is critical to the development of health biotechnology or that the system undermines research, that either is true. The effects are in reality much more subtle.

This does not mean that opinion is not relevant to public policymaking. Far from it, opinion reflects the attitude of those working in industry, in the research sector, and in health care and allows for the consideration of a broader set of facts. These individuals will act on their beliefs, attitudes, and perceptions—whether those beliefs, attitudes, and perceptions are right or wrong. Thus, policymakers must take into account beliefs, attitudes, and perceptions. For example, the OECD recognized that many citizens of its member states believed that human DNA sequences were and ought to be held unpatentable.<sup>126</sup> The OECD suggested that this attitude was because of a misunderstanding of the patent system and wondered how to educate the public about the benefits of the patent system. Similarly, policymakers may wish to address prevailing attitudes and perceptions in industry, the research community, or the general public about the patent system in regard to health biotechnology.

To date, what the empirical evidence demonstrates is a real fear on behalf of clinical laboratory directors and researchers based on the belief that patent holders can and will prevent them from conducting their research.<sup>46,47</sup> It could be that these directors are wrong about whether patent holders could actually enforce their rights or whether they would actually do so. Nevertheless, regardless of the legal rules and business decisions about which they may have limited knowledge, researchers and laboratory directors act on their beliefs and, so, stop the existing research projects or do not begin others.

A lack of good empirical evidence is no excuse for governments to refrain from developing policy. Although the scientific community may be prepared to wait until hypotheses are fully tested and retested, the policy world cannot work that way. Policymakers must make their decisions here and now, based on the evidence that does exist and on the best hypotheses available. The health care system cannot wait, for example, for the true dimensions of concerns over the effect of patents on clinical research and on the delivery of health services to be clear: political and social issues are too pressing.

**Politics and ideology**—Layered on top of the interaction of laws, practices, and institutions—both at the national and international levels—are politics and ideology. Politics played a fundamental role in shaping the institutional and individual responses to the Myriad controversy and, thus, cannot be ignored. Diverging views on public versus private health care, on technology transfer policy, and within the scientific community on the nature of the scientific enterprise, all had an effect on how Myriad brought its test to market and how national and international actors responded.

In the United States, with its private health care system and strong belief in patents and with a significant population with strong religious beliefs, the politics surrounding the Myriad controversy focused on three elements. The first of these concerns was over the quality of health care services. It took the form of a worry that, because of the way Myriad marketed its genetic tests, patients would be less likely to seek genetic counseling, leading to a misunderstanding of test results and that the risk of breast cancer would be exaggerated.<sup>178</sup> The second concern was heard mostly from religious groups that objected to any form of ownership of human genes (see for example, the public statement issued by a group of religious leaders in the United States that “humans...are creations of God, not humans, and as such should not be patented as human inventions”<sup>179</sup>). This objection has not, in itself, led to any policy change but has represented an important interest group opposed to gene patents. The third concern is the belief that gene patents stifle research and development by making it too difficult or expensive for researchers to obtain patented inventions necessary to work in the field.<sup>44</sup><sup>172</sup> Interestingly, the issue of cost did not play a significant part in the US debate around Myriad.

In Europe, there were many fronts to the opposition procedure against Myriad's patents. One of these concerned the quality of tests. As previously discussed, the various groups that launched the procedure against Myriad's patents argued that not only did Myriad's tests not capture all mutations in the breast cancer gene but also Myriad was using its patents in such a way as to block others from conducting this research and from developing and offering more accurate tests. This represented a threat not only to health care but also to the European research centers wanting to enter the field. Second, as in the United States, there was concern that patients would not be required to obtain genetic counseling, leading to lack of follow-up. Third, those in the health care system feared for the high costs of genetic tests.

In Canada, federal-provincial relations over health care, the ability of health care administrators to determine how best to introduce new technologies and, finally, cost all played a role. Although the obvious differences between private and public health care systems had a significant influence in shaping the political dimensions of the Myriad controversy, so did other general factors. These included a sense that, particularly in Europe, researchers and health administrators should not submit to the will of a US company. There were also important differences in underlying ideology with respect to the role of the market. Although North America and the United Kingdom have largely encouraged the commercialization of biotechnology research produced in universities, continental Europe has generally been more hesitant.



Would the same political phenomenon have resulted if Myriad were a European or Canadian company? It is unclear whether Myriad's business strategy is one that could have easily grown out of one of these two regions given the commitment each country has to a public health care system. Nevertheless, if it had, it is hard to tell whether the reaction would have been so vigorous. The fact that Myriad was a US company within the context of competition between countries over biotechnology may have played a role in how events unfolded.

Finally, there are the politics of science. Although many studies have attempted to uncover the concerns that scientists have about the effects of increased patenting on research, on closer inspection, much of the dissatisfaction around Myriad's patents was the lack of credit for work done and the fact that European researchers felt effectively excluded from follow-on research.

## CONCLUSION: A RATIONAL RESPONSE?

Just as the causes of the Myriad controversy and its escalation are multifactorial and cannot be explained solely by legal rules, our response to the controversy must also take into account not only law but also practices and institutions. Each had a significant role in mediating the controversy. Any policy response must, therefore, take them all into account.

However, a bigger question remains: what is the goal of a policy response? A policy response to gene patents may be considered rational for different reasons. For example, policy may try to control the cost of genetic services or may, instead, concentrate on controlling costs of health services generally. Alternatively, the policy response may aim at better administering the health care system by introducing greater flexibility. Finally, the policy may aim simply to win a political debate, stay in power, or resolve conflicts between competing government departments.

No country has actively engaged in a discussion of what it hopes to achieve through its patent policy. Instead, most countries deal with patent law as a technical matter unconnected to their overall policies on health, industry, and agriculture. If nothing else, this study has shown that the patent system is not a mere technical matter: it has a significant impact on health delivery, the biotechnology industry, and public debate. To avoid another crisis such as the one that erupted over Myriad's patents, countries need to first set out their goals with respect to science and technology—is it to maximize innovation, maximize access to innovation, or develop a scientific infrastructure—and then adapt their patent laws to best facilitate those goals.

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## APPENDIX

### List and affiliation of workshop participants and commentators

The people listed below, and several others who preferred to remain anonymous, provided their comments and insights of the report to the authors. Some of these participated in the workshop held in Edmonton in November 2006, whereas others commented on various drafts of the report. The report represents an amalgam of the comments of everyone who participated and documentary evidence. Statements should not be taken as being attributed to any particular commentator.

The commentators include the following:

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