

MYRIAD GENETICS, INC. LITIGATION IN THE UNITED STATES AND
AUSTRALIA

A REVIEW



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Table of Contents

Introduction

Chapter 1 - Background

- i. What is breast cancer?
- ii. Treatments, therapeutics and diagnostic testing
- iii. Breast cancer gene
- iv. Myriad Genetics, Inc.

Chapter 2 - Juridical and Policy History

- i. Precedents
- ii. Health care systems
- iii. Policy Context

Chapter 3 -The Cases

- i. Myriad in America
- ii. Myriad in Australia

Chapter 4 -The Arguments

- i. Plaintiffs
- ii. Defendant - Myriad
- iii. Ultimate court decisions
- iv. Summary

Chapter 5 - Post-Litigation Outcomes

Conclusion

Introduction

The legality of gene patents has come under intense scrutiny in the past several years. At the heart of the gene patent debate lies Myriad Genetics, Inc., a Utah-based biotechnology company that, since the 1990's, has held exclusive rights to administer commercial diagnostic tests to detect mutations in the breast cancer genes (BRCA 1 & 2), which have been linked to the development of breast cancer in patients. In recent years, this controversial subject has since moved into the courtroom where it has been the source of much transnational public dispute.

In this thesis I will develop a comparative analysis of two of the prominent international court cases dealing with the breast cancer genes: the legal battle in the United States' between Myriad Genetics and Association for Molecular Pathology, *et al.* (*Association of Molecular Pathology (AMP) v. Myriad*) and Australia's litigation between Myriad and Cancer Voices of Australia. By constructing a comparative analysis of the Myriad cases in the United States and Australia, I hope to provide an account of the differing approaches to evaluating the patent eligibility of genes, for which both nations are using the BRCA litigation as a conduit to facilitate debate on this particular subject.

This thesis is anchored to several key objectives. The first is to establish the historical foundations of Myriad in the United States and Australia. The second is to analyze the differing intellectual property rights contexts for each country that gives a framework for understanding the similarities and differences in the court decisions. The third is to identify the identical and unique arguments made in both court systems regarding the relevant patents and claims.

To accomplish the objectives, I will begin by providing a succinct background on: the history of breast cancer and treatment methods, the search for the breast cancer gene, and a company profile of Myriad Genetics, Inc. I will then detail the commercial development of Myriad Genetics in the United States and Australian markets following with the juridical and policy contexts unique to each country. The legal histories of each country will be provided, with a detailed description of the unique arguments asserted by the plaintiffs and defendant (Myriad).

In conclusion, I will discuss the repercussions of the recent Supreme Court decision in the United States, and will emphasize the significance of this debate as a landmark case.

Chapter 1: Background

What is Breast Cancer?

Throughout human history, breast cancer has been an elusive and devastating malaise. It has affected the lives of individuals from all social spheres, from genteel queens to hardworking peasants (Olson, 2005). Early efforts to classify and define the disease were primarily limited by the poor understanding of the origins of cancer. Contemporary developments in scientific technologies have led scientists to develop a better understanding of the causes of the disease and the molecular foundations.

A broad, working definition of breast cancer today is defined as the errant growth and buildup of “malfunctioning” cells in the breast tissue. The accumulation of cells causes an aggregate of cells to form a lump (tumor) of tissue. The tumor itself can either be classified as benign (non-invasive) or malignant (cancerous and invasive) (“What you need to know about breast cancer”).

In the United States, breast cancer has the second highest mortality rate among cancer patients; lung cancer is the first. In 2008, a comprehensive investigation into the international incidence and mortality rates for breast cancer was conducted where it was determined that, in 2008 alone, approximately 1.4 million new cases of breast cancer were diagnosed globally and 460,000 deaths attributed to breast cancer occurred (Ma & Jemal, 2013).

The causes and risk factors associated with the development of breast cancer are numerous and wide-ranging (dietary habits, reproductive history, medications, etc.). Throughout the centuries, families and scholars alike have noted the occasional proclivity of certain families to have a history of breast cancer in their pedigree (Moulin, 1983). With the emergence of

genetic technologies in the past several decades, it is now possible to ascertain an individual's risk of inheriting a genetic susceptibility to developing breast cancer.

Treatments, therapeutics and diagnostic testing

Since the acknowledgement of the disease as a unique entity, doctors and men of science alike have attempted to devise appropriate treatments and methods to diagnose the presence of the disease. Archaic treatments typically centered on primitive, elemental approaches to restore a perceived humoral imbalance by bleedings, purges, and enemas. In most cases, recognition of breast cancer in patients was dependent on an advanced progression of the disease that displayed noticeable external symptoms. Endeavors to surgically remove breast tumors were attempted; however, underdeveloped surgical methods and a poor understanding of the importance of cleanliness led to a high mortality rate in patients who underwent surgical intervention for their tumors.

Beginning in the late 1700s, advances in scientific technologies (microscopes) and surgical techniques (anesthesia) led to a revolution in the way physicians approached breast cancer patients. The development of the microscope allowed researchers to conduct cellular investigations in breast tumor cells that allowed scientists to further nuance the general understanding of breast cancer. In the early 20th century, developments in x-ray technology and radiation therapy further advanced the ability for early detection and treatment of breast cancer. Currently the preferred procedure to detect breast cancer in patients is by conducting mammograms in at-risk patients and following up with a biopsy of a questionable site when appropriate.

Since the advent of genetic testing in the late 20th century, early detection for the risk of developing breast cancer can now be reliably established by analyzing the unique genetic background of individuals and establishing their potential risks of developing familial breast cancer (Moulin, 1983).

Breast Cancer Gene

In the late 20th century, there was a furious international effort to establish the genetic underpinnings of breast cancer. In 1990, the proverbial “gun-shot” in this race to find the genetic link to breast cancer development was fired with Mary-Claire King’s discovery of chromosome 17 linkage to risk susceptibility for breast cancer. After King’s discovery, the next step for scientists was to find and sequence the actual gene (Gold and Carbone, 2010).

Although scientists around the globe were conducting inquiries and making advancements in isolating the gene, the race was ultimately “won” in 1994 by Mark Skolnick. Skolnick and his team at the University of Utah used access to the large pedigree history database of Mormon families in Utah to correctly identify that mutations in the BRCA 1 highly correlated with the development of breast cancer (Gold and Carbone, 2010). Not long after the identification and sequencing of BRCA 1, researchers identified a second gene, BRCA 2 located on chromosome 13, which also had a strong association with the development of breast cancer in patients.

Myriad Genetics, Inc.

Formed in 1991, Myriad Genetics, Inc. is a spin-off entity of the Center for Genetic Epidemiology at the University of Utah. The foundation of Myriad's business model rests in the research and development of novel molecular diagnostic tests for genetic diseases, of which their breast and ovarian cancer diagnostic test (BRACAnalysis[®]) is prominent. An integral component of Myriad's operation, one that has generated the most public and academic backlash, is the patenting of novel discoveries in genetic mutations and their association to developing diagnostic techniques. The controversy over Myriad's patents stems from the fact that the patents give Myriad exclusive rights to the patented product (in this case it is the breast cancer genes). This means that research and the development of genetic tests involving the genes is restricted by the presence of the patents.

Chapter 2: Juridical and Policy History

Federal and international intellectual property (IP) rights and patent laws were significant in shaping the decision of the courts in both the United States and Australia. In this chapter a brief description of each piece of legislation will be provided, and in the subsequent chapter a more in-depth description of the significance of each law will be juxtaposed against the specific opinions of the courts. It is significant to lay out the legal context that each decision was adjudicated within to better understand the ultimate legal repercussions in each country.

Precedents

The patenting of biological material in the U.S. resides on a spectrum that ranges from the manufacturing of proteins to the patenting of a specific gene sequence. In addition, there are subcategories of biotechnological patents that specify whether an invention is a method or technique to complete a process, or a type of material or composition of matter (like proteins).

A landmark case on the patentability of biological materials that is often cited in the BRCA arguments is *Diamond v. Chakrabarty*. In this specific case, an engineered bacterium was developed that had the ability to rapidly degrade oil spills. The contested issue in *Chakrabarty* was that a living organism, the engineered bacterium, was not patentable subject matter. The Supreme Court eventually adjudicated that case, and asserted that the bacterium, despite being a living organism, was manmade, and thus patent eligible (Robinson & Medlock, 2005).

In the United States District Court, Myriad relied on the precedent *Parke-Davis & Co. v. H. K. Mulford Co.* to support their argument that their patents were valid. In *Parke-Davis*, a purified adrenaline compound was found to have therapeutic properties that the natural occurring form did not. The Judge presiding in *Parke-Davis* found that the isolated adrenaline compound

was patentable subject matter on the grounds that it could not have been anticipated that the purified form would hold unique therapeutic value (*Association for Molecular Pathology v. Myriad Genetics, 2010*, 114).

Another significant biotechnological patent dispute was *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* The patents in this particular dispute centered on a method to administer a specific drug to a patient, and use detected metabolite levels to adjust the dosage of the drug. In 2012, the Supreme Court unanimously invalidated the patents on the grounds that the claimed methods were not patentable subject matter (Sherkow, 2013).

The Myriad case is significant for both U.S. and Australian courts in that it is the first case to be adjudicated that deals specifically with the legality of patenting genes. In previous suits, the litigation often surrounded two parties specifically disputing the ownership of the claimed invention, while the Myriad case sought to invalidate the patents completely on the grounds that they were not valid (vanZimmerman, 2013). Prior to the Myriad litigation, there had been debate –between policymaking bodies and academic communities alike- over the legality of patenting biological materials in both the United States and Australia; however, there had been no real legal catalyst to spur the discussion to actual reform.

Health Care Systems

It is significant to briefly consider the differing health care systems in the U.S. and Australia as a potential mitigating factor in prompting the Myriad litigation in the respective countries. In 1984, Australia instituted Medicare, a program that provides universal access to health care to its citizens. Australian citizens also have the option of purchasing private health

insurance. The benefits of purchasing private health insurance in Australia range from quicker access to doctors to more variety in selecting a health care provider. In addition, private health care will sometimes cover, either fully or partially, services and procedures that Medicare will not (Private Healthcare Australia). In respects to genetic testing, Medicare will only cover the costs of a diagnostic test under two conditions: the diagnostic test is being used to confirm a clinical observation, or if the patient has a first-degree genetic relative with the condition (ALRC, 2012). For individuals with private insurance, insurance companies do not typically cover testing services unless the assessment is required for treatment and/or therapeutic purposes.

At the time of this writing, in the United States, the health care system is more complicated with no guaranteed universal access. Citizens often are required to purchase health insurance either through their employer, or privately. In both occasions, the individual is often responsible for paying copays and other fees to maintain the insurance. Often, a genetic test is purchased directly by the patient. Not all insurance companies will cover diagnostic tests; however, more are including them under their repertoire of covered services (NIH). If an individual has a family history of breast cancer, insurance companies will be more likely to cover the costs of the service (FORCE). Medicare – a federally funded health insurance plan for the elderly- will cover the cost of the diagnostic test if an individual has a family history of cancer, and if he/she meets other criteria (such as age). Medicaid – federally funded health insurance for low-income families- has similar coverage requirements to Medicare.

Policy Context

The United States and Australia are both a part of the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). The TRIPS

agreement was created as a multilateral treaty amongst all member states to standardize intellectual property rights worldwide. Specifically, the agreement is meant to provide guidelines for how intellectual property rights should be regulated. Despite the United States and Australia both endorsing the TRIPS agreement, they each have unique approaches to certain aspects of intellectual property regulation within their respective jurisdictions.

In the United States, it is significant to first understand what makes an invention patentable subject matter. Patents in the United States are governed by the Patent Act, which was established by the United States Patent and Trademark Office (USPTO). For an invention to be patentable under the U.S. Patent Act it must meet the criteria of novelty and non-obvious subject matter. The USPTO will define an invention as novel unless; “the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention (35 U.S.C. 102)”. Non-obvious subject matter simply means that the invention could not have been something that could have been developed or discovered by most individuals within a population. Under U.S. patent law, it is understood that materials and methods found in the natural world are not patentable subject material; however, as evidenced by the Myriad case, this specific principle is often subject to debate. A comment made by Justice Sotomayor in the Supreme Court oral arguments in *AMP v. Myriad* illustrates this concept:

I can bake a chocolate chip cookie using natural ingredients -- salt, flour, eggs, butter -- and I create my chocolate chip cookie. And if I combust those in some new way, I can get a patent on that. But I can't imagine getting a patent simply on the basic items of salt, flour and eggs, simply because I've created a new use or a new product from those ingredients (AMP v. Myriad. 35. Supreme Court Oral Arguments. 2013).

In 2011, there was a shift in patent law in the United States. Traditionally, the U.S. has operated under the first-to-invent criteria for granting patents. When the Leahy-Smith America Invents Act was passed, the U.S. effectively transitioned from first-to-invent to first-to-file system. The concept of “first to file” simply means that a patent will be granted by the USPTO to the inventor, or co-inventors, who first filed for a patent on a specific invention. This is a particularly significant piece of legislation when you consider that one of the contested issues in the Myriad patent debate was that Myriad was not the only group to file patent applications on the BRCA1/2 genes.

Australia’s main piece of legislation that provides the framework for regulating the patent system is the Patents Act of 1990. The criteria threshold for patent eligibility, as laid out in the Patent Act, is very similar to the criteria established in the U.S. The criterion includes: novelty, utility, and an “inventive step” (comparable to non-obviousness).

Australian policy makers and legal scholars have disputed the legitimacy of gene patents as well. The federal government of Australia has remitted the issue to several policymaking bodies in Australia, which produced numerous reports. Most significant in influencing the courts’ opinions on the Myriad case has been the report published by the Australian Law Reform Commission (ALRC) titled *Genes and Ingenuity*, and a report by the Advisory Council on Intellectual Property (ACIP). The report by the ALRC recommended not excluding genes from patentability in Australian courts; however, several minor adjustments were suggested including creating an exception for research purposes (meaning research could be conducted on patented material without violating patent protection) and limiting the scope of claim language (ALRC, 2004). In 2010, the Australian Senate published a report in which it repeatedly stressed the

importance of conducting inquiries into the contemporary standards for patent eligibility (Australian Senate Community Affairs Committee, 2010).

In 2012, the IP Laws Amendment (Raising the Bar) Act was passed. The act modified several existing pieces of Australian legislation that regulated intellectual property in Australia (including the Patent Act of 1990). Most significant for the Myriad case was the creation of a research exception clause that allowed research to be conducted on an invention without infringing on the patent. With the passing of this Act, research labs in Australia can continue research on the BRCA1/2 genes even if the patent licensee decides to enforce its licensing agreement.

Chapter 3: The Cases

Myriad in America

By the late 1900s, the United States Patent and Trademark Office (USPTO) had granted Myriad several patents that covered the BRCA1/2 genes and various methods of detecting mutations within the genes themselves. The patents effectively gave Myriad exclusive control over the genes, and placed restrictions on manipulation (in terms of research and the development of diagnostic genetic tests particularly for commercial uses) for the BRCA1/2 genes.

From the onset of their patent accumulation that gave them exclusive control over the breast cancer genes, Myriad's exercise of their patents was controversial. There were three main arguments, although they are not the only areas of concern, from scientists, policymakers, and the clinical community alike against Myriad holding exclusive rights over the genes: 1) Myriad's patents restricted research with the genes in the scientific community, 2) Myriad was creating a monopoly on diagnostic testing services available to the general population, and 3) the patents granted to Myriad were invalid as patenting a product of nature (i.e. a gene) should not be patentable subject matter (Gold, 2010). Despite the controversy that surrounded their patents, Myriad developed a successful business strategy in the United States that allowed them to effectively distribute their testing services to physicians, clinicians, and potential clients (Gold, 2010).

Myriad's strategy in international markets was dependent on demand for their diagnostic testing services. The commercial model Myriad implemented when venturing into international markets was to license out their services to one exclusive provider in a specific region. In some cases, this particular model worked well, as is evidenced by Myriad's relationship with Genetic

Technologies, Inc. in Australia; however, in multiple regions, such as in England and Canada, Myriad faced opposition from patent office and health care agencies (Parthasarathy, 2007).

In their pursuit of exclusive control over the BRCA1 and BRCA2 genes, of which both are highly linked to hereditary breast cancer, Myriad engaged in several legal battles with various biotechnology companies and research labs simultaneously attempting to file for patent rights over the genes. In the case of OncorMed, a biotech company that had been granted a patent on BRCA1 by the USPTO in the early 1990s, the resulting infringement suit against Myriad was settled out of court, with Myriad obtaining OncorMed's patents (vanZimmeren, 2013; Gold, 2010).

In the United States, there were three specific lawsuits that were filed against Myriad for their patent restrictions; OncorMed, University of Pennsylvania, and the Association of Molecular Pathology (AMP). The lawsuits involving OncorMed and the University of Pennsylvania were settled out-of-court, making the lawsuit involving AMP the only case that progressed far enough into the court system to be objectively evaluated. The lawsuit was first filed against Myriad in early 2009 with multiple individuals and organizations as the plaintiffs (including the ACLU, physicians, laboratory directors, and women with a vested interest in the availability of the diagnostic test for breast cancer). Specifically what were being challenged were fifteen unique claims in seven of the patents Myriad held (Table 1).

Table 1. Fifteen of the original challenged claims in the U.S. Court

Patent #	Claim #	Type of Claim	Claim Language
US 5747282	1	Composition of Matter	An isolated DNA coding for a BRCA1 polypeptide (Sequence ID NO: 2)
US 5747282	2	Composition of Matter	An isolated DNA of claim 1 with Sequence (SEQ) ID NO: 1
US 5747282	5	Composition of Matter	Isolated DNA with at least 15 consecutive nucleotides of SEQ ID NO: 2
US 5747282	6	Composition of Matter	Isolated DNA with at least 15 consecutive nucleotides of SEQ ID NO: 1
US 5747282	7	Composition of Matter	Specific mutations at certain placed in the claimed sequences
US 5747282	20	Method	A method of screening select cells for a cancer therapeutic
US 5837492	1	Composition of Matter	Isolated DNA found on BRCA2 gene; comprising sequence (SEQ ID NO: 2)
US 5837492	6	Composition of Matter	Isolated DNA coding for a mutation in the BRCA2 gene
US 5837492	7	Composition of Matter	Isolated DNA sequence with mutation defined in SEQ ID NO: 1
US 5693473	1	Composition of Matter	An isolated DNA molecule that is an altered form (mutated) of the BRCA1 DNA.
US 5709999	1	Method	A method for detecting a germline alteration in a BRCA1 gene
US 5710001	1	Method	A method for screening a tumor sample from a human subject for a somatic alteration in a BRCA1 gene
US 5753441	1	Method	A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises comparing germline sequence of a BRCA1 gene or BRCA1 RNAcDNA
US 6033857	1	Method	A method for identifying a mutant BRCA2 nucleotide sequence in a suspected mutant BRCA2 allele
US 6033857	2	Method	A method for diagnosing a predisposition for breast cancer in a human subject, which comprises comparing

Claim language cited from source patents: USPTO patent search

The case was first heard in 2010. The presiding judge on the case – Judge Robert Sweet- invalidated all fifteen of the challenged claims. For the method claims, Judge Sweet determined that the claims failed to fulfill the necessary criteria of “machine or transformation” (vanZimmeren, 2013). For claims covering DNA sequences, Judge Sweet ruled that isolated nucleic acid sequences were not patentable subject material.

Upon Judge Sweet’s ruling, Myriad appealed the decision to the U.S. Court of Appeals for the Federal Circuit (CAFC). In 2011, Judges Lourie, Moore, and Bryson affirmed Judge Sweet’s ruling for the method claims, but partially reversed his ruling on DNA molecules. Both Judges Moor and Lourie agreed that claims on DNA were patentable subject matter, while Judge Bryson opposed by asserting that DNA was not patentable subject material. In 2012, after being remanded back down to the CAFC after Myriad appealed to the Supreme Court, the CAFC once again upheld its decision (vanZimmeren, 2013).

The U.S. Supreme Court eventually adjudicated the case. In 2013, the Supreme Court unanimously ruled that, “A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated but cDNA (complementary DNA) is patent eligible because it is not naturally occurring” (USPTO, 2013). cDNA is complementary DNA synthesized from mRNA.

Myriad in Australia

In 2002, Myriad entered into a licensing agreement with Genetic Technologies, Inc. Genetic Technologies (GTG) was chosen specifically to be Myriad's exclusive representative in Australia as GTG had accused Myriad of violating patents they held on "junk DNA". GTG leveraged their patents on non-coding DNA ("junk DNA") to form a cross-licensing deal with Myriad in which GTG would license Myriad the rights to their non-coding DNA in exchange for the BRCA license (O'Neil, 2009).

In 2003, amongst growing concern in Australia that GTG was going to enforce stringent licensing practices for the BRCA genes, GTG's CEO and co-founder Dr. Merv Jacobson asserted that he would not enforce the BRCA testing rights in Australia stating they were "GTG's gift to Australia". In 2009, GTG's new CEO Michael Ohanessian once again raised concerns over the possibility of Myriad's patent enforcement in Australia when he announced that GTG would enforce its exclusive rights granted by the licensing agreement between GTG and Myriad. GTG's decision to enforce the BRCA testing rights was reversed in late 2009 when Ohanessian was deposed as the CEO of GTG (vanZimmeren, 2013).

Unlike in the United States where multiple claims in several of Myriad's patents were challenged, in Australia only the legitimacy of one patent (patent 686004) was challenged. Additionally, only claims 1- 3 in one patent were challenged in the Australian courts (Table 2).

Patent #	Claim	Type of Claim	Claim Language
Patent 686004	1	Composition of Matter	An isolated nucleic acid coding for a mutant or polymorphic BRCA1 polypeptide....
Patent 686004	2	Composition of Matter	An isolated nucleic acid as claimed in claim 1 which is a DNA coding for a mutant BRCA1 polypeptide...
Patent 686004	3	Composition of Matter	An isolated nucleic acid as claimed in claim 1 which is a DNA coding for a polymorphic BRCA1 polypeptide...

Cited from; *Cancer Voices Australia v Myriad Genetics*, 2013

The patent was challenged exclusively on the argument that gene sequences not being patentable subject material. In 2010, Cancer Voices of Australia and Mrs. Yvonne D’Arcy filed a lawsuit against Genetic Technologies and Myriad. In 2011, GTG was removed from the proceedings (per their request), which left Myriad as the sole defendant (vanZimmeren, 2013).

In 2013, the Federal Court of Australia heard the case as the litigation subject matter (a matter of Commonwealth law) falls within the Federal Court’s jurisdiction. Judge Nicholas upheld the patent on the grounds that the process of extracting the DNA (making it isolated nucleic acid) fulfilled Australia’s patentable subject requirement. The decision was appealed to the Full Court of the Federal Court of Australia. In August 2013, the appeal was heard; however, a decision has not been reached. When the opinion of the Appeals Court is released, the decision may be appealed to the High Court of Australia (“What are the court hierarchies?”).

Chapter 4: The Arguments

In both the United States and Australia, there were specific challenges to the individual patents and disputed claims. In the United States, these challenges ranged from the impact of the patents on patient rights to the impediment to research that the patents created. The central challenge in both Australian and U.S. courts was that the claimed “inventions” (i.e. isolated genetic material) were not to be considered patentable material under established policy and precedent. In their interpretation of the unique arguments presented in each suit, the judges and justices relied extensively on legal precedent to guide their opinions on analyzing the case.

Plaintiffs

As previously stated, there were multiple plaintiffs listed in the Myriad case adjudicated in the United States. All plaintiffs, whether an individual or organization such as the American College of American Genetics, represented a unique criticism against Myriad’s BRCA patents that stemmed from their interactions with Myriad and the patents themselves.

One particular concern raised by the plaintiffs in the U.S., particularly by the women who had a vested interest in obtaining screening, was that Myriad’s patents restricted patient access to hereditary breast cancer screening. Several of the plaintiffs (including Ms. Kathleen Raker, Ms. Patrice Fortune, Ms. Lisbeth Ceriani) had difficulties in affording the diagnostic test offered by Myriad as either their insurance companies would not cover the screening Myriad offered, and/or they could not afford the test out-of-pocket (*Association for Molecular Pathology v. Myriad Genetics, 2010*. 61). A contingent assertion made by plaintiffs is that other companies and laboratories could perform the same diagnostic screening service for a fraction of the costs; however, Myriad sent cease and desist letters to others who offered any form of testing involving

the patented genes (see *Myriad Genetics v. University of Pennsylvania*)(*Association for Molecular Pathology v. Myriad Genetics*, 2010. 63). The plaintiffs also asserted that Myriad's "monopoly" on BRCA1&2 diagnostic testing restricted the improvement, in terms of quality and efficiency, of diagnostic screening surrounding the patented genes, which in turn, had negative consequences for patients seeking an accurate and speedy assessment of their risk.

Another specific argument raised against Myriad's patents was that gene patents in general impede scientific research surrounding the patented material. In support of their assertion, the plaintiffs cited a study conducted by Dr. Mildred Cho in 2001 in which a survey of lab directors revealed that 53% of the surveyed directors decided not to develop a novel genetic test applicable to a clinical population because of a patent/license (Cho, 2003). Additionally, the plaintiffs asserted that Myriad restricted access to a large repository of patient and genetic data that could be used to determine trends in inheritance and other significant information (*Association for Molecular Pathology v. Myriad Genetics*, 2010. 72).

Unlike in the United States where the case involved a broad spectrum of plaintiffs, only two stated applicants were on the suit in Australia: Cancer Voices of Australia (an independent cancer advocacy group) and Yvonne D'Arcy (a cancer survivor). The applicants had two main assertions; the first challenge to the disputed claims was similar to a concern voiced in the United States, that the isolated DNA claimed in the patent was not significantly different from a natural state of affairs. In section 18 of the *Patent Act of 1990* it is stated that:

(2) Human beings, and the biological processes for their generation, are not patentable inventions.

(3) For the purposes of an innovation patent, plants and animals, and the biological processes for generation of plants and animals, are not patentable inventions.

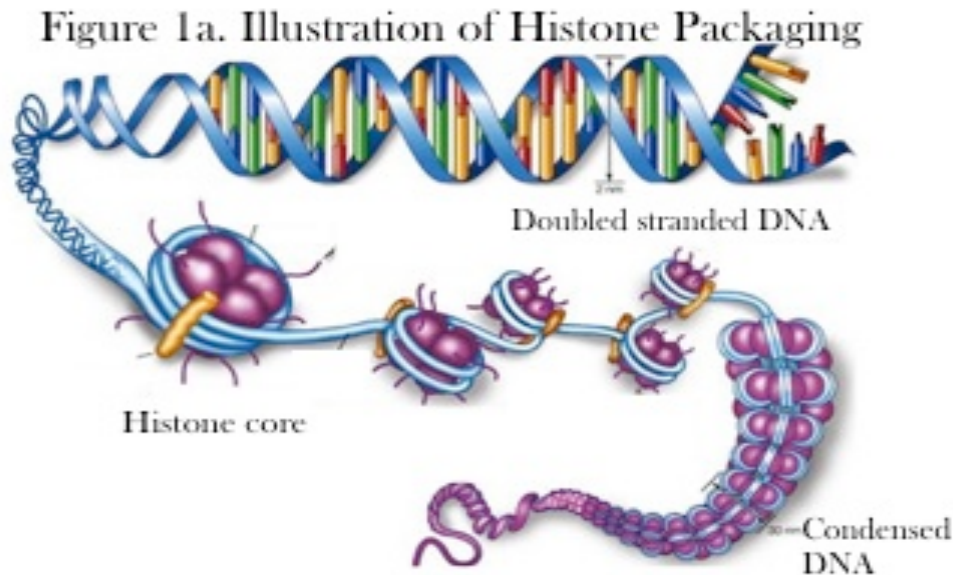
The applicants asserted that the claimed invention in the patent did not satisfy the requirements of section 18 in the Act, mainly the criteria of manner of manufacture (Cancer Voices Australia v Myriad Genetics Inc., 2013.8). The second assertion made by the applicants, mainly Cancer Voices of Australia, was that although GTG did not specifically enforce the patents in Australia, if the patents were allowed to be upheld there would always be the threat that GTG would enforce its rights, which could in turn negatively impact research surrounding the genes. This specific objection was not much addressed in the case as section 199C in the newly established Intellectual Property Laws Amendment (Raising the Bar) Act of 2012 cited research as an exemption to patent infringement, thereby rendering the argument that the patents could potentially restrict research moot.

Defendant – Myriad

In the United States, Myriad offered several arguments as to why their patents and claims were valid, and thus should be upheld by the court. Broadly, Myriad asserted that the plaintiff's complaints should be dismissed "in light of the carefully considered policy of the USPTO" (Association for Molecular Pathology v. Myriad Genetics, 2010. 107).

In regards to their composition of matter claims, Myriad asserted that the patented DNA was "markedly different" from the DNA found in nature. Myriad claims that the isolated DNA in the patents is structurally and functionally different from naturally occurring DNA. . The first

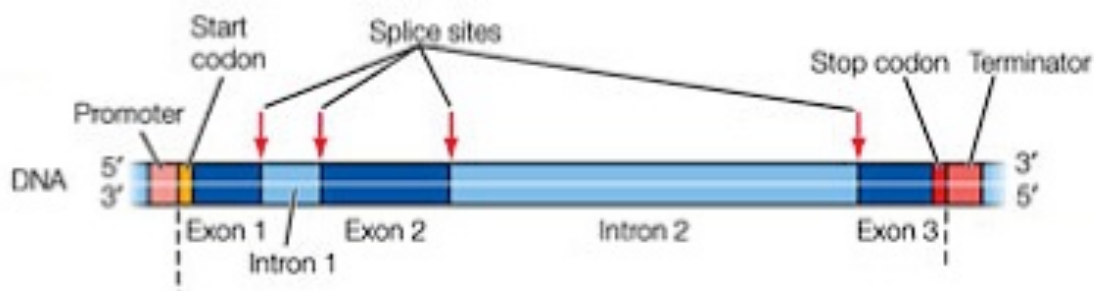
structural difference Myriad emphasized was that native DNA possesses “packing proteins”, also known as histones (Figure 1a).



Adapted from: LIFE: THE SCIENCE OF BIOLOGY, Eighth Edition © 2007 Sinauer Associates, Inc. and W.H. Freeman & Co.

Myriad asserted that in the process of isolating the gene the histones are removed, which makes a structural difference between the native DNA and the isolated form. The second structural difference that Myriad emphasized was that native DNA contains non-coding segments called introns. In the isolated form, the intron segments are removed, leaving just the coding regions called exons (Figure 1b) (*Association for Molecular Pathology v. Myriad Genetics, 2010. 132.*).

Figure 1b. Illustration of Exon/Intron Regions in DNA Strand



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This structural difference between the native DNA and the isolated DNA delineates the isolated form as “different” from the naturally occurring form. The main functional difference that Myriad emphasized was that the isolated DNA can be used in other applications (like diagnostic tests), whereas native DNA would be unsuitable; therefore, the isolated form has utility (*Association for Molecular Pathology v. Myriad Genetics, 2010. 134*).

For the method claims, Myriad claimed that their claimed techniques satisfied the requirements of the “machine or transformation test” (a concept that dictates the patentability of a process or method), and thus should not be viewed as a mental process (*Association for Molecular Pathology v. Myriad Genetics, 2010. 138*).

In Australia, Myriad’s arguments were similar. Myriad asserted that the disputed claims were valid as the claimed DNA “consists of an artificial state of affairs, providing a new and useful effect that is of economic significance” (*Cancer Voices Australia v Myriad Genetics Inc., 2013.*

8). Myriad relied on their assertion that native, cellular DNA is structurally and functionally

different from the isolated DNA claimed (Cancer Voices Australia v Myriad Genetics Inc., 2013. 8). As method claims were not debated in the Australian court, Myriad did not present arguments on this matter.

Ultimate Court Decisions

As determined, the fundamental challenge to Myriad's patents was that they were invalid on the grounds that the patented subject matter, the BRCA1/2 genes, violated the established restriction on placing patents on "products of nature". In the District Court, Judge Sweet asserted that:

... the sole task of this court is to resolve whether the claimed compositions and methods constitute statutory subject matter or fall within the judicially created products of nature exception to patentable subject matter (Association for Molecular Pathology v. Myriad Genetics, 2010.)

Ultimately, Judge Sweet invalidated all fifteen claims that were challenged by the plaintiffs. His decision to invalidate the claims was based on the specific "type" of claim: composition claims and/or method claims. Composition claims are claims that pertain to the composition of the patented subject. Method claims are claims that concern the method of performing or doing a particular act or test.

Court precedent in the U.S. has determined that in order for biological material to be patentable subject matter, it must "possesses a new or distinctive form, quality, or property compared to the naturally occurring article" (Association for Molecular Pathology v. Myriad Genetics, 2010. 111). In addition, it was previously established that "purification of a natural compound, without more, is insufficient to render a product of nature patentable" (114). Throughout the legal disputes,

Myriad asserted that the isolated DNA claimed in their patents was “markedly different” from the DNA found in nature, and thus was patentable subject matter. In terms of the structural differences asserted, Judge Sweet concluded that:

“Not only are the coding sequences contained in the claimed DNA identical to those found in native DNA, the particular arrangement of those coding sequences is the result of the natural phenomena of RNA splicing”. Thus, the existence of introns in native BRCA1 DNA is completely irrelevant to the question of structural differences (*Association for Molecular Pathology v. Myriad Genetics, 2010.* 129).

Additionally, in terms of the functional differences, Judge Sweet concluded that for any primer or other genetic technology to be used successfully, it must match the native form (any variation would negate its function); thus, there are no differences “in kind” between the native and isolated DNA (*Association for Molecular Pathology v. Myriad Genetics, 2010.* 130). For the composition of matter claims, Judge Sweet drew on this knowledge and more to render his opinion that the “isolated” DNA did not satisfy the requirements of the Patent Act.

For the methods claims, Judge Sweet concluded that the terms “analyzing” and “comparing” in the claim language identified the claims as an abstract mental process, which did not satisfy the “transformative” step required for a method claim to be valid. Additionally, Judge Sweet invalidated claim 20 in patent US5747282 (Table 1) on the grounds that the act of screening cells was a scientific method and not a novel technique.

Myriad appealed the decision of Judge Sweet to the Federal Appeals Court on the grounds that court precedent does not exclude all “products of nature” from patent eligibility, and that the district court did not accurately distinguish the patented isolated DNA as “markedly different”

from DNA found in-situ. During the appeals case, the argument of whether or not the DNA claimed in the patent was different enough from naturally occurring DNA to be considered a patentable invention was considered. Judges Lourie and Moore reversed Judge's Sweet judgment that the patented DNA was not patentable subject matter on the grounds, in part, that breaking chemical bonds creates a new entity, which would qualify the biological material as patentable subject matter. In the official court report it was stated:

Man has whittled the chromosomal DNA molecule down to a 15 nucleotide sequence-defining the parts to be retained and discarded. And the result is a product with a function that is entirely different from the full gene from which it was obtained (Association for Molecular Pathology v. Myriad Genetics, 2011. 28).

Judge Bryson dissented by arguing that the process of isolating genetic material does not make the isolated genetic material patentable subject matter. Judge Bryson continued his opinion by asserting that the composition claims could eventually negatively impact research and the development of novel sequencing methods, such as whole genome sequencing, as the patents prevented any sequencing of the BRCA genes (Association for Molecular Pathology v. Myriad Genetics, 2011. 90).

When the case finally made its way to the Supreme Court to be settled in 2013, the Judges unanimously ultimately concluded "A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated" (Association for Molecular Pathology v. Myriad Genetics, 2013. 2). To define, cDNA is double stranded complementary DNA artificially created from single stranded mRNA (Figure 2). The Judges determined that

“cDNA is patent eligible because it is not naturally occurring (inside the body)” (*Association for Molecular Pathology v. Myriad Genetics, 2013. 2*).

Figure 2. Basic Synthesis of cDNA

mRNA 5' CCGAUAGCAAUCCAGUAAAAA 3'

PRIMER



mRNA strand with primer attached



mRNA 5' CCGAUAGCAAUCCAUA AAAAA 3'

DNA 3' GGCT ATCGTT AGGTAT TTTTT 5'

An enzyme binds to the primer and synthesizes a new strand of DNA based off of mRNA 'template'



mRNA 5' C

AA

AA 3'



DNA 3' GGCT ATCGTT AGGTAT TTTTT 5'

The mRNA strand is degraded and an enzyme comes in and binds to the remaining pieces to synthesize a new strand that is complementary to the DNA strand created from the



5' CCGATAGCAATCCATAAAAAA 3'

3' GGCTATCGTTAGGTATTT TTT 5'

Thus, a newly created 'cDNA' strand is made

cDNA strand



= ENZYME

In the United States Supreme Court, the method claims were also determined to be invalid as the techniques claimed in the patents were well understood and utilized by many geneticists, and thus were not novel experimentation approaches developed solely by Myriad (*Association for Molecular Pathology v. Myriad Genetics*, 2013. 22).

In Australia, Justice Nicholas asserted that the act of “isolating” the genetic material from a cell constituted creating a naturally created state of affairs. He continues by stating that the patent did not cover genetic material as it is found in the cell, but rather an isolated molecule whose state has been altered by human intervention, and thus was patentable material under established policy and law (*Cancer Voices Australia v Myriad Genetics Inc.*, 2013.41).

Summary

As we have observed, there were similarities and discrepancies between the Myriad debate in the U.S. and Australia. The differing social, political, and legal contexts of each region dictated the differing approaches to the various concerns raised in the cases. Furthermore, each individual court system has unique precedents that directed the decisions of the Judges.

In both suits, it was the validity of gene patents that was under scrutiny; however, in the United States the plaintiffs cited several social injustices (namely clinical access to diagnostic testing services) that contributed to the invalidity of Myriad’s patents. Additionally, while both applicants in the U.S. and Australia asserted that Myriad’s patents had adverse implications for research, the Australian applicants’ claim was weakened by the presence of legislation (*Patent Amendment- Human Genes and Biological Materials*) that had already emphasized the research exception clause to patented material.

Ultimately, there is a threshold difference for patentability in the United States and Australia. In the United States, products of nature are excluded from being patent eligible subjects. If a biological or natural artifact is patented, it must be proven to be “markedly different” from what is found in nature. In Australia, patentability rests on an “artificial state of affairs” being created; there must be a “manner of manufacture” that generates the artificial state (Desai, 2013; Parker & Longshaw, 2013). As the Australian suit moves through the courts, the ultimate outcome will allow for a more thorough evaluation of the differing approaches to the gene patent debate between the U.S. and Australian patents systems.

Chapter 5: Post-litigation Outcomes

Despite the Supreme Court's verdict in the United States, Myriad still holds a multitude of valid, unchallenged patents that claim portions of the BRCA1&2 genes (particularly cDNA). The presence of these unchallenged patents has already generated controversy post-litigation in the United States. Immediately after the Supreme Court's decision in the U.S., biotech companies began announcing their intent to begin offering testing services for the breast cancer genes. When two companies, Ambry Genetics and Gene-by-Gene, advertised BRCA testing services, Myriad filed patent infringement suits on both companies claiming that their valid patents still prevented other companies from offering testing on the BRCA 1&2 genes for commercial purposes (Conley, 2013). Currently, the litigation involving the two-biotech companies is evolving, and will likely take months to years to unfold. In September of 2013, Counsyl, Inc. (a California based genetic testing provider), preemptively filed a suit against Myriad asserting that eight patents Myriad currently holds are invalid, and thus their company should be allowed to develop and market diagnostic testing for the breast cancer genes. A court date has been set for January 2014 to evaluate these assertions against Myriad ("BRCA Resources").

Public reaction to the Supreme Court's decision was varied. Some expressed satisfaction with the verdict. The Executive Director of the Public Patent Foundation, Daniel Ravicher, asserted that, "[b]ottom line, diagnostic genetic testing is now free from any patent threat, forever, and the poor can now have their genes tested as freely as the rich" ("Supreme Court Invalidates Patents..."). Others, most notably biotechnology companies, were dissatisfied with the ruling as they claim that it creates further uncertainty about the parameters of patentability. The American

Intellectual Property Law Association claimed that the court's verdict had "continued to cut back on the scope of technologies eligible for patent protection" (Zuhn, 2013).

In response to the Supreme Court's verdict, Dr. Bob Cook-Deegan at the Duke Institute for Genome Sciences and Policy asserted:

My guess is that Myriad in the end will probably not win, and yes, those doing gene testing will be less concerned about patent infringement liability, but in the meantime, Myriad will have staved off competition for as long as possible. These new cases are in a race with patent expiration, because the broadest BRCA patents begin to expire next summer (Morgan, 2013).

Several Harvard scientists also released nonchalant statements over the Supreme Court's decision, claiming that the ruling would have minimal effect on Myriad as a company, and the patenting of biological materials (Mirza, 2013). Many have claimed that Myriad will not suffer commercially as their diagnostic testing services are well ahead of their competitors in terms of quality, as they have held exclusive rights to develop the test for the last 2 decades. Additionally, they also are in possession of a large database of genetic information of which they can use for diagnostic purposes to compare specific types of mutations (Mirza, 2013).

This large database of genetic information Myriad has amassed over the years has also come under fire. It was created from the screening of thousands of patients, and contains various information regarding BRCA mutations. It is considered to be a trade secret that gives Myriad a competitive advantage over competitors as they can use their database to develop more nuanced testing services (Baker, 2012). Several researchers have argued that this private database of genetic data inhibits the scientific and clinical community from accurately making assessments

about the clinical significance of certain mutations, and their prevalence rate in certain populations (Cook-Deegan *et al*, 2013).

In Australia, the appeals case was heard in August of 2013. At the time of this writing, a decision has not yet been reached regarding the validity of the patent in Australia. As the United States Supreme Court has ruled against the validity of gene patents, many scholars and legal experts are extrapolating to determine if the Australian courts will follow the U.S.'s example in invalidating Myriad's patents. Some have cited the failure of recent gene patent legislation (*Patent Amendment- Human Genes and Biological Materials*) in the Australian Parliament as evidence that Australia will not follow in the path of the United States in invalidating gene patents; however, it is also emphasized that Australia had recently made efforts to "harmonize" their patent laws with international court systems (Parker & Longshaw, 2013).

Conclusion:

The significance of the Myriad court decision in the United States goes far beyond simply settling the matter of the BRCA1&2 gene patent dispute. The Supreme Court's decision in the Myriad debate has set a landmark for the patenting of biological materials, particularly genes, in the future. Unfortunately, there are still shades of gray regarding the legality of patenting biological materials and processes. Thus, there will likely be many legal battles in the future that aim to further define the parameters of patentability.

The varying considerations and concerns that were raised in the Myriad litigation in the United States and Australia illustrate the varying responses to the complexities that these cases raised. What are the limitations of patentable subject matter when it comes to scientific discoveries? At what point does a product that is found in nature or a derivative of a natural product become classified as patentable subject matter? As innovative scientific discoveries and methods are created, the patent system will have to continue to redefine the patent eligibility of biological materials and techniques. Ultimately, policy and precedent in individual jurisdictions will have to resolve these challenges and questions.

As genetic technologies become a more routine tool for clinicians and doctors to use in diagnosis and treatment, it is crucial that legal experts and policy makers create the necessary frameworks that support the prompt and accurate delivery of these novel technologies. As these frameworks evolve, communication between all relevant stakeholders (including patients, doctors, researchers, and policymakers) will promote a more harmonious relationship between the disciplines of science, law, and medicine.

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