

# Breast Cancer Gene Research and Medical Practices

Transnational perspectives in the  
time of BRCA

978-0-415-82406-4

Chapter 8

## **The BRCA patent controversies: an international review of patent disputes**

ESTHER VAN ZIMMEREN, DIANNE NICOL, RICHARD GOLD,  
JULIA CARBONE, SUBHASHINI CHANDRASEKHARAN,  
A. LANE BALDWIN AND ROBERT COOK-DEEGAN

(CC BY-NC-ND 3.0)

## 8 The BRCA patent controversies

### An international review of patent disputes<sup>1</sup>

*Esther van Zimmeren, Dianne Nicol, Richard Gold, Julia Carbone, Subhashini Chandrasekharan, A. Lane Baldwin and Robert Cook-Deegan*

#### 1 Introduction

A book focusing on transnational perspectives on BRCA would certainly be incomplete without a chapter on the international uproar regarding patents on the BRCA gene sequences and testing methods. BRCA ‘gene patents’ have been the focus of intense controversy for decades and – more recently – the subject of court battles in the US and Australia. Most conspicuously, the US Supreme Court handed down its ruling on whether human genes are patentable subject matter on 13 June, 2013 (*AMP v. Myriad* [2013]).

General patentability criteria are globally uniform and technology-neutral (requiring that the invention is new, involves an inventive step and is capable of industrial application).<sup>2</sup> National patent systems show considerable variation, however, in how each criterion is applied, either through patent legislation or as developed through case law. As with any other field of technology, biological materials are, in principle, capable of fulfilling these criteria. In all jurisdictions, however, a question of threshold must be addressed before these patentability criteria are applied. This question concerns whether or not the invention constitutes patentable subject matter. Although not traditionally viewed as satisfying this threshold requirement, many kinds of living matter are now considered to be eligible, and as a consequence patents have intruded on the field of human genetics as well. This intrusion has not gone unnoticed and has led to a ‘policy storm’ (Gold and Carbone 2010) surrounding the desirability of human gene patents since the late 1980s.

At the centre of this storm is Myriad Genetics Inc (hereinafter Myriad). Myriad is a biotech spin-off from the Center for Genetic Epidemiology at the University of Utah. It is not the only owner of patents related to human genes, mutations and diagnostic methods with respect to the BRCA1 and BRCA2 genes. However, it has been singled out in the policy storm largely because of the way in which it chose to use its patent rights. Myriad accumulated sufficient patent rights to create a service monopoly in the US, but it did not achieve that level of dominance in any other jurisdiction. It also made a number of commercialization decisions that did not sit well within the research community (Baldwin and Cook-Deegan 2013, Gold and Carbone 2010, Parthasarathy 2007).

Efforts to identify the BRCA genes started with the International Breast Cancer Linkage Consortium with researchers from all over the world. Mary-Claire King's discovery of chromosome 17 linkage to a risk susceptibility locus for breast cancer (Hall *et al.* 1990) set off a furious competition to find the actual gene by comparing DNA from those who developed cancer to others who did not develop cancer within family pedigrees in search of DNA changes correlating with developing cancer (Davies and White 1996, Marshall 1997). The race to be the first to isolate and sequence the genes (and to be the first at the patent office) was fierce. Over the course of this race to uncover these enigmatic 'breast cancer genes', several research teams published the gene sequences and filed for patents.<sup>3</sup> The race to BRCA1 on chromosome 17 was won in 1994 by Mark Skolnick and his colleagues at the University of Utah, also affiliated with Myriad Genetics, who identified mutations in BRCA1 and cloned and sequenced the gene (Davies and White 1996, Miki *et al.* 1994). There were more doubts about which team had actually 'won' the race to BRCA2 on chromosome 13, with the team affiliated with Michael Stratton in the UK publishing first and securing a UK patent, but with Myriad having filed a patent application just days before that publication after 'getting wind' of Stratton's progress. The patent race led to a complex international patent landscape and often to errors in the filed sequences, which were later employed to challenge some of the BRCA patents in Europe (see Section 2 of this chapter).

In addition to the intense patent race, Myriad's stringent enforcement and licensing practices also contributed to its negative public image (Gold and Carbone 2010). In the US, once Myriad had obtained its patents, it attempted to eliminate the BRCA testing by competing laboratories. Until the Supreme Court ruling, Myriad was successful in 'clearing the market' of US competitors. Outside the US, Myriad applied a different strategy. In each country or region, Myriad identified an exclusive licensee for single-mutation tests (once a mutation had been identified in a family), while it intended to perform the more expensive first-line sequence-based proband testing at its own laboratory in Utah, obliging clinicians to send samples to the US (Gold and Carbone 2010).

In Europe, each country has its own health care and laboratory system, meaning Myriad had to engage in country-by-country licensing negotiations. With respect to the UK and Ireland, Myriad established a strategic alliance with Rosgen Ltd for BRCA testing. Rosgen then negotiated an agreement with the UK's Department of Health that would allow the national health authority, the National Health Service (NHS), to perform the testing. Cancer Research UK (CRUK), which held a BRCA2 patent in the UK (see Section 2.2), licensed its patent to OncorMed with the stipulation that the NHS could continue to provide testing services for free. Rosgen soon went bankrupt, which effectively ended Myriad's agreement with the NHS. Myriad and the NHS did not agree on a replacement license (Llewellyn 2003, Parthasarathy 2007). However, Myriad found another private company, Lab21, which was willing to sign a licence agreement for the BRCA test. For the Swiss, German and Austrian markets, Myriad licensed Bioscientia to market its test for proband testing and 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, in practice, no laboratory in France was ever licensed to perform the testing (Gold and Carbone 2010). In 2012, Myriad opened its own laboratory in Germany and offices in four European countries (see below).

In Canada, Myriad awarded the private company MDS Laboratories (MDS) the exclusive right to market the BRCA tests. Myriad performed proband sequencing in Utah, but MDS arranged for individual mutation testing within its 'network of physicians and hospitals' (Gold and Carbone 2010). In Australia, Myriad entered into a strategic licensing agreement with Genetic Technologies Ltd (GTG), a Melbourne-based biotechnology company. The alliance resulted from Myriad's alleged infringement of GTG's patents claiming rights to intron sequence analysis and genomic mapping, the so-called 'junk DNA' patents (Nicol 2005). As a result of the agreement, GTG became Myriad's exclusive licensee in Australia and New Zealand for a number of its products, including its breast and ovarian cancer tests. The CEO of GTG indicated in 2003 that he had no intention of enforcing the BRCA patents on behalf of Myriad, but that rather they were 'GTG's gift to Australia'. When GTG announced its plans to take back that gift in 2008, a firestorm erupted, and the company backed down.

In response to Myriad's restrictive licensing practices, at least nine US laboratories stopped offering BRCA testing (Cho *et al.* 2003). These licensing practices led to patent litigation in the US (see Section 4.2) and Australia (see Section 5.2) as well as opposition procedures at the European Patent Office (EPO) (see Section 2.2) and various legislative proposals and policy measures in Europe, Canada, the US and Australia (see Sections 2.3, 3.2, 4.3 and 5.3). Moreover, many clinicians simply ignored the enforcement practices and offered testing quietly under the radar.

The research, legal and policy contexts in which these decisions were made have been described in several case studies (Gold and Carbone 2010, Parthasarathy 2007, Williams-Jones 2002). This chapter reviews these case studies and draws on a number of formal and informal interviews with stakeholders as well as workshops and conference presentations by key players (i.e. Gold and Carbone 2010, Van Overwalle 2007). It also provides an update of recent developments in litigation, policy and decision-making processes. The chapter has two objectives: first, to highlight features that distinguish the Myriad case from other patent cases; and second, to explain how BRCA patent disputes have unfolded very differently in Europe, Canada, the US and Australia with different roles of institutional actors in diverse legal and legislative fora and the use of alternative solutions.

In the following sections, we describe – more or less chronologically – how BRCA gene patent controversies have travelled around the world. In Section 2, we start off in Europe in the 1990s with a short description of the particularities of the European 'multilevel' patent regime, followed by a sketch of the procedures against the BRCA patents at the European Patent Office (EPO). Contrary to the European story, no formal means were used to contest Myriad's patent rights in

Canada: the Ontario Ministry of Health took the lead using informal pressure to steer Myriad away from its restrictive licensing practices (Section 3). We move to the US in Section 4, where we learn that, in the early 2000s after Myriad settled lawsuits with OncorMed and the University of Pennsylvania, for a few years the gene patent debate was mainly a topic for academics and advisory committees. This quickly changed when the American Civil Liberties Union (ACLU) and the Public Patent Foundation (PPF) challenged Myriad's patents at the New York City federal district court, where Judge Sweet decided that 'isolated' nucleic acid molecules could not be considered patent-eligible subject matter. Whereas Sweet's decision was initially reversed by the Court of Appeals of the Federal Circuit (CAFC), in June 2013 the US Supreme Court confirmed Sweet's conclusion regarding 'isolated' DNA sequences. In contrast, in Australia, Judge Nicholas reached the opposite conclusion, ruling that 'isolated' nucleic acids *are* patentable subject matter (Section 5). However, as the appeal in the Australian case remains to be decided, the patentable subject matter requirement may still converge. After a brief analysis of positions on gene patents in emerging economies and at the international level (Section 6), we conclude with an inventory of the available toolkit for contesting patents and licensing practices and some closing remarks on the potential impact of the recent case law on the new generation of sequencing technologies (Section 7).

## **2 Europe**

### ***2.1 Background***

In order to fully comprehend how the Myriad case proceeded in Europe, it is important to have a basic understanding of the structure and distinctive features of the European patent system. The European patent system is a complex, multilevel system:<sup>4</sup> in addition to the national patent offices that grant patents that are valid only within each country, the European Patent Office (EPO) can grant so-called 'European patents'.<sup>5</sup> Once European patents have been granted, they become a 'bundle' of national patents, which means that the patents need to be translated and validated in the designated countries and can only be litigated in each country's courts in case of a dispute. This can lead to high litigation costs, and these costs deter patent litigation in Europe. Fortunately, the EPO offers some alternative routes for challenging patents, such as the so-called 'post-grant opposition procedure', which is an internal administrative procedure within the EPO.

The EU and EPO have adopted a uniform approach to gene patents. Because the EU wanted to harmonize patent law between the member states with respect to biotechnology, it thus approved a directive on the legal protection of biotechnological inventions (EU Biotechnology Directive) (Council and European Parliament 1998, Gold and Gallochat 2001). This directive stipulates conditions for patenting biotechnological processes and products, including materials of human origin. The EPO incorporated the directive as part of its implementing regulations (Brody 2007, Gold and Gallochat 2001). The European baseline is that discoveries are

not patentable, but a 'technical' or useful application of a discovery may be patentable. The simple discovery of one of its elements, including DNA sequences or partial sequences, cannot constitute patentable inventions. However, elements 'isolated' from the human body or otherwise produced by means of a technical process may constitute a patentable invention, even if the structure of those elements is identical to natural elements.<sup>6</sup> Despite this, a mere DNA sequence without indication of a function does not contain any 'technical information' and is therefore not a patentable invention (Council and European Parliament 1998, para. 23). Typically, the EPO has awarded patents for DNA sequences by treating them in the same way as other chemical substances without much reference to the information that DNA encodes.

## **2.2 Opposition and appeal at the EPO**

The European story of Myriad's patents shows the importance of a well-timed and accurate disclosure of the invention at the patent office. Filing dates of applications are extremely important. Delays or errors may have a disastrous impact on patent prosecution (the process for getting a patent granted by a patent office). In August 1995, Myriad and its co-applicants (e.g. the University of Utah Research Foundation) filed four separate patent applications at the EPO for the sequences, mutations and diagnostic tests regarding the BRCA1 and BRCA2 genes. In 2001, the EPO granted EP699754 for a diagnostic method for breast and ovarian cancer, EP705903 for 34 mutations in the BRCA1 gene and methods for detecting the mutations and EP705902 for the BRCA1 gene itself and for several applications. In November 1995, Cancer Research UK (CRUK), led by Mike Stratton, first applied for patent protection in the UK (national patent) based on the BRCA2 sequence and several diagnostic methods. This UK application was followed by an EPO application in November 1996, claiming priority<sup>7</sup> on the basis of the UK applications. The EPO granted patent EP858467, sometimes referred to as the Stratton patent, in 2003. Myriad applied for protection in December 1996 for a variant of the BRCA2 gene, several mutations and a range of diagnostic applications. Patent EP785216 was granted in 2002. Myriad opposed the Stratton patent on the BRCA2 gene. One of the deficiencies of the Stratton patent, the filing of incomplete sequences, was the consequence of the 'race to the patent office'. The opposition division allowed the rectification of the claims, but on appeal the Stratton patent was revoked (T902/07, 2010). CRUK thus has a UK BRCA2 patent but no EPO patent.

A number of scientists and clinical geneticists, including Mary-Claire King and Dominique Stoppa-Lyonnet, expressed concern about the potential impact of the patents on their research and access to health services. They spoke out against the 'Myriad patents', asserting that they would prevent scientists from assessing the quality of Myriad's tests, developing more comprehensive or accurate BRCA tests (Puget *et al.* 1999) and developing treatments (Benowitz 2003, Lecrubier 2002). Fuelled by these concerns, a French association of research institutes and hospitals and an informal coalition of the Belgian, Dutch, British, Danish and

German genetic societies opposed the first BRCA1 patent (EP699754).<sup>8</sup> The number of opponents accumulated with later opposition procedures (Matthijs and Halley 2002).

The opposition and appeal procedures did not result in the revocation of all the patents, but they were quite successful in limiting their scope.<sup>9</sup> For instance, for patent EP785216 the claims were restricted to a particular sub-population of Ashkenazi descent. Despite the criticism on this discriminatory limitation (Abbott 2005), the amendment was ultimately accepted. The opponents tried to raise broader policy concerns about the eligibility of gene sequences for patent protection, their impact on research and health services and their compatibility with 'public order and morality',<sup>10</sup> but success in narrowing patent claims was mainly due to arguments based on 'traditional' patentability criteria regarding novelty, inventive step, industrial applicability and disclosure.<sup>11</sup> Those procedures took place within the EPO, and no litigation has raised issues of patent eligibility.

As a result of narrowing the patent claims through the various EPO procedures, fears within the European BRCA community about the patents have diminished significantly. By curbing the scope of the patents, the EPO has decreased their clinical relevance for genetic diagnostics. For the most part, the patents have been ignored and will begin to expire in late 2014. Moreover, the patent owners have allowed their patents to lapse in several countries, which is possible in Europe, as the patents are considered a 'bundle of national patents' that must be maintained (including the payment of fees) on the national level. Testing by laboratories located in those particular countries thus no longer entails any risk of patent infringement liability.<sup>12</sup> In view of the expansion of Myriad's activities in Europe, this situation has become quite important. In the past, Bioscientia was Myriad's exclusive licensee in Europe (see Section 1). Nonetheless, BRCA testing has persisted in many European laboratories. To date, Myriad has refrained from aggressive patent enforcement in Europe. To do this, it would first have to start infringement procedures before national judges in all the relevant countries, which would be expensive and time-consuming. However, Myriad did open a molecular diagnostic laboratory in 2012 in Munich, where they will carry out BRCA*Analysis*<sup>TM</sup>. It also established sales and marketing offices in Munich, Paris, Milan, Madrid and Zurich (Myriad 2013). It remains to be seen whether this expansion will entail changes with respect to Myriad's enforcement strategies.

### **2.3 Policy and law reform**

Several national advisory bodies have weighed in on the debate about the patent eligibility of gene sequences. For instance, the Nuffield Council of Bioethics in the UK noted that DNA sequences should be regarded as 'just genetic information', distinguishing them from other patentable chemical compounds, and they recommended that patentability requirements (novelty, inventive step, industrial applicability) be applied more stringently to DNA patents (Nuffield Council 2002). Two years later, the Danish Council of Bioethics echoed these arguments based on the 'information content' of gene sequences in its report *Patenting Human Genes*

*and Stem Cells* (Danish Council of Bioethics 2004). The Danish Council argued that, while the informational nature of DNA would not be a reason to preclude patents entirely, it may be a reason to limit the effects of DNA patents, such as through the granting of compulsory licences for public interest reasons, allowing users to apply the patented invention without the consent of the patent owner with fair compensation (Danish Council of Bioethics 2004). Moreover, several geneticists who had been active as opponents of Myriad patents at the EPO formed a working group under the umbrella of the European Society of Human Genetics (ESHG) and issued recommendations, ranging from a limitation of patentable subject matter to a higher bar for patentability requirements, the introduction of compulsory licences for public health and the use of alternative licensing models, such as patent pools and clearinghouses (ESHG Working Party on Patenting and Licensing 2008).

For the EU Biotechnology Directive to take effect, legislatures in the EU member states needed to transpose it into national law. In the process of doing so, some countries decided to go beyond the rules imposed by the directive and added provisions, creating new tools for judges or governments when dealing with restrictive licensing practices. The BRCA patent situation was the main driver for these initiatives. France and Belgium created mandatory licensing regimes for diagnostic testing in the interest of public health, enabling the French and Belgian government to put a regime into place that allows the use of a particular patented invention without the authorization of the patent owner (Debrulle *et al.* 2007, van Zimmeren and Van Overwalle 2011, van Zimmeren and Requena 2007). To our knowledge, these licensing regimes for public health have never been invoked, but their existence effectively limits the enforceability of diagnostic patents and is a tool for persuading patent owners to collaborate. In addition, the Belgian legislature also modified the research exception, extending its scope from ‘research on’ to ‘research with’ the patented invention, enabling further BRCA research without the risk of patent infringement (Van Overwalle and van Zimmeren 2006).

### **3 Canada**

#### ***3.1 Background***

The storm surrounding Myriad and its patents played out very differently in Canada than in Europe. Rather than being led by clinicians, patients or civil society, health departments responsible for the public health care system took the lead. The Canadian story began in 2000, after Myriad and its Canadian exclusive licensee, MDS Laboratories, met with provincial health care procurement officers. At the time, the Ontario Ministry of Health and Long-Term Care had already begun considering genetic testing and its implications for the health care system. During the six months that the Ontario Health Ministry was contemplating its response, Myriad and MDS issued so-called ‘cease-and-desist letters’ to several provincial governments, including Ontario, in May and June 2001. This surprised ministry officials and led the Minister of Health to state that the government had

not violated any valid patent. In response, the Republican senator from Utah, Orrin Hatch, threatened to put Canada on the ‘watch list’ for international trade violations, and the Biotechnology Industry Organization (BIO) threatened to move its annual meeting from Toronto. This reflected a complete misunderstanding of what the province was doing and resulted in an intensification of the policy storm (Gold and Carbone 2010).

### **3.2 Policy and law reform**

While the Myriad storm in Canada may have been turbulent, it did not lead to any legislative reform at either the federal level (with jurisdiction over patent law) or the provincial level (with jurisdiction over the provincial health care systems). A federal parliamentary committee, the Standing Committee on Health, briefly discussed the topic of gene patents in 2001 in the course of examining a bill on assisted reproduction, but it wrongly stated that genes could not be patented in Canada (Standing Committee on Health 2001). Instead, Canadian provincial governments adopted a simple strategy using the leverage of their procurement power, since they regularly purchase patented goods (i.e. medicines, equipment, diagnostic kits). The provinces focused on creating a united front so as to send a signal not only to Myriad, but to the entire diagnostics industry that they needed to adopt a flexible approach to licensing in Canada.

What concerned the provinces most was not the fact that Myriad had a patent on a gene, but that Myriad was interfering with the efficiency of the administration of their health care system. As Myriad attempted to use its patents to require that samples be sent to its Salt Lake City laboratories, provinces were left with no flexibility regarding how to screen their populations (using less expensive tests together with family histories to identify who ought to receive the expensive test). Moreover, if Myriad’s model were to prevail, provincial health care systems could never centralize genetic testing so as to build expertise and efficiencies in diagnostics (Gold and Carbone 2010).

The provinces, with the assistance of one federal department, Health Canada, employed soft law measures to demonstrate their opposition to Myriad’s business strategy in the form of the organization of an expert policy forum, an inter-provincial report approved by the First Ministers and a reference to a federal expert panel on biotechnology to investigate the issue of gene patents and their effect on the health care system. None of these steps flowed from strict regulatory authority, but they generated pressure to thwart Myriad’s monopoly.

Canada’s largest province according to population, Ontario, took the lead in dealing with Myriad. It organized a policy forum that brought together industry, health professionals and patent experts in December 2001. The policy forum’s objective was to discuss and explore ways for Ontario to deal with Myriad’s demands as well as the expected future demands from other firms. The final report, entitled *Genetics, Testing and Gene Patenting: Charting New Territory in Healthcare*, recommended a combination of measures. These included a federal government review to ensure the continuation of clinical genetics research,

a review of competition law policy and the introduction of a research exemption into the Canadian Patent Act (Ontario 2002). A month later, all other Canadian provinces agreed with the report's recommendations (Gold and Carbone 2010).

Throughout 2002, Ontario maintained the lead on this issue. However, in the spring of 2003, it was hit by a more immediate health crisis: SARS. All of the government's attention turned to address that virus. Further, the feeling was that Myriad and other firms had received the message that they needed to change their business strategy in Canada. Therefore, the continued work on the Myriad dossier was not viewed as a priority. Then, in October 2003, Ontario elected a new government. This new government was apparently content to let the issue of gene patents rest and considered the united policy response among the provinces sufficient for sending a clear message to industry (Gold and Carbone 2010).

Meanwhile, at the federal level, Health Canada took up the mantle of the debate over gene patents. It engaged Industry Canada, which is responsible for the Canadian Patent Act, in discussions about how to resolve the problem, but Industry Canada and Health Canada could not agree on a solution. Instead, in 2004, they jointly commissioned the Canadian Biotechnology Advisory Committee (CBAC) to examine the issue. In 2006, CBAC issued its report *Human Genetic Materials, Intellectual Property and the Health Sector*, in which it called on the federal government to take proactive measures, such as introducing a research exemption and a targeted compulsory licensing provision for health care (CBAC 2006). The Canadian federal government never responded to the recommendations.

### **3.3 'Post-Myriad' atmosphere**

In the absence of a forcing action such as a lawsuit, policymakers, laboratory directors and hospitals seemed satisfied that, despite a lack of overt federal government action, industry understood that Myriad's business strategy was not acceptable in Canada. This assumption turned out to be incorrect. In 2008, Warnex Inc issued letters to laboratories across Canada informing them – incorrectly as the patent did not issue until 2012 – that it was the exclusive licensee of the patent on the JAK2 gene related to myeloproliferative disorders. The patent application had been filed by a French public laboratory, which had exclusively licensed it to Ipsogen, a diagnostics company in France. Ipsogen had developed a diagnostic kit that it marketed in the US, but it decided to leave the Canadian market to Warnex (Piper and Gold 2008). Warnex proposed to discuss having tests of the JAK2 gene conducted in its laboratory. Laboratory directors saw Warnex's letters as a reprise of the Myriad business model and complained to Health Canada. Given that the patent had not been issued, laboratories and provincial health administrators simply ignored the letters. Nevertheless, laboratory directors began, once again, to worry.

Following Warnex, further concerns began when the Canadian patents over the Long QT genes, related to a fatal heart condition, were issued. While there were no formal threats, the authors have been told that several laboratories either stopped working on the development of a test for Long QT, or they never began

to develop a test. Efforts to develop comprehensive cancer gene panels have also been reported to the authors to have been hampered by fears over issued gene patents, including the patents related to the BRCA1 and BRCA2 genes. Canadian laboratories and hospitals have thus been left with great uncertainty. With the absence of any litigation or legislative proposal, they remain frustrated at the lack of clarity as evidenced by their calls that genes should not be considered patentable subject matter in Canada (Richer *et al.* 2012).

## 4 United States

### 4.1 Background

The BRCA patent landscape in the US is relatively muddled.<sup>13</sup> The most significant are 24 patents assigned or licensed exclusively to Myriad Genetics. Fifteen claims in seven patents were challenged in *Association for Molecular Pathology et al. v. Myriad Genetics et al. (AMP v. Myriad)*. The background behind these patents and the ensuing litigation is complicated. A company named OncorMed licensed a University of California patent on Mary-Claire King's BRCA1 discoveries regarding the inherited risk of breast and ovarian cancer (Marshall 1997). While the Myriad team is credited with winning the race to the BRCA1 gene itself, the first BRCA1 patent was granted to OncorMed. US patent 5,654,155 was issued on 5 August, 1997, on a 'consensus sequence of BRCA1' (Murphy *et al.* 1997). Several other patents were initially licensed to OncorMed.

As patents were granted by the US Patent and Trademark Office (USPTO), a complex patent landscape with dispersed patent ownership emerged in the US. OncorMed owned the rights to some mutations, while Myriad owned the rights to others. Both companies had claims on the entire BRCA1 gene. This may be puzzling to those not familiar with patents, but it is not uncommon for patents to overlap, because there are different patent examiners handling different applications, and there is no systematic way to coordinate the separate examination processes. With ownership divided and overlapping, several solutions existed: ignoring the patents, sorting out legitimate inventorship by way of an administrative procedure (called interference) at USPTO, aggregating patent rights and knocking other companies out of the market, cross-licensing and competing or litigating. The choice was to litigate, and it was initiated by OncorMed.

### 4.2 Litigation

OncorMed filed suit against Myriad on 17 November, 1997. Myriad counter-sued on 2 December, after receiving its first of many BRCA1 patents (US 5,693,473) (Shattuck-Eidens *et al.* 1997).<sup>14</sup> Before the case went to trial, OncorMed and Myriad settled out of court with the BRCA patent rights conveyed to Myriad. In a second case, *Myriad v University of Pennsylvania*, Myriad had sent several notification and cease-and-desist letters to, and eventually filed suit against, the University of Pennsylvania (Penn) for offering BRCA testing. Penn had been

proposed as a clinical testing core for a cluster of federal grants studying the use of genetic testing in clinical practice. The case was settled when Penn agreed not to perform testing for other institutions.

*AMP v. Myriad*<sup>15</sup> is the only diagnostic gene patent case that has proceeded far enough to address the merits of patent claims. The two lawsuits between Myriad, OncorMed and Penn were settled before they went to trial under terms known only to the parties directly involved. *AMP v. Myriad* was filed by the ACLU and PPF on 12 May, 2009. As with the European oppositions, it involved many plaintiffs, including women who wanted to be tested, physicians who wanted to order tests, three laboratory directors who had received enforcement letters from Myriad as well as organizations representing those constituencies (in total more than 20 plaintiffs).

*AMP v. Myriad* became by far the most important and conspicuous case over gene patents. There have been 11 previous cases that centred on gene patents decided by the Court of Appeals for the Federal Circuit (CAFC), which hears patent appeals from all 94 US federal district courts. Those cases, however, concerned ownership and control of patent rights for therapeutic proteins, not whether patents should be granted in the first place (indeed, in previous cases, all the parties wanted such rights to exist). *AMP v. Myriad*, in contrast, was much more about changing the law than divvying up the profits. It was a public interest lawsuit rather than litigation among competitors, and as such, it drew in constituencies not generally party to patent suits.

In March 2010, Judge Robert Sweet of the New York federal district court stunned the patent world by ruling that all challenged patent claims were invalid. In his 156-page decision, he reasoned that DNA is ‘the embodiment of genetic information’. Furthermore, Judge Sweet argued that the claimed isolated DNA was not ‘markedly different’ (standard derived from the famous *Chakrabarty* case) from DNA, as it exists in nature and could not be considered patent-eligible subject matter. Furthermore, the general method claims were also not considered patent-eligible. All the challenged claims were thus held invalid. The case was appealed to the CAFC, which decided in July 2011 that the general method patents were indeed invalid (affirming Judge Sweet), but it reversed Judge Sweet’s judgment that ‘isolated’ DNA molecules cover patent-ineligible products of nature. Judge Bryson dissented, saying such DNA molecules were not ‘markedly different’ from their naturally occurring counterparts and were not patentable subject matter.

The case was further appealed to the US Supreme Court. The Supreme Court then remanded the case to the CAFC for reconsideration in light of its decision in *Mayo v. Prometheus* (2012), a case about diagnostic methods in general, not genetic diagnostics, and about methods not molecules. The CAFC reaffirmed its decision in *AMP v. Myriad* in August 2012. That decision was appealed, and the Supreme Court finally agreed to address the question: ‘Are human genes patentable?’ In June 2013, the Supreme Court ruled that a naturally occurring DNA sequence is a product of nature and therefore not patent-eligible simply because it has been ‘isolated’. The core rationale for this holding was that Myriad did

not create a composition of matter ‘with markedly different characteristics from anything found in nature’ in line with Judge Bryson’s dissent. However, the Court also held that cDNA is patent-eligible, because it is not naturally occurring (in other words, cDNA is sufficiently man-made).

### **4.3 Policy and law reform**

Conflict in the US over gene patents has not been restricted to litigation; it has also played out in administrative procedures and in proposed legislation. It all started with a highly contentious debate within the National Institutes of Health (NIH) about patenting human gene fragments focusing on ‘expressed sequence tags’ (ESTs). ESTs were considered great scientific tools for identifying genes for further characterization. NIH filed several EST patent applications, which triggered a vigorous debate within NIH about the propriety of applying for such patents. In 1994, the new NIH director, Harold Varmus, decided to abandon the NIH EST patent applications. The EST patent controversy was just beginning to die down when the BRCA1 gene was discovered in 1994.

As indicated above, not only questions of patenting but also questions as to how patents on genetic and genomic inventions should be licensed prompted the gene patent policy storm. Because of the degree of uncertainty and controversy surrounding DNA technologies, the NIH Office of Technology Transfer developed ‘best practices’ as to when, and whether, to patent DNA-based inventions and how to license such inventions for use (NIH 2004). In addition, in 2007 a group of academic institutions published a paper, later endorsed by the Association of University Technology Managers (AUTM), proposing ‘Nine Points to Consider’ when licensing university-generated intellectual property (Stanford 2007). Point 2 argues that patents on diagnostics should be pursued with an eye to avoiding patent logjams, taking care to preserve broad access and to avoid constraints on research.

The controversies over gene patents and their impact on access to genetic testing have bred several US initiatives for statutory reform ranging from the creation of an exemption from infringement liability for diagnostic use (2002) to a declaration that DNA sequences and products derived from them would be patent-ineligible subject matter (2007). These bills were, however, never subject of a hearing or put to a vote. A report from 2006 by the National Research Council (NRC) recommended establishing an exemption to patent infringement liability to allow independent verification of test results (Merrill and Mazza 2006). A federal advisory committee, the Secretary’s Advisory Committee on Genetics Health and Society (SACGHS), also recommended the inclusion of a statutory exemption tailored to diagnostics that was not confined to verification testing but covered all diagnostic use (SACGHS 2010). It also recommended the adoption of a research exemption. In 2011, as bills that became the America Invents Act were moving through Congress, a use exemption for verification genetic testing was proposed along the lines of the 2006 NRC report, but it was withdrawn in the face of intense

controversy. Those embroiled in *AMP v. Myriad* were concerned about how a legislative measure might colour the court decisions. In its place, Section 27 of the America Invents Act called for USPTO to submit a study of verification genetic testing, a report still pending release to Congress.

## 5 Australia

### 5.1 Background

The BRCA patent landscape is much less cluttered in Australia than in the US.<sup>16</sup> Despite this, there has been wide-ranging activity in Australia in the contexts of patent litigation, policy and law reform. This frenetic activity can in no small part be attributed to concerns about the risk that Myriad might start enforcing its BRCA patents and the likely impact that this might have on breast cancer research and diagnostic testing services.

### 5.2 Litigation

Proceedings challenging the validity of Myriad's foundational BRCA1 patent in Australia were commenced on 26 November, 2010, on the sole ground that isolated gene sequences are not patentable subject matter. Questions relating to the patentability of diagnostic methods and satisfaction of the general patentability criteria were not raised. The first instance decision in *Cancer Voices Australia v. Myriad Genetics* was handed down on 15 February, 2013. Judge Nicholas upheld the validity of the patent on the basis that '[i]solated nucleic acid is the product of human intervention involving the extraction and purification of the nucleic acid found in the cell', thus satisfying the Australian requirement for patentable subject matter of an 'artificially created state of affairs' (*National Research and Development Corporation v Commissioner of Patents* 1959). The decision has been appealed and was heard in August 2013.

The *Cancer Voices* case is unusual, not only because of the limited nature of the challenge to the Myriad patent, but also because of the parties to the case. Public interest litigation is rare in Australia. The case was initiated by Cancer Voices Australia, a national network of state-based organizations representing cancer sufferers. The other applicant is a breast cancer sufferer, Yvonne D'Arcy. In practical terms, the final decision in this case is unlikely to impact BRCA testing for two reasons: first, the patent is not being enforced in Australia, but is a 'gift' to the Australian people; second, even if the sequence claims are ultimately held to be invalid, the method claims (which are not subject to challenge in this case) are still likely to be infringed by conventional BRCA testing should GTG decide to enforce the patent in the future. It remains to be seen whether the final decision in this case will have broader legal implications for the patentability of genes in Australia and to what extent the Australian courts will follow the lead from the US Supreme Court, if at all.

### **5.3 Policy and law reform**

In 2003, the Australian Law Reform Commission (ALRC) was given a reference by the Australian government to inquire into the impact of gene patents on human health. The final report of the gene patent inquiry, *Genes and Ingenuity* (ALRC 2004), illustrates that BRCA patents were a key focal point for discussion. Despite concerns about the BRCA patents, the ALRC decided not to recommend excluding genes from the patent system but rather supported more nuanced amendments to patent law, including changes to the requirements for patentability (particularly inventive step and utility), limitations on the scope of patent claims, the introduction of an exception from infringement for research purposes and changes to the laws allowing compulsory licensing and Crown use (use for government purposes without prior authorization from the patent owner). The ALRC also called for granting agencies to provide guidelines on how patented inventions resulting from publicly funded research should be used.

Following the ALRC report, the Advisory Council on Intellectual Property (ACIP) was requested to explore the need for a statutory exception from patent infringement for experimental purposes (ACIP 2005). The ACIP recommended an experimental use exception, which largely reflects current industry practice (Nicol and Nielsen 2003). Then, in 2009, the Australian Senate commenced an independent inquiry into gene patents. Many recommendations largely mirrored those of the ALRC (Australian Senate Community Affairs Committee 2010). One of the key recommendations was that the government should respond to the senate inquiry as well as to the ALRC and ACIP inquiries. In November 2011, some seven years after the ALRC completed its report, the Australian federal government finally issued a formal response to that report as well as the ACIP and senate reports. The government largely accepted their recommendations, noting that the recently enacted *Intellectual Property Laws Amendment ('Raising the Bar') Act 2012* (Cth) addressed many of these (Australian Government 2011). The major reform aspects of the Raising the Bar Act included the introduction of an experimental use exception to infringement and modification of the inventive step and utility requirements. While the experimental use exception provides some protection for research use of patented inventions, it may have limited applicability with regard to the use of BRCA and other gene patents for genetic testing purposes because it is limited to 'research on' the patented invention.

In addition to the Raising the Bar Act, two other relevant bills have been introduced into the Australian Parliament over the past few years. The first was introduced in 2010 and sought to exclude genes and other biological materials from patenting. The bill did not proceed to vote because it was not supported by a parliamentary review committee. The reason provided by the committee was that it was considered too blunt an instrument and that it could have more negative than positive consequences (Australian Senate Legal and Constitutional Affairs Legislation Committee 2011). A second government-sponsored bill was introduced into parliament in late May 2013. In addition to a number of other amendments to patent law, this bill was intended to amend the Australian Crown use provisions to

clarify that the provision of health services (including genetic testing services) can constitute so-called 'Crown use'. Unfortunately, however, although the bill was passed by the House of Representatives of the Australian Parliament, it was not passed by the Australian Senate before the end of the parliamentary session. As a consequence, the bill has now lapsed and will need to be introduced again following the election of a new parliament towards the end of 2013. Until then, it remains unclear whether Crown use provisions can be relied on by the government to step in when patients are denied reasonable access to health care by the unreasonable act of a patent holder. Nonetheless, the fact that the government has introduced this amendment to the Crown use provisions provides a very clear indication that it is prepared to rely on these whenever the need arises.

## **6 Emerging economies and international perspective**

To our knowledge, Myriad's patent enforcement activities have mainly occurred within these developed countries. However, this does not mean that developing countries are immune from the risks associated with gene patent enforcement. Obviously, the extent of the risk facing each of these countries will vary, depending on a range of factors. First, companies may decide not to take out patents on DNA sequences in developing countries because the market in those countries does not warrant patent protection. Second, there is a wide diversity in scientific capacity and infrastructure to support health research and health care delivery. Third, the extent of patentability of DNA sequences differs (WHO 2005).

Brazil, China and India<sup>17</sup> are, however, becoming increasingly active in gene-based research and its applications. At the same time, their patent policies with respect to patent eligibility of DNA sequences diverge. The Brazilian Patent Act and Biotechnology Examination Guidelines do not consider isolated biological material an invention. Nevertheless, claims on DNA sequences are not excluded in cases where they would fit within the interpretation of a 'chemical compound'.<sup>18</sup> This approach is ambiguous (WHO 2005) and seems to be somewhere between the European and the (recently modified) US approach. The Indian guidelines from March 2013 appear to be compatible with the decision of the US Supreme Court, as they state that DNA sequences that are 'directly isolated from nature' are not patentable subject matter.<sup>19</sup> In contrast, the approach taken in the Chinese guidelines seems to be more closely aligned with the EPO policy, providing that DNA sequences, including those isolated from the human body as well as those obtained by other means, are a 'chemical substance', which is patentable.<sup>20</sup> While the Myriad controversy has not spread into these emerging economies, there may have been some spill-over effects from the policy storm in the other jurisdictions. Time will tell whether the decision of the US Supreme Court will lead to changes in the approaches to patentability in these jurisdictions.

There has been surprisingly little debate and guidance in this area at the international level, except for the initiatives of the Organization for Economic Cooperation and Development (OECD). In comparison to the fierce discussions on the national and European levels, the organizations most responsible for

regulating intellectual property (IP) law at the international level, including the World Intellectual Property Organization (WIPO) and the World Trade Organization (WTO), have generally stayed out of the limelight. The OECD filled the gap left by WIPO and the WTO with its report *Genetic Inventions, IPR and Licensing Practices* (OECD 2002) and with licensing guidelines (OECD 2006). In the report, a number of potential remedies were examined in line with the proposals by national advisory committees described above, such as ‘raising the bar’ for the patentability requirements as well as research or experimental use exceptions, compulsory licences, licensing guidelines, patent pools and clearinghouses and the role of competition law (OECD 2002).

## 7 Concluding remarks

Increasingly, patent cases are going global and are featuring on the front pages of our newspapers (see for instance *Apple v. Samsung*). The debate surrounding Myriad’s patents on BRCA1 and BRCA2, however, appears to be unique in its vigour and persistence. This paper’s primary objective was to explain what makes this case distinctive. First, litigation in the US and Australia has focused primarily on the fundamental question of whether or not a human gene is patent-eligible subject matter and not on the ‘traditional’ patentability criteria of novelty, inventive step and industrial applicability (this is different in the opposition procedures in Europe, see Section 2.2). Typically, patent cases tend to concentrate on which of the contending parties will secure exclusive rights; but BRCA cases have challenged whether genes can be patented at all. This underlines the fundamental nature of the dispute. Second, the Myriad case has occupied the minds of patients, scientists, clinical geneticists, medical doctors, patent attorneys, lawyers, academics, business people, investors, analysts, economists, journalists, politicians, policymakers, advisors and legislators for more than a decade in several jurisdictions. The case has offered a significant opportunity for new and unexpected constituencies who are not usually interested in the intricacies of patent law (Murray and van Zimmeren 2011) to enter the debate about patents and make their voices heard.

Our second objective was to emphasize the variety of legal and policy responses in Europe, Canada, the US and Australia. The chapter clearly shows the different roles of institutional actors in diverse fora. In some countries (like France and Belgium), legislatures have crafted new tailored regimes in response to Myriad’s restrictive licensing practices. Policymakers and advisory committees have proposed a variety of alternative mechanisms. Opposition (and appeal) procedures that already exist at some patent offices are another potential venue to invalidate or limit the scope of patents.

Advisory committees and councils in Europe, Canada, the US and Australia and the OECD have repeatedly issued reports questioning the rationale behind the patenting of genes and raised concerns about their implications. Notably, however, there has been little indication of a desire to create an absolute bar on the patenting of (isolated) DNA sequences in any of these reports. Rather, the reports

Table 8.1 Spectrum of ‘tools’

	<i>Europe</i>	<i>Canada</i>	<i>US</i>	<i>Australia</i>
<b>Post-grant opposition/review</b>	yes (at EPO inter partes)	no	yes (after AIA at USPTO inter partes)	no
<b>Litigation</b>	yes (national) <sup>1</sup>	yes	yes	yes
<b>Compulsory licence for public health (esp. diagnostics)</b>	yes (national)	yes (but not specific to diagnostics)	no	in process of implementation (crown use)
<b>Research exception/exemption, experimental use doctrine</b>	yes (national research exceptions)	yes (judicially created)	yes (judicially created, but very limited)	yes (but limited to ‘research on’)
<b>Diagnostic exemption</b>	no (but, very broad Belgian research exception)	no	no	no

<sup>1</sup> This will change as soon as the unitary patents and the unified patent court are operational.

have focused on rethinking the full spectrum of ‘tools’ for contesting undesirable patents and licensing practices (see Table 8.1). Some of these tools could be invoked in an early stage of the procedure at the patent office (i.e. third party submissions, re-examinations, oppositions), while others have appeared after the grant of the patent, allowing the use of the invention without the authorization of the patent owner in particular circumstances (i.e. research or diagnostic exceptions or exemptions) – with compulsory licences as a last resort mechanism. In particular, new provisions allowing compulsory licensing for diagnostic use have been incorporated into several national patent laws in Europe (including in France and Belgium) in response to the *Myriad* case and are in the process of being incorporated into the Crown use provisions in Australia. Similar proposals have also been floated in the US and Canada in the academic legal literature, but have not been formally incorporated into law.

The judgment of the US Supreme Court has invalidated patents on isolated DNA sequences, which may render some of the earlier proposals unnecessary. However, the *Myriad* storm has not fully dissipated, and it remains uncertain whether and when it might fully subside. In the months following the Supreme Court judgement, *Myriad* has sued various companies – *Ambry*, *Gene by Gene*, *Quest*, *GeneDx*, *InVita* and *LabCorp* – for patent infringement. Several companies have also counter-sued or petitioned for declaratory judgment of non-infringement in separate court procedures. As this chapter was going to press, that litigation was still pending. Depending on their outcome, those cases may begin to develop case law about gene patents.

Moreover, the US Supreme Court decision has reinvigorated global discussions about gene patents, and although the US court has made it clear that DNA is not

rendered patentable by merely being isolated, isolated DNA sequences are still patentable in many other jurisdictions, including Europe, Canada and Australia. In Europe, the European Commission must meet annual reporting obligations with regard to the development and implications of patent law in the field of biotechnology and genetic engineering through the Biotechnology Directive. In December 2012, the Commission decided to set up an expert group that will assist it in preparing its report. This may provide an opportunity to reconsider the issue of patent-eligible subject matter. Given the similarities between US and Canadian patent law, the fact that the US Supreme Court has held claims over isolated genomic DNA to be invalid will cast doubt on the validity of the same claims in Canada. In Australia, Judge Nicholas made a brief analysis of EU policy and US case law in his judgment (up until the CAFC decision, as the US Supreme Court decision was not yet available) before stating that Australian law is different and concluding that isolated sequences are patent-eligible. It remains to be seen to what extent the Australian appeal court will align with his position or follow the US Supreme Court.

Concerns about the Next-Generation Sequencing (NGS) technologies were looming in the background of *AMP v. Myriad*, although there was no clear consensus on whether NGS infringed BRCA1 and BRCA2 patents. Since NGS technologies, such as single-molecule sequencing, do not require amplifying specific exons of genes, tests using such methods may not infringe on genetic diagnostic claims that use PCR. Some experts have indeed interpreted claims on patented diagnostic methods this way, including some claims in Myriad's patents. Scholars have also argued that the composition of matter claims, such as those on BRCA1 and BRCA2 cDNA sequences, are not infringed on by NGS (Holman 2012, Price 2012). Whether Whole-Genome Sequencing (WGS) and Whole-Exome Sequencing (WES) infringed on BRCA1/2 and other gene patents has also been an area of considerable debate. While some have raised concerns that clinical WGS and WES applications face a patent thicket (SACGHS 2010) others have suggested that the problem is not so severe (Holman 2012). Additional uncertainty has also stemmed from evolving business models for clinical WGS/WES in which actual sequencing and clinical interpretation are uncoupled. This 'uncoupling' has complicated the assessment of infringement liability, because – at least in the US – infringement of most patents occurs only in cases when all steps of an alleged act of infringement are performed by a single entity (*Akamai and McKesson* [2012]). This would mean that if sequencing analysis and other steps (e.g. diagnosis or interpretation) are separated, infringement is 'split,' and no one party may be held liable.

Concerns about patent infringement have clearly deterred some providers, such as Ambry Genetics, from including BRCA in NGS breast cancer panels,<sup>21</sup> and until recently no US providers would offer testing for BRCA1/2 using NGS platforms. The fear that a legacy of claims on individual genes could impede WGS has motivated much of the opposition among the leaders at the NIH, and they – with support from the Department of Justice – have successfully argued that executive branch policy should change three decades of practice granting claims on isolated DNA at the USPTO. This proved persuasive to the US Supreme Court.

The outcome of *AMP v. Myriad* has encouraged many providers to enter the market quickly with competitive NGS tests for BRCA1/2 and to include these in multigene cancer risk panels.<sup>22</sup> However, in light of recent (*AMP v. Myriad* [2013], *Mayo v. Prometheus* [2012]) and anticipated case law (*Akamai and McKesson*, which appears to be moving up to the Supreme Court), some degree of uncertainty will likely persist, especially for diagnostic method claims. Moreover, a thorough freedom to operate analysis will be necessary for each specific test to assess the risk of patent infringement. For tests with large numbers of genes, such as cancer panels with one hundred or more genes, a freedom to operate analysis will often be quite expensive. Business practices such as bundling patent licenses through patent pools or clearinghouses (van Zimmeren *et al.* 2011) and sharing clinical data could reduce patent-related uncertainty and facilitate the development of the next generation of breast cancer diagnostics.

This opens the door for a new generation of patenting and licensing strategies, tailored to the changing diagnostic testing environment unencumbered by expensive opposition and litigation procedures. Technology is moving quickly, while courts, policymakers and legislators are trailing behind. Therefore, valuable, alternative market-based measures, such as patent pools and clearinghouses (van Zimmeren *et al.*, 2011; Nicol, 2010; OECD, 2006) that may facilitate patent licensing in the biomedical sector and that could serve as a sustainable, international model for diagnostic testing, should be welcomed more openly by legislators, industry, academia, patient advocates, professional societies and funders.

## Notes

1. A longer version of this chapter will likely be published in *Biotechnology Law Report*.
2. For reasons of uniformity, the wording of Article 27(1) of the *Agreement on Trade-Related Aspects of Intellectual Property Rights* (TRIPs 1994) is used here. The terms ‘inventive step’ and ‘capable of industrial application’ are generally deemed to be synonymous with the terms ‘non-obvious’ and ‘useful’ of US patent law.
3. Deciding on the right time to file a patent application is notoriously difficult, in particular in competitive and rapidly developing areas, such as the biomedical sector. Inventors need to take a decision as to whether they want to delay filing in order to gather more data to support the invention risk being outrun by a competitor, or alternatively they may file early to secure a filing date ahead of their competitor, risking that their application contains errors or will be rejected for lacking adequate experimental support (cf. White 2007). Determining the right time is especially challenging in jurisdictions that operate a first-to-file rather than a first-to-invent system. In a first-to-file system, the right to the grant of a patent for a given invention lies with the first person to file a patent application for protection of that invention, regardless of the date of the actual invention. In contrast, in a first-to-invent system, the date of the actual invention is decisive. Nowadays, the first-to-file system rules. In the past, Canada and the US had a first-to-invent system. Under this system, when two people claimed the same invention, such a dispute could be solved by way of an ‘interference proceeding’ between them to review evidence of conception, reduction to practise and diligence. In March 2013, the US shifted toward what has been called a first-inventor-to file system.
4. We note that the European patent system will soon become even more complex. After more than 40 years of negotiations, the EU institutions have finally agreed on

- the establishment of a ‘patent with a unitary effect’ and a specialized patent court (van Zimmeren, forthcoming). The patent is called ‘unitary patent’ or ‘patent with unitary effects’, because not all EU member states will participate. Spain and Italy did not agree with the translation arrangements associated with the unitary patent.
5. Please note that European patents are not EU patents; the membership of the EPO goes beyond the membership of the EU.
  6. Article 5 of the EU Biotechnology Directive.
  7. A patent application may claim priority from another application that was filed prior to it in order to take advantage of the filing date of information disclosed in that earlier application. Claiming priority is advantageous, because the earlier effective filing date reduces the number of prior art disclosures that need to be taken into account in the examination of the application (novelty and inventive step). This therefore increases the likelihood of obtaining a patent. The priority system, based on an international treaty (the Paris Convention), is useful in filing patent applications in many countries, as the costs of some of the filings can be delayed up to a year, and the earlier applications for the same invention will not be taken into account against the later applications.
  8. According to Article 99 EPC (1973):
 

[w]ithin nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, *any person* may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations’ (emphasis added). ‘Opposition may only be filed on the grounds that: (a) the subject-matter of the European patent is not patentable under Articles 52 to 57; (b) the European patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art; (c) the subject-matter of the European patent extends beyond the content of the application as filed, or, if the patent was granted on a divisional application or on a new application filed under Article 61, beyond the content of the earlier application as filed. (Article 100 EPC)
  9. We note that, around the time the opposition procedures were launched, the patents were assigned to the University of Utah Research Foundation.
  10. In Europe, ‘public order and morality’ is regarded as an exception to patentability: ‘European patents shall not be granted in respect of: (a) inventions the commercial exploitation of which would be contrary to “ordre public” or morality; such exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States.’
  11. The patent application should disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 83 EPC). Moreover, the patent claims shall define the matter for which protection is being sought. They shall be clear and concise and be supported by the description (Art. 84 EPC). Applications or patents may be amended in proceedings before the EPO, and applicants will be given at least one opportunity to voluntarily amend the application, but amended claims may not contain subject-matter which extends the scope beyond the content of the application as filed.
  12. Another loophole identified in the past was the lack of patent protection in Malta. A Maltese biotechnology firm, Synergene, offered a ‘legitimate’ alternative for Myriad for BRCA testing (Check 2002).
  13. In a search done in March 2013 of US patents and patent applications that include the terms ‘BRCA1’ or ‘BRCA2’ in their claims, 598 results were found, of which 143 were granted patents.
  14. Myriad’s broadest BRCA1 patents were granted the following year: US patent 5,747,282 claimed ‘isolated’ BRCA1 DNA molecules and variants and fragments with BRCA1 sequences (that is the molecules themselves); US patent 5,753,441

- claimed methods for detecting differences between a BRCA1 sequence from a person's sample and the disclosed BRCA1 reference sequence.
15. The suit initially included the USPTO as a defendant, but legal grounds under dispute were narrowed on appeal, and the USPTO was dropped as a defendant. The case name thus also changed from *Association for Molecular Pathology, et al. v. US Patent and Trademark et al. (AMP v. USPTO)* to *Myriad* as the defendant (*AMP v. Myriad*).
  16. A search in March 2013 on the Auspat database ([www.ipaustralia.gov.au/auspat/index.htm](http://www.ipaustralia.gov.au/auspat/index.htm)) for Australian patents and patent applications that included the term 'BRCA' revealed five lapsed applications. There were 20 results for 'BRCA1', with one granted patent (777341), three live applications and the remainder being lapsed or ceased applications. There were 10 results for 'BRCA2', with one repeat from the 'BRCA1' search, one live application, one refused application and the remainder lapsed or ceased.
  17. In India, since (at least) 2008, the Molecular Medicine Group of Reliance Life Sciences has been offering a diagnostic test sequencing the entire BRCA1 and BRCA2 genes (for more information, see [www.rellife.com/molecular\\_medicine.html](http://www.rellife.com/molecular_medicine.html)). We are not aware of other commercial sources in India, or in Brazil and China, at this time.
  18. Article 18 (III) of the Brazilian Industrial Property Law states that living beings, in whole or in part, are not considered patentable. Article 10 (IX) states that natural living beings, in whole or in part, and biological material encountered in nature or isolated including the genome or germplasm of any natural living being are not considered to be inventions. The law does, however, allow for the patenting of chemical products, provided they fulfil the patentability criteria. As far as DNA sequences are regarded as chemical products and the claims are written in accordance with the guidelines, they may be patentable. For more information, see Industrial Property Law No.9.279 of 14 May, 1996, available at [www.wipo.int/wipolex/en/text.jsp?file\\_id=125397](http://www.wipo.int/wipolex/en/text.jsp?file_id=125397), and 'Diretrizes de Exame de Patentes nas Áreas de Biotecnologia e Farmacêutica', available at [www.inpi.gov.br/images/stories/Diretrizes\\_Farmacêutica\\_e\\_Biotech.pdf](http://www.inpi.gov.br/images/stories/Diretrizes_Farmacêutica_e_Biotech.pdf) (31 December, 1994, under revision).
  19. According to Section 11 of India's Biotechnology Examination Guidelines (2013), Section 3 (c) of the Indian Patents Act prescribes that the mere discovery of a scientific principle or the formulation of an abstract theory or discovery of any living thing or nonliving substance occurring in nature is not a patentable invention. Products such as microorganisms, nucleic acid sequences, proteins, enzymes, compounds, etc., which are directly isolated from nature, are not patentable subject matter. However, processes of isolation of these products can be considered subject to requirements of Section 2 (1) (j) of the Act. For more information, see: <http://nbaindia.org/uploaded/Biodiversityindia/Legal/14.%20The%20Patents%20Act,%20201970.pdf> and [www.ipindia.nic.in/whats\\_new/biotech\\_Guidelines\\_25March2013.pdf](http://www.ipindia.nic.in/whats_new/biotech_Guidelines_25March2013.pdf).
  20. Section 9.1.2.2 of China's State Intellectual Property Office (SIPO) Examination Guidelines (2010), Part II, Chapter 10 provides: 'No matter it is a gene or a DNA fragment, it is, in substance, a chemical substance. The said gene or DNA fragment includes those isolated from microorganism, plant, animal or human body, as well as those obtained by other means. As stated in Section 2.1 of this Chapter, a gene or DNA fragment found in the nature and existing in its natural state is merely a discovery. It falls into "scientific discoveries" as provided for in Article 25.1 and is unpatentable. However, a gene or a DNA fragment per se and the process to obtain it are subject matters of patent protection if it is isolated or extracted for the first time from the nature, its base sequence is unknown in the prior art and can be definitely characterized, and it can be exploited industrially.' For more information, see: [http://english.sipo.gov.cn/laws/lawsregulations/201101/t20110119\\_566244.html](http://english.sipo.gov.cn/laws/lawsregulations/201101/t20110119_566244.html) and [www.sipo.gov.cn/zlsqzn/sczn2010eng.pdf](http://www.sipo.gov.cn/zlsqzn/sczn2010eng.pdf)

21. [www.pbs.org/wgbh/nova/next/body/gene-patents-and-personalized-medicine/](http://www.pbs.org/wgbh/nova/next/body/gene-patents-and-personalized-medicine/).
22. [www.genomeweb.com/sequencing/competition-myriad-heats-us-testing-labs-launch-brca-tests-hereditary-cancer-pan](http://www.genomeweb.com/sequencing/competition-myriad-heats-us-testing-labs-launch-brca-tests-hereditary-cancer-pan).

## References

- Abbott, A. (2005) 'Genetic patent singles out Jewish women', *Nature*, 436: 12.
- ACIP (2005) *Patents and Experimental Use*. [www.acip.gov.au/reviews\\_completed.html](http://www.acip.gov.au/reviews_completed.html)
- Akamai Technologies v. Limelight Networks, Inc. and McKesson Technologies, Inc. v. Epic Systems Corp.* (Fed. Cir. 2012) (en banc).
- ALRC (2004) *Genes and Ingenuity: Gene Patenting and Human Health*, Report No. 99. [www.alrc.gov.au/publications/report-99](http://www.alrc.gov.au/publications/report-99)
- AMP v. Myriad*, 569 U.S. (2013).
- AMP v. USPTO*, 653 F.3d 1329 (Fed. Cir. 2011).
- AMP v. USPTO*, 702 F. Supp. 2d 181 (S.D.N.Y. 2010).
- Australian Government (2011) *Response to Senate Community Affairs References Committee Gene Patents Report*. [www.ipaustralia.gov.au/about-us/what-we-do/gene-patents-response](http://www.ipaustralia.gov.au/about-us/what-we-do/gene-patents-response)
- Australian Senate Community Affairs Committee (2010) *Report on Gene Patents*. [www.aph.gov.au/senate/committee/clac\\_ctte/gene\\_patents\\_43/report/index.htm](http://www.aph.gov.au/senate/committee/clac_ctte/gene_patents_43/report/index.htm)
- Australian Senate Legal and Constitutional Affairs Legislation Committee (2011) *Report on the Patent Amendment (Human Genes and Biological Materials) Bill 2010*. [www.aph.gov.au/senate/committee/legcon\\_ctte/patent\\_amendment/report/index.htm](http://www.aph.gov.au/senate/committee/legcon_ctte/patent_amendment/report/index.htm)
- Baldwin, A. L. and Cook-Deegan, R. (2013) 'Constructing narratives of heroism and villainy: a case study of Myriad's BRACAnalysis and Genentech's Herceptin', *Genome Medicine*, 5.
- Benowitz, S. (2003) 'European groups oppose Myriad's latest patent on *BRCA1*', *Journal of the National Cancer Institute*, 95: 8–9.
- Brody, B. (2007) 'Intellectual property and biotechnology: the European debate', *Kennedy Institute of Ethics Journal*, 17: 69–110.
- Canadian Biotechnology Advisory Committee (2006) *Human Genetic Materials, Intellectual Property and the Health Sector*. Ottawa: CBAC.
- Cancer Voices Australia v. Myriad Genetics, Inc.* [2013] FCA 63.
- Check, E. (2002) 'Malta provides loophole for breast-cancer screen', *Nature*, 419: 767.
- Cho, M.K., Illangasekare, S., Weaver, M.A., Leonard, D.G.B., Merz, J.F. (2003) 'Effects of patents and licenses on the provision of clinical genetic testing services', *Journal of Molecular Diagnostics*, 5: 3–8.
- Council and European Parliament (1998) *Directive 98/44 of the European Parliament and of the Council of 6 July 1998 on the Legal Protection of Biotechnological Inventions*, OJL2013/13.
- Danish Council of Bioethics (2004) *Patenting Human Genes and Stem Cells*. Copenhagen: Danish Council of Bioethics.
- Davies, J. and White, M. (1996) *Breakthrough: The Race to Find the Breast Cancer Gene*. USA: Wiley and Sons.
- Debrulle, J., De Cort, L. and Petit M. (2007) 'La licence obligatoire belge pour raisons de santé publique'. In Van Overwalle, G. (ed.) *Gene Patents and Public Health*. Brussels: Bruylant.
- EPC (1973) *Convention on the Grant of European Patents* (European Patent Convention) of 5 October, 1973, as revised by the Act revising Article 63 EPC of 17 December, 1991, and the Act revising the EPC of 29 November, 2000, Decision Administrative Council of the European Patent Organisation of 28 June, 2001, OJ EPO 2001, Special edition 4: 55.

- ESHG Working Party on Patenting and Licensing (2008) 'Patenting and licensing in genetic testing – recommendations of the European Society of Human Genetics', *European Journal of Human Genetics*, 16: S3–S9.
- Gold, E. G. and Carbone, J. (2010) 'Myriad Genetics: in the eye of the policy storm', *Genetics in Medicine*, 12, 4 Suppl.: S39–S70.
- Gold, E. G. and Gallochat, A. (2001) 'The European biotech directive: past as prologue', *European Law Journal*, 7: 331–66.
- Hall, J. M., Lee, M. K., Newman, B. et al. (1990) 'Linkage of early-onset familial breast cancer to chromosome 17q21', *Science*, 250: 1684–1689.
- Holman, C. M. (2012) 'Debunking the myth that whole-genome sequencing infringes thousands of gene patents', *Nature Biotechnology*, 30: 240–44.
- Lecrubier, A. (2002) 'European institutions are challenging Myriad Genetics patent monopoly on the BRCA gene', *EMBO Reports*, 3: 1120–22.
- Llewelyn M. (2003) *Implications of Intellectual Property Rights on Public Healthcare: The UK as Case Study*; ATRIP Annual Congress, Tokyo, 4–6 August.
- Marshall, E. (1997) 'The battle over BRCA1 goes to court, BRCA2 may be next', *Science*, 278: 1874.
- Matthijs, G. and Halley, D. (2002) 'European-wide opposition against the breast cancer gene patents', *European Journal of Human Genetics*, 10: 783–84.
- Mayo v. Prometheus*, 132 S.Ct. 1289 (2012).
- Merrill, S.A. and Mazza, A-M. (eds.) (2006) *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health*, Washington, D.C., National Academies Press
- Miki, Y., Swensen, J., Shattuck-Eidens, D. et al. (1994) 'A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1', *Science*, 266: 66–71.
- Murphy, P.D., Allen A.C., Alvares C.P. et al. (1997) *Consensus Sequence of the Human BRCA1 Gene*, United States patent application, 5 August.
- Murray, K. and van Zimmeren, E. (2011) 'Dynamic patent governance in Europe and the United States: the Myriad example', *Cardozo Journal of International and Comparative Law*, 19: 287–342.
- Myriad Genetics, Inc. (2013) *2012 Annual Report*, Salt Lake City.
- National Research and Development Corporation v. Commissioner of Patents* (1959) 102 CLR 252.
- Nicol, D. (2005) 'Balancing innovation and access to healthcare through the patent system – an Australian perspective', *Community Genetics*, 8: 228–34.
- . (2010) 'Collaborative licensing in biotechnology: a survey of knowledge, experience and attitudes in Australia', *Biotechnology Law Report*, 29: 465–83.
- Nicol, D. and Nielsen, J. (2003) *Patents and Medical Biotechnology: An Empirical Analysis of Issues Facing the Australian Industry*. Hobart: Centre for Law and Genetics Occasional Paper No. 6.
- NIH (2004) 'Best practices for the licensing of genomic inventions', *Federal Register* 69.
- Nuffield Council of Bioethics (2002) *The Ethics of Patenting DNA*. London: Nuffield Council of Bioethics.
- OECD (2002) *Genetic Inventions, IPR and Licensing Practices*. Paris: OECD.
- OECD (2006) *Guidelines for the Licensing of Genetic Inventions*. Paris: OECD.
- Ontario Ministry of Health and Long-Term Care (2002) *Genetics, Testing and Gene Patenting: Charting New Territory in Healthcare*. Ontario: Ontario Ministry of Health and Long-Term Care.
- Parathasarathy, S. (2007) *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care*. Cambridge: MIT Press.

- Piper, T. and Gold, E. R. (2008) *Practices, Policies and Possibilities in Licensing in Human Genetics*. Report for Health Canada, Montreal, Canada: The Innovation Partnership. [www.theinnovationpartnership.org/data/documents/00000015-1.pdf](http://www.theinnovationpartnership.org/data/documents/00000015-1.pdf)
- Price, W.N. (2012) 'Unblocked future: why gene patents won't hinder whole genome sequencing and personalized medicine', *Cardozo Law Review*, 33: 1601-32.
- Puget, N., Stoppa-Lyonnet, D., Sinilnikova, O. et al. (1999) 'Screening for germ-line rearrangements and regulatory mutations in BRCA1 led to the identification of four new deletions', *Cancer Research*, 59: 455-61.
- Richer, J., Nelson, T.N., Evans, J. Armstrong, L. Lauzon, J. and McGillivray, B. (2012) 'CCMG statement on gene patents', *Clinical Genetics*, 82: 405.
- SACGHS (2010) *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests*. [http://oba.od.nih.gov/oba/sacghs/reports/SACGHS\\_patents\\_report\\_2010.pdf](http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf)
- Shattuck-Eidens, D.M., Simard, J., Durocher, F., Emi, M. and Nakamura, Y. (1997) *Linked Breast And Ovarian Cancer Susceptibility Gene*, United States patent application, 2 December.
- Standing Committee on Health, Parliament of Canada (2001) *Assisted Human Reproduction: Building Families*. Ottawa, Canada: Standing Committee on Health Parliament of Canada.
- Stanford University (2007) 'In the public interest: nine points to consider in licensing university technology'. <http://otl.stanford.edu/documents/whitepaper-10.pdf>
- TRIPs (1994) *Agreement on Trade-related Aspects of Intellectual Property Rights* (TRIPs-Agreement). Annex 1C to the Marrakesh Agreement establishing the World Trade Organization (Marrakesh, Morocco, 15 April, 1994).
- UC v. Lilly*, 119 F.3d 1559 (1997).
- Van Overwalle, G. (ed.) (2007) *Gene Patents and Public Health*. Brussels: Bruylant.
- Van Overwalle, G. and van Zimmeren, E. (2006) 'Reshaping Belgian patent law: the revision of the research exemption and the introduction of a compulsory license for public health', *IIP Forum*, 64: 42-49.
- van Zimmeren, E. (forthcoming) 'European patent reform: transforming the governance network and enhancing innovation?'. In E. Sorensen, A. K. Hagedorn, B. Damgaard and A. Agger (eds) *Public Innovation in Europe*. Bentham Science.
- van Zimmeren, E. and Requena, G. (2007) 'Ex-officio licensing in the medical sector: the French model'. In: Van Overwalle, G. (ed.) *Gene Patents and Public Health*. Brussels: Bruylant, 123-47.
- van Zimmeren, E., Vanneste, S., Matthijs, G., Vanhaverbeke, W., Van Overwalle, G. (2011) 'Patent pools and clearinghouses in the Life Sciences', *Trends in Biotechnology*, 29: 569-76.
- van Zimmeren, E. and Van Overwalle, G. (2011) 'A paper tiger? Compulsory license regimes for public health in Europe', *IIC*, 42: 4-40.
- White, N.L. (2007) 'Time waits for no man: deciding when to file a patent application in Europe', *Nature Biotechnology*, 25: 639-41.
- WHO (2005) *Genetics, Genomics and the Patenting of DNA: Review of Potential Implications for Health in Developing Countries*. Geneva. [www.who.int/genomics/FullReport.pdf](http://www.who.int/genomics/FullReport.pdf)
- Williams-Jones, B. (2002) 'History of a gene patent: tracing the development and application of commercial BRCA testing', *Health Law Journal*, 10: 123-46.