8 The BRCA patent controversies

An international review of patent disputes[1]

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).[2] 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.[3] 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 (Llewelyn 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:[4] 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'.[5] 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.[6] 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[7] 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).[8] 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.[9] 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',[10] but success in narrowing patent claims was mainly due to arguments based on 'traditional' patentability criteria regarding novelty, inventive step, industrial applicability and disclosure.[11] 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.[12] 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 BRAC*Analysis*™. 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.[13] 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).[14] 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[15] 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.[16] 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 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[17] 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'.[18] 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.[19] 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.[20] 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'

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

[1] 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, InVitae 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,[21] 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.[22] 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) 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). 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, and 'Diretrizes de Exame de Patentes nas Áreas de Biotecnologia e Farmacêutica', available at www.inpi.gov.br/images/stories/Diretrizes_Farmaceutica_e_Biotec.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,%201970.pdf and 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 and www.sipo.gov.cn/zlsqzn/sczn2010eng.pdf

21. 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.

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

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

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

Australian Senate Community Affairs Committee (2010) *Report on Gene Patents.* 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

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, OJ* L2013/13.

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

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

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

Williams-Jones, B. (2002) 'History of a gene patent: tracing the development and application of commercial BRCA testing', *Health Law Journal,* 10: 123–46.

9 From BRCA to BRCAness

Tales of translational research

Pascale Bourret, Peter Keating and Alberto Cambrosio

> At some point one has to pass from explanation to mere description.
> Wittgenstein, *On Certainty* § 189

The roots of this chapter[1] lie in an unexpected event – unexpected, that is, for social science observers. We are referring to the decisive and recent turn in BRCA research and related clinical activities. Previously confined largely to *hereditary* breast and ovarian cancer (HBOC), around 2004 the field shifted sharply in the direction of *sporadic* cancers, a transition marked by the coining of the notion of *BRCAness* (Turner *et al.* 2004). There are several reasons why this somewhat esoteric event attracted our attention. The most important is that the discovery of the BRCA susceptibility genes and of their role in the development of HBOC in the 1990s has often been used by science studies scholars as a prototypical illustration of the 'molecularization' of contemporary oncology (and of the life sciences in general), and, even more importantly, as a paradigmatic example of the establishment of a new kind of clinical practice centred on the management of risk rather than actual disease (see Bourret 2005, Gibbon 2007, Löwy and Gaudillière 2008, Parthasarathy 2007). These observations have occasionally been coupled with the critical remark that hereditary forms of breast cancer, which represent only a small percentage of the total number of cases, attracted more than their fair share of funding. This, critics argued, revealed an inherent bias in medical research.[2] The transition from hereditary to sporadic cancers belies or qualifies these traditional lines of argument – first, by vindicating the original investment in BRCA research, insofar as it has obviously led to insights and applications that extend beyond the narrow domain of family mutations; and second, by showing the need to revisit social scientists' focus on risk as the defining characteristic of this new set of practices, since these practices now concern patients who are suffering from the actual disease as opposed to 'asymptomatic' patients with a history of familial risk.[3]

To avoid any misunderstanding, let us clearly state that we do not claim that a concern with translational research has replaced an initial focus on risk – in other words, that in the clinical domain there has been a sharp shift away from risk. These two elements are not mutually incompatible: in the case of BRCA, while early work

centred on hereditary risk, it was also performed as part of translational research initiatives (in fact, as mentioned below, it immediately became a poster child of this kind of research), and nowadays risk continues to be an important element of the shifting BRCA landscape (see also Figure 9.5). What we are claiming is that *social scientists* (as contrasted with clinicians and biomedical researchers) have focused their attention on the risk component, thus overlooking the translational research dimension that provides for a more consistent account of the BRCA trajectory and, in particular, its present interest in sporadic cancers. As far as biomedical practitioners are concerned, we can also speak of a transition – namely, the expansion of BRCA clinical activities that used to be mostly confined to the hereditary domain to the sporadic cancer domain. As we will argue in this chapter, however, clinical researchers were investigating the clinical utility of BRCA in the sporadic cancer domain already in the 1990s, albeit with limited success – only managing to establish a robust connection around 2004–2005 via the notion of BRCAness.

How should this crossing over (to use a chromosomal metaphor) from the hereditary to the sporadic domain be described? When we asked clinicians involved in BRCA research, it was their turn to be surprised, since they saw no sharp divide between these two domains. They viewed the field from a more practical stance. Far from operating within two separate, self-contained socio-technical worlds, clinical oncologists have long been confronted with patients affected with both hereditary and sporadic forms of the disease. Work on HBOC has, of course, led to the emergence of a specific form of clinical activity – a 'clinic of mutations' (Bourret 2005, Rabeharisoa and Bourret 2009) – as well as related professional figures (the 'onco-geneticist'), but the oncology ward remains the locus of clinical encounters and exchanges between different types of patients and specialists. This is particularly true in the case of institutions such as Guy's Hospital in London, where local demographics present clinicians with an inordinate number of young black women who suffer from a very aggressive form of breast cancer known as 'triple negative' (more on this below), which has been linked to BRCAness. Basic researchers have a similar perspective – for instance, Laura van't Veer, the lead author of a highly cited paper from 2002 in *Nature* on breast cancer genomics (van't Veer *et al.* 2002, with over 3,700 citations by October 2012). Dr van't Veer has been simultaneously involved in the investigation of BRCA hereditary susceptibility genes and of somatic gene mutations at the Netherlands Cancer Institute and has participated in the hospital's familial breast cancer clinic. In keeping with this trend, we have noted that the term genetics itself has undergone a marked shift in meaning. Previously, it referred to the transmission of hereditary characters, now it refers more broadly to molecular processes, such as DNA transcription and expression, which take place in all somatic cells, and no longer concerns only germline (inherited) cells (Keating and Cambrosio 2001). This is why Dr van't Veer's dual activities, far from creating divided loyalties or a split personality, cohere in a consistent, albeit differentiated, domain of practice.

Wherein lies that domain? To answer this question, we must foreshadow our principal argument, which consists of an alternative account of the BRCA story – one that, as already suggested, defines translational research, not risk, as

the central characteristic of this domain. Translational research first emerged in the early 1990s in the course of a series of initiatives funded by the National Cancer Institute in the US. Aimed at reducing the perceived gap between basic research and clinical applications, the original impetus for these initiatives was provided by the characterization of cancer susceptibility genes, in particular BRCA (Brown 2007, Butler 2008, Kohli-Laven *et al.* 2011). More than a mere interface, or bridge, between clinical activities and fundamental research, translational research has morphed into a distinct sphere of activity, albeit one with fuzzy boundaries. The BRCA story, and the sequence of events that has led from the hereditary to the sporadic domain via the emergence of liminal notions such as BRCA-like, BRCA-associated and, especially, BRCAness, illustrates the fact that translational research operates simultaneously on several research fronts.

In our analysis, we draw on Michel Morange's (1997) fruitful suggestion that, in order to understand innovation in the life sciences, one should take into account not only the specific content of scientific practices, but also their temporal dynamics – i.e. the order in which they intersect and assemble. Innovations can fail because they come too early or, arguably, too late – at a moment when alternative configurations have already been stabilized. In the present case, BRCA translational researchers had to juggle with pre-existing and emerging areas of clinical and laboratory research on chemotherapeutic drugs, targeted therapies, molecular oncogenesis pathways, epigenetic mechanisms, pathological and clinical classifications and biomedical instrumentation (to name a few). Moreover, the need to demonstrate the clinical utility of their findings played a key role in this process. BRCA-related activities thus represent, in our view, a paradigmatic instantiation of translational research – one that cannot be reduced to the mechanical interplay of predetermined interests or strategies, given the emergent nature of the opportunities seized by researchers and clinicians.

Setting the stage for BRCAness

In 2004, three British authors from the London-based Breakthrough Breast Cancer Research Centre published a paper entitled 'Hallmarks of "BRCAness" in sporadic cancer' (Turner *et al.* 2004).[4] The article introduced a new notion, BRCAness, which became the rallying point of a number of contributions that set BRCA research on a new laboratory and clinical trajectory. The authors defined BRCAness as a *phenotype* – i.e. as a number of clinical and molecular characteristics – which some sporadic cancers share with cancers occurring in BRCA1/2 germline mutations carriers. Traditionally, the term phenotype refers to the observable characteristics of a given organism, whereas the counterpart notion of genotype refers to the genetic 'instructions' contained in the organism's germline cells. In the present case, the term phenotype was extended to include molecular entities in addition to gross anatomical features: another instance of molecularization. But what struck us as rather peculiar and thus warranting further examination is the choice of uniting BRCA – a gene and its mutations – with the phenotypic characteristics of sporadic cancers by coining the threshold notion of BRCAness.

The history of these developments is relatively complex, and we can only provide a capsule version of the events. In the 1980s and 90s, given the available technologies, a viable option for dissecting the molecular components of cancer – i.e. for identifying genes involved in its aetiology – was to analyse families harbouring several cases of the disease. So-called 'linkage studies' of large families led researchers to the chromosomal locus of susceptibility genes, such as BRCA, opening the door for their subsequent characterization. Although hereditary cancers are relatively rare, the search for inherited mutations was perceived as a shortcut, providing quick and easy access to molecular mechanisms whose understanding could subsequently inform the analysis of somatic mutations. This strategy – resting as it did on the 'ability to generalize knowledge gained from germline mutation carriers' (Maxwell and Domcheck 2012: p. 3) – panned out in several instances, but not in the case of breast cancer. While researchers successfully managed to identify a locus in 1990 and to clone BRCA1, BRCA2 and related mutations in 1994 and 1995, respectively, they failed to find equivalent BRCA mutations in cases of sporadic cancer, despite a significant research effort.[5] As was opined in an editorial from 1995 in *Nature Genetics* (Boyd 1995), 'interesting though these findings are, it remains curious that BRCA1 alterations in sporadic breast cancers have yet to be described, in spite of a mutation search the intensity of which is probably without parallel in cancer molecular genetics.'

As a result, a number of scientists in the 1990s began to look for mechanisms other than mutations that could silence BRCA and thus lead to cancer. Research on an epigenetic mechanism known as DNA methylation led to a series of contrasting results that we cannot go into detail about here. Suffice it to say that studies carried out in cells lines (Rice *et al.* 1998) were first contradicted by studies carried out on breast cancer tissue (Magdinier *et al.* 1998) and then confirmed by other studies (Catteau *et al.* 1999). A close look at these contributions shows that, from the very outset, they confronted the issue of clinical utility by trying to establish correlations between their results and subtypes of breast cancer. Pathologists had long recognized that breast cancer comes in different subtypes, which were initially described via the visual (histopathological) examination of tissues. Starting in the 1980s using first biochemical and then in the 1990s immunohistochemical methods, pathologists introduced a new classification based on the presence or absence of hormonal receptors on tumour cells, in particular the oestrogen (ER) and progesterone (PR) receptors. These were soon joined by a third entity, known as HER2 (Human Epidermal Growth Factor Receptor 2). Beyond its diagnostic and prognostic dimensions, this new categorization directly translated into therapeutic choices: hormone therapy is offered only to patients with positive hormone receptor status, while the new 'revolutionary treatment' trastuzumab (known commercially as Herceptin; Bazell 1998), introduced in 1998, targets HER2-positive patients. While the original study by Magdinier *et al.* (1998) had concluded that no connection existed between methylation status and pathological prognostic factors – thus pointing to a lack of clinical utility – now the study by Catteau *et al.* (1999) pointed to a possible, but unproven correlation between methylation and receptor status. There was, however, an additional question: did methylation

in sporadic cancers lead to the inactivation of BRCA function as mutations did in hereditary cancer? A study by Esteller *et al.* (2000) provided indications that this was the case, but its results, marred by uncertainties (Allemani *et al.* 2004), remained tentative.

Thus, to summarize the two main factors of the situation so far: (a) the strategy of looking for the genetic characteristics of cancer in hereditary cases and then transposing the results to sporadic cancers, which was successfully deployed in other instances, was unsuccessful in the case of BRCA mutations; (b) these negative findings produced a search for alternative mechanisms of silencing BRCA functions in sporadic cancers, although initial studies in the second half of the 1990s produced uncertain results that did not pass the test of clinical utility. As we will see below, the situation changed significantly in the new century when novel technologies, notably gene expression profiling (GEP), began to uncover the molecular nature of breast cancer. In particular, GEP changed 'the way breast cancer is perceived . . . breast cancer is now perceived as a heterogeneous group of different diseases characterized by distinct molecular aberrations, rather than one disease with varying histological features and clinical behaviour' (Reis-Filho and Pusztai 2011: p. 1812). How did this lead to BRCAness?

BRCA-associated, BRCA-like and BRCAness

The availability of the new GEP technology did not necessarily simplify our understanding of breast cancer. In fact, one could argue that it made it even more complex, because clinicians and researchers now had to cope with three different ways of framing the disease: (a) GEP studies, (b) immunohistochemical investigations carried out by research pathologists and (c) the line of work initiated by the aforementioned methylation studies postulating the existence of a BRCA phenotype.

The first series of findings appeared in 2000 when Perou *et al.* published an article in *Nature* that introduced their novel GEP-based classification of breast cancers. It has since become a classic (over 4,000 citations by October 2012; see also the follow-up article by Sorlie *et al.* 2001, which has received almost 3,200 citations by the same date). A doctor of philosophy rather than a clinician, Charles Perou embodies the transgressive ethos of translational research, having achieved not only the rank of professor of genetics, but also of pathology and laboratory medicine. Perou's contribution came at a time (in the late 1990s) when BRCA-mutated tumours could not be distinguished clinically from sporadic cancers. Practitioners generally agreed that 'these kinds of family syndromes [HBOC] have no clinical definition' (Essioux and Bonaïti-Pellié 1997: p. 38). Nonetheless, the clinical specificity of these tumours quickly became a burning issue among clinicians in charge of treating patients already affected by the disease, and of implementing chemopreventive strategies for patients at risk of getting the disease. At the turn of the century, it became clear that BRCA tumours are largely ER receptor-negative, and yet practitioners (for instance, in the French Cancer Genetics Group; see Bourret *et al.* 2006) continued to ask: 'are BRCA-negative receptor

tumours and sporadic negative receptor tumours identical?' (fieldwork, 22 April, 2003). Perou and his team did not immediately tackle this issue, as they had not included cases of BRCA carriers in the work leading to their 2000 publication. The resulting classification did not feature a specific BRCA category but did, however, comprise a molecular subtype termed 'basal-like tumours' that would later overlap with BRCA. Specifically, a team of researchers that included Perou (Grushko *et al.* 2004) subsequently examined a collection of cases they termed 'BRCA1-associated breast cancers' and concluded that 'the *BRCA1* mutant tumors appear to have a profile that is most consistent with the basal-like subtype' (p. 506), thus connecting sporadic basal-like tumours and BRCA mutant tumours.

In the meantime, at the phenotypic corner of the triangle, an international (US, UK, Sweden) consortium (Hedenfalk *et al.* 2001) had used GEP to compare hereditary and sporadic breast cancers and reached the conclusion that some sporadic and BRCA hereditary cancers might be related at the level of phenotype rather than genotype (Hedenfalk *et al.* 2001). Additional contributions brought partial support for the phenotypic hypothesis: Jazaeri *et al.* (2002) found indications (albeit in ovarian cancer) of the existence of 'BRCA-like' phenotypes in sporadic cancers, while van't Veer *et al.*'s highly cited paper from 2002 also described, albeit in passing, a sporadic tumour that ended up being classified as BRCA, most likely because of a methylation mechanism. Figure 9.1 shows the number of citations received by the early papers connected to the phenotypic hypothesis. As can be seen, the paper by Magdiner *et al.* (1998), which concluded that methylation patterns lacked clinical utility, did not fare as well as the paper by Catteau *et al.*

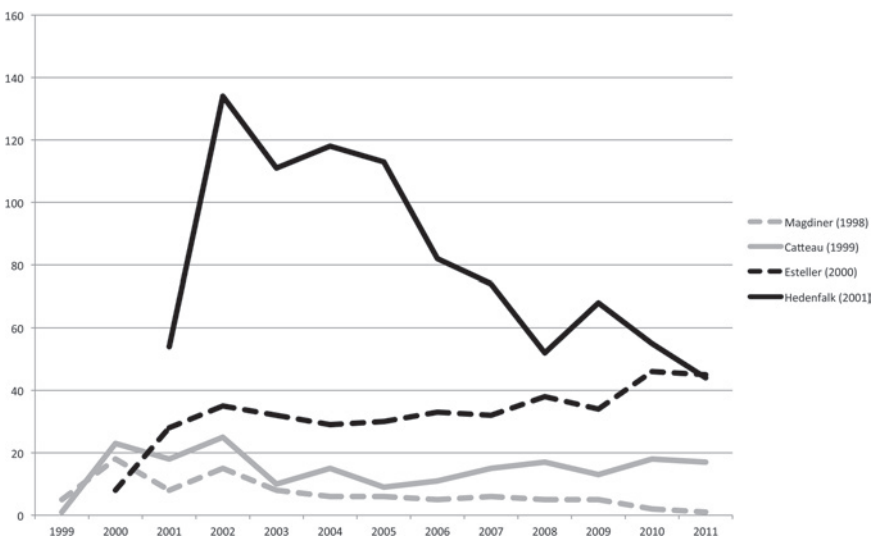

Figure 9.1 Number of citations received by the Magdiner *et al*. (1998), Catteau *et al.* (1999), Esteller *et al.* (2000) and Hedenfalk *et al.* (2001) articles.

Source: Thomson Reuters Web of Science.

(1999), which reached the opposite conclusion, and both attracted less attention than the paper by Esteller *et al.* (2000), which hypothesized methylation's role of inactivating BRCA. However, among these four early papers, the prize for most citations clearly goes to Hedenfalk *et al.* (2001), the paper that postulated the existence of a phenotypic, rather than genotypic, connection between hereditary and sporadic breast tumours. These findings immediately attracted the attention of researchers in the field, as the quick rise in citations makes clear.

Pathologists had not been passively waiting for molecular biologists to reclassify diseases. Since GEP is a 'grind and bind' approach whereby cells are destroyed to extract RNA, pathologists opted for immunohistochemical (IHC) technologies that display the presence or absence of receptors *in situ* (thus preserving tissue and cellular structures for histopathological examination) and as such are consistent with their traditional *modus operandi*. By characterizing tumours in terms of three main receptors (ER, PR and HER2), pathologists developed a system whose clinical utility, unlike the more experimental GEP molecular subtypes, was hard to dispute, since it had been evolved in constant interaction with clinical activities. While this bifurcation created a further puzzle – namely, how to align the two approaches – for our present purposes, the relevant issue is that pathologists defined a breast cancer category characterized by the absence of the three main receptors (ER, PR and HER2), which they then called, somewhat unimaginatively, triple-negative breast cancers. It soon appeared that BRCA mutant tumours were often triple-negative while, vice-versa, a large proportion of triple-negative tumours harboured BRCA defects.

The origins of triple-negative breast cancer (TNBC) as a nosological category cannot, however, be ascribed to the mechanical application of IHC tests. Many uncertainties surround the determination of IHC status, and several national and international standardization initiatives have been launched during the last decade in an attempt to increase the reliability and especially the consistency of IHC measurements, which are ultimately triangulated with clinical variables.[6] Moreover, as a nosological entity, TNBC is far from robust, as evinced by articles with titles such as 'Triple negative breast cancer: disease entity or title of convenience?' (Carey *et al.* 2010) or 'Triple negative breast cancer: proposals for a pragmatic definition' (Eiermann *et al.* 2012). Indeed, TNBC is also pragmatically defined as those tumours that do not respond to existing treatments. A number of agents, such as tamoxifen, have long been used for treating hormone-positive patients, and when the trastuzumab became available for HER2-positive patients, this led to the definition of triple-negative tumours as those tumours for which no treatment existed. As noted by a UK oncologist, 'The reason why we know it [TNBC] now is just because Herceptin was developed. . . . It's definitely not a biological entity . . . it's a practical clinical entity based on practicality, which means that we need to find treatments for it' (interview, 24 June, 2011). A measure of both the uncertainties surrounding TNBC and of its increasingly strategic position in breast cancer is provided by a surprisingly specific statement from 2012 by the U.S. Senate committee overseeing funding for the National Cancer Institute. No doubt spurred by the present climate of patient activism, the committee reported

that it 'remain[ed] concerned about the toll of triple negative breast cancer and urge[d] NCI to collaborate with [other agencies] to help improve treatment and survival rates' (Ong 2012).

The situation we just described is neatly summarized by a Venn diagram consisting of three overlapping circles of basal-like, triple-negative, and BRCA-associated breast cancers (see, for example, Figure 9.1 in Carey *et al.* 2010). In other words, BRCAness emerged from the timely intersection of these three lines of work. As the next section shows, however, the situation was more complex.

BRCAness, at last

Let us now return to BRCAness. The article by Turner *et al.* from 2004, which introduced this term, and the follow-up article by the same team (Farmer *et al.* 2005) carried the notion of a BRCA *phenotype* well beyond the scope covered in the paper by Hedenfalk *et al.* (2001). Comparing the citations received by these three papers, Figure 9.2 is consistent with the hypothesis that, while the article from 2001 attracted the attention of researchers, the contributions from 2004 and 2005 displaced it and became the *locus classicus* for subsequent work on this topic. Let us examine how.

The authors of the paper from 2004 explicitly refer to Perou's molecular subtypes as the starting point for their exploration of BRCAness, drawing a direct connection between familial BRCA1 tumours and basal-type sporadic tumours. Rather than assimilate the two, however, they retained and brought to the fore the distinctive

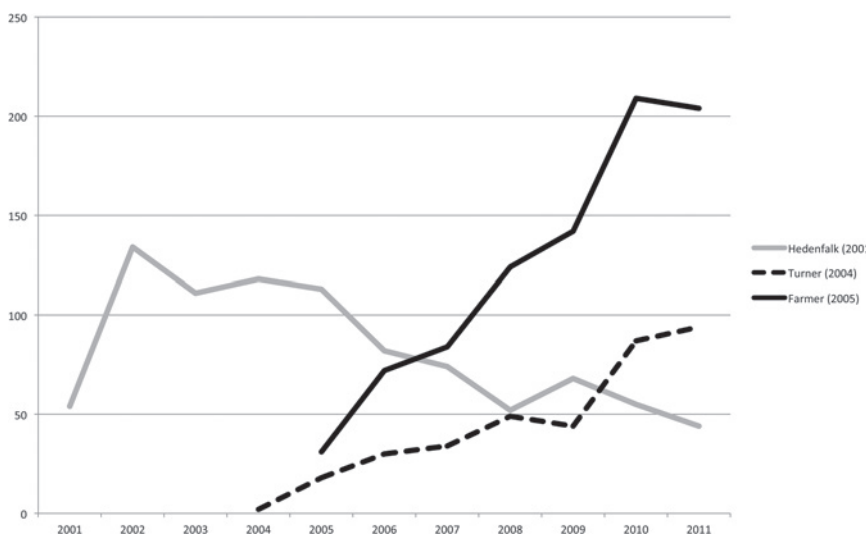

Figure 9.2 Number of citations received by the Hedenfalk *et al.* (2001), Turner *et al*. (2004) and Farmer *et al.* (2005) articles.

Source: Thomson Reuters Web of Science.

nature of the phenotype. They claimed that the inactivation of BRCA gene function might have causes other than mutations or methylation, including the 'dysfunctions of other genes acting in the same biochemical pathway'. According to the authors the elucidation of 'the many components of the pathways and numerous potential mechanisms of inactivation' was one of the main challenges of the new emerging group of 'BRCAness tumours' (Turner *et al.* 2004: p. 818). The key term here is 'pathways': it signals a shift from a narrow focus on genes and mutations to the examination of the complex chains of cellular reactions in which genes and their products are (dys)functionally involved. While we cannot go into detail here about this important transition, it should be noted that it did not take place in the contained atmosphere of laboratories, but in close connection to therapeutic investigations. The sobering clinical fact was that drugs designed to block specific pathological proteins had short-term effects, as tumours quickly developed resistance to those substances. This was ascribed to a tumour cell's capacity to develop alternative pathways to circumvent the original pathway blocked by the drug.

BRCAness did more than enshrine the existence of a BRCA phenotype; it did so by explicitly correlating BRCA phenotype with DNA repair pathways (Box 1 in Turner *et al.* 2004). The identification and characterization of BRCA genes as cancer susceptibility genes in the previous decade had led researchers to investigate their role and to conclude that their key function was to repair damaged DNA. Mutations disable this tumour-suppressing function, thus leading to an accumulation of DNA breaks and errors and, in the end, to cancer.[7] BRCAness meant that, in sporadic cancers, factors other than mutations could disable the BRCA-associated repair pathways, causing the affected cells to behave as their hereditarily mutated counterparts. But the import of the new notion did not stop there. In a remarkable argumentative turn, Turner and colleagues suggested that clinicians could, in fact, take advantage of these biopathological processes by translating them into a therapeutic strategy to fight cancer. In other words, in addition to clinically expanding the BRCA domain to sporadic cancers, the London group simultaneously opened therapeutic avenues. This is where, as detailed below, BRCAness intersected with two older lines of work: the mechanisms described by the notion of 'synthetic lethality', and pharmaceutical research on compounds known as PARP inhibitors.

Before examining these intersections, we would like to emphasize the translational nature of this line of work. As shown in Figure 9.2, the article by Farmer *et al.* (2005), which was published side-by-side with an article by a British–Swedish team (Bryant *et al.* 2005) proposing a similar approach, is the most cited of the two BRCAness articles published by the London group. This is hardly surprising, insofar as in this 'seminal article' (Domcheck 2011: p. 4224) 'a new concept' in cancer chemotherapy was detailed – namely, the therapeutic strategy outlined in the more programmatic paper from 2004. In order to get a sense of its reach, we can identify who, and in what domain, cited that article. We can do so by extracting from the citing articles a list of the journals they co-cite (two journals are co-cited when they are cited together in the same reference list). Using network analysis software, we can then map clusters of co-cited journals, thus providing an indication of the specialty areas corresponding to the citing journals. Figure 9.3

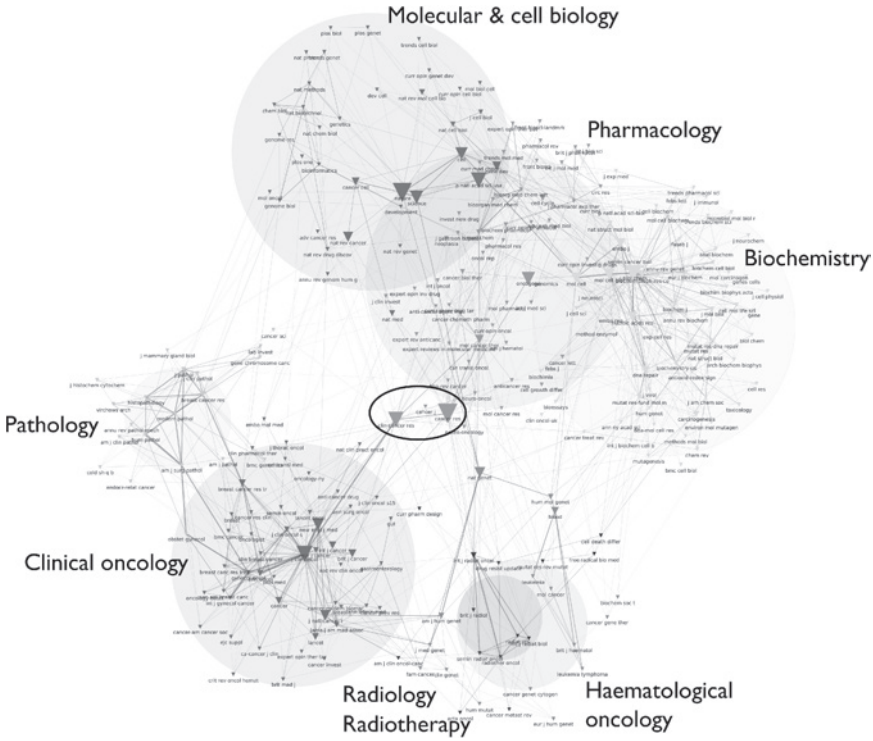

Figure 9.3 Co-citation map of the journals cited by articles citing Farmer *et al.* (2005). We processed and mapped co-citation data downloaded from Thomson Reuters Web of Science with CorTexT, a software platform for the analysis of heterogeneous and semantic networks (www.cortext.fr).

shows the resulting map with a number of clinical specialties at the bottom; at the top are fundamental research specialties. Two large nodes (the size of the nodes is proportional to the number of citations) representing the journals *Cancer Research* and *Clinical Cancer Research* connect these two poles, thus displaying once again the translational research nexus.[8] What is more, in the portrait *Nature* devoted to his work, astutely entitled 'Talking up translation' (Cressey 2010), Alan Ashworth, the last author of the BRCAness paper from 2004, openly advocated a translational approach as the necessary framework for producing clinically relevant research. Such a framework, as we endeavour to show, implies not only the intersections of separate lines of work – i.e. the establishment of a *collective,* which, as pointed out by Michel Callon (2012), should not be equated with a community (epistemic of otherwise), insofar as its members do not necessarily share a common understanding or common approaches (see also Amin and Cohendet 2004) – but also a temporal dimension, without which, as Morange (1997) maintains, such a collective would fail to assemble. This can be further exemplified by examining two additional intersections.

Synthetic lethality and PARP inhibitors: more intersections

As mentioned in the previous section, the London team proposed turning the tables on cancer and exploiting the properties of BRCA-mutated or BRCA-like cells – in other words, those at the origin of cancerous formations – in order to kill those same tumour cells via a mechanism called synthetic lethality. This somewhat complex notion is predicated on the aforementioned understanding of the plasticity of cellular processes: when a vital pathway is blocked by a chemotherapeutic drug or an antibiotic, an alternative pathway steps in to reestablish the original functions, thus creating resistance to treatment. In the present case, tumour cells with BRCA mutations have lost the capacity to use this major DNA repair pathway. When cisplatin – a key component of oncology's chemotherapeutic arsenal – plays havoc with those cells' DNA, they are killed. Cancer, however, bounces back by activating an alternative pathway known as PARP, and cisplatin-resistant tumours take over. If *both* pathways are simultaneously blocked, for instance when using a second chemotherapeutic agent from the PARP-inhibitors' family, the cells die (hence the notion of a combination that is both *synthetic* and *lethal*), or at least this is the hypothesis. Most importantly, in the present case, the London team did not confine their hypothesis to 'inherited BRCA1 or BRCA2 deficiency *per se*' but suggested that 'this approach may be more widely applicable in the treatment of sporadic cancers with "BRCAness" or other impairments of the homologous recombination pathway' (Farmer *et al.* 2005: pp. 919–20).

Where do synthetic lethality and PARP inhibitors come from? The geneticist Theodosius Dobzhansky (1900–1975) first advanced the notion of synthetic lethality in 1946, well before the advent of cisplatin, BRCA and present-day notions of pathways. Defined in simple terms as the process whereby mutations in several genes lead to cell death whereas a mutation in a single one of those genes does not lead to such an outcome, it was used in the study of model organisms (in particular the fruit fly *Drosophila* and the yeast *Saccharomyces cerevisiae*) as a tool (a 'genetic screen') to explore cellular processes and genotype–phenotype relations. Fast-forwarding to the late 1900s, an influential article by Hartwell *et al.* (1997) adopted Dobzhansky's notion in a programmatic article on the integration of genetic approaches in the discovery of anticancer drugs.[9] The London team seized this reconfigured notion in turn and translated it into the specific BRCAness domain, first by extending its definition from mutation-based transformations to phenotypic deficiencies, and second by changing it from a laboratory tool into a chemotherapeutic strategy. In order to do this, however, a second intersection was necessary – namely, a similarly long-lived line of work on PARP inhibitors.

Although the first PARP enzyme was described in the 1960s (Chambon *et al.* 1963), research on drugs that inhibit these enzymes did not begin until the 1980s. Figure 9.4 shows the increase of publications on this topic, which since 1995 has undergone marked growth (the drop between 2005 and 2008 can be accounted for through institutional factors – namely, the fusion of pharmaceutical research programmes following corporate mergers; see Ferraris 2010 and the inset in Figure 9.4). PARP-1 had been touted as a 'viable cancer target' since the 1980s, when

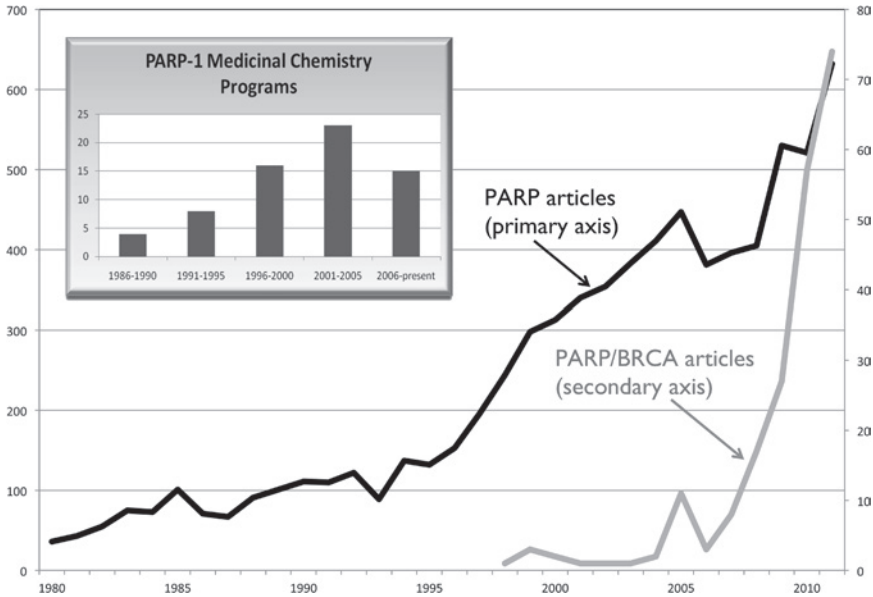

Figure 9.4 Number of articles published on PARP (primary axis) and on PARP and BRCA (secondary axis). The inset shows the number of PARP industrial programmes.

Source: PubMed. Inset reprinted with permission from Ferraris, D. V. (2010) 'Evolution of Poly(ADP-ribose) Polymerase-1 (PARP-1) inhibitors. From concept to clinic', *Journal of Medicinal Chemistry,* 53: 4561–84, © 2010, American Chemical Society.

researchers first proposed that 'dramatic synergistic potentiation of cell killing by alkylating agents and [PARP] inhibitors may be of use in the treatment of human leukaemia' (Durkacz *et al.* 1980: p. 595). This suggestion, however, came too early and thus went unheeded. In fact, the history of programmes set up to develop PARP inhibitors in the 1990s clearly resembles a case of drugs looking for a disease insofar as the medicinal chemistry programmes wandered through a series of therapeutic domains, such as cardiology, inflammation, diabetes and, of course, cancer (Ferraris 2010). PARP inhibitors did not find a disease until they crossed the path of BRCAness. Figure 9.4 also shows (on a different scale) the very rapid growth of articles on PARP and BRCA, beginning in 2006.

This was a mutually constitutive process: PARP inhibitors embarked on a new career thanks to BRCAness and, at the same time, BRCAness became a therapeutic object rather than a purely conceptual one. One of the consequences is that the clinical utility of BRCA testing may be profoundly redefined. According to the Manchester medical geneticist Gareth Evans (personal communication, August 2012), 'the recent development of drugs that target the homologous recombination repair deficiency typical of BRCA-null cancer cells [i.e. PARP inhibitors] has led to an increased referral of women who have developed TNBC to genetic services for rapid genetic testing' (see also Evans *et al.* 2011). The ripple effect of

the redefinition of the therapeutic role of PARP inhibitors can also be felt beyond TNBC, as it leads clinicians to ask whether *all* women with breast cancer should be tested for mutations at the time of diagnosis (Narod 2012).

Did these intersections give rise to an unmitigated success story? Not quite. After very promising results in early-phase clinical trials, PARP inhibitors have so far produced disappointing outcomes in phase III trials in both hereditary and sporadic breast cancer (see, for example, Guha 2011). These results have not led to the rejection of the hypothesis that PARP inhibitors represent a promising therapeutic avenue. In fact, a number of authors (Domcheck *et al.* 2011, Maxwell and Domcheck 2012), while resorting to their own form of critical inquiry (Boltanski and Thévenot 1999, Lynch 1982), have complained that therapeutic research related to BRCA-associated cancers has stalled – not due to intrinsic deficiencies, but because of a number of regulatory and socio-economic issues. These include the small size of the target patient population, although targeted therapies have been approved for tumours that affect even smaller numbers of patients. Indeed, BRCAness would expand the number of patients eligible for the new treatment. Another issue is the regulatory requirement of clearly defining the target population – namely, via an approved diagnostic test. The situation here is marred by uncertainties, especially in the US, given the monopoly of Myriad Genetics on BRCA testing thanks to its controversial patents (see, for example, Kepler *et al.* 2010), the ongoing and equally controversial attempts to modify the FDA regulatory framework for diagnostic tests (Bourret *et al.* 2011), and the fact that, to date, only one experimental test has been proposed for BRCAness (Konstantinopoulos *et al.* 2010). This is clearly a case of an innovation having arrived late on the scene, as the intellectual property field has been already staked out, depending, of course, on ongoing litigation.

A third issue concerns the ethical and regulatory obstacles resulting from the availability of active therapies for breast cancer, which makes comparisons of the new agents with the existing standard of care especially difficult. One could argue, in this respect, that BRCA-associated cancers, given their often dismal prognosis and the fact that they do not respond to existing therapies, should not be conflated with the general breast cancer category. While this is another instance of the kind of problems experienced by late arrivals, it is also a telling example of genomics' potential to reshuffle established disease ontologies and the practices they support. Last but not least, we ought to mention a more 'intrinsic' issue, as illustrated by the following episode. The excitement generated by the positive results of a phase II clinical trial gave way to disappointment when iniparib, the first PARP inhibitor to reach the phase III stage, failed to show the expected benefits at that stage before turning out to be not a PARP inhibitor after all (Rios and Puhalla 2011, Roop 2011). This episode extends ontological uncertainty to include the drugs themselves, confirming the relational and thus evolving nexus of drugs and diseases (Cambrosio *et al.* 2012).

It could be objected that our account of BRCAness relates to activities that primarily concern laboratory or, at best, clinical research rather than actual clinical practices. As shown in this paper, however, and as a component of translational

research initiatives, BRCAness is hardly confined to the laboratory. Moreover, in a highly protocolized domain such as oncology, any sharp distinction between clinical research and clinical routines is moot: today's experimental protocol is tomorrow's routine treatment. In the present case, the management of breast cancer patients with BRCA or BRCA-like mutations or anomalies is a topical issue in breast cancer clinical circles. A quick search in clinicaltrials.gov (a registry and results database established by the US National Health Institute, listing publicly and privately supported clinical trials) shows that, at the time of writing this article (November 2012), there were 104 clinical trials indexed with 'PARP', of which 39 were co-indexed with 'breast cancer', while of the 154 clinical trials indexed with 'BRCA', 24 were co-indexed with 'PARP' – not a negligible number.

Conclusion

We will conclude with an image: a map of the BRCA domain from 2009–2012. Figure 9.5 shows the semantic network of terms extracted from the titles and abstracts of articles published during this period. We used text-mining techniques to select relevant terms and mapped their co-occurrences with network analysis

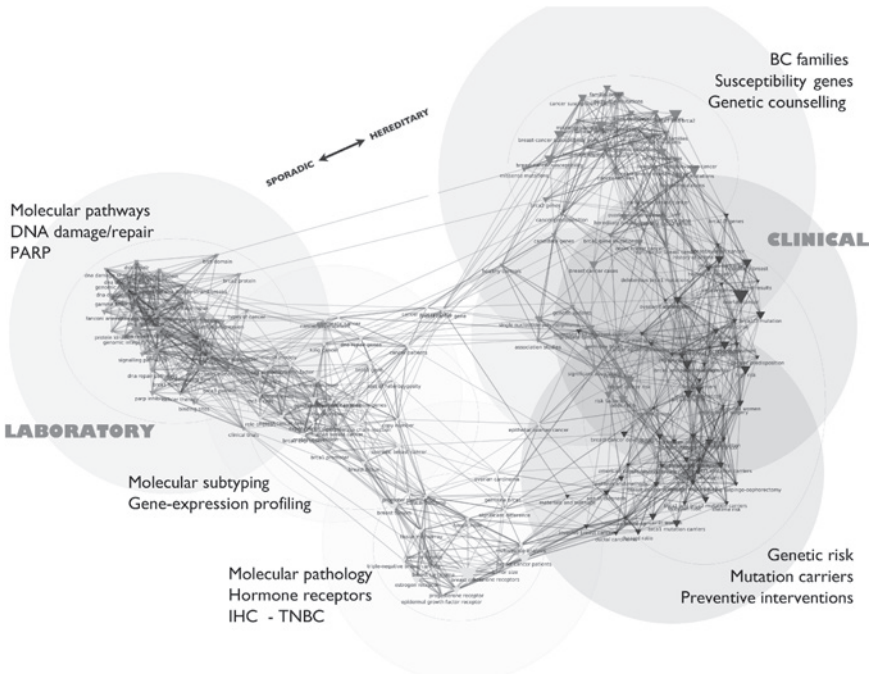

Figure 9.5 Semantic network of concepts extracted from the titles and abstracts of BRCA-related articles published from 2009–2012. We used CorTexT (see Figure 9.3) to text-mine titles and abstracts of articles downloaded from PubMed and to map the resulting concepts.

software. The map as a whole displays the thematic structure of this domain. On the right, we see the more traditional clinical pole, with a cluster on the top referring to the hereditary domain as defined by the analysis of familial forms of cancer and germline mutations. At the bottom is another large cluster focused on the assessment of risks for mutation carriers as well as preventive interventions, such as mastectomy and salpingo-oophorectomy. The left side of the map displays the laboratory pole characterized by a cluster on investigations of DNA damage, DNA repair pathways and PARP inhibitors and by a cluster on gene-expression profiling and molecular subtyping. At the bottom centre we find a cluster corresponding more closely to pathology, its immunohistochemical analysis of hormone receptors and the resultant definition of triple-negative breast cancers.

The left and right sides of the map also display a tension between the sporadic and hereditary domains. However, as described in this chapter, we should understand this tension as both creative and essential, a tension predicated on the very existence of the translational continuum. This does not mean that separate areas cannot be distinguished within the continuum, but that these areas are the components of a hybrid research collective (to use Callon's notion once again), which interact and collaborate in ways that go beyond explicit initiatives. Less a translation from one domain to another (from hereditary to sporadic cancer), these activities amount to the reconfiguration of a cancer research domain that generates novel entities, such as BRCAness, as well as related lines of therapeutic innovation. Once again, the term 'emergence' is meant to emphasize the temporal dimension of these processes. Future work exploring these processes should focus on characterizing the ongoing trajectory of BRCAness – for instance, by investigating the circulation of this notion and of the practices to which it relates, and its implementation in clinical trials and clinical settings. In parallel, one could explore how the events related in this chapter contribute to the ongoing redefinition of the notion of patient, how these refer back to existing notions of familial risk and how they do or do not contribute to the characterization of the elusive notion of 'personalized medicine'. For now, we hope we have demonstrated the heuristic interest in exploring the BRCA domain by conceiving of it as the result of multiple associations with different entities and processes, rather than reducing it to preestablished categories that do not take into account the fluidity of research practices, their capacity to shift boundaries and connect previously unconnected elements, and thus lead to novel configurations.

Notes

1. Research for this chapter was made possible by grants from the Canadian Institutes for Health Research (CIHR MOP-93553), the Fonds Québécois de la Recherche sur la Société et la Culture (FQRSC SE-124896 and SE-164195), the Social Sciences and Humanities Research Council of Canada (SSHRC 410–2011–2290) and the French National Cancer Institute (INCa 0610/3D1418/SHS08). Our special thanks go to Jean-Philippe Cointet and Andrei Mogoutov, who developed the software platform CorTexT and who contributed decisively to the production of

Figure 9.5. We would also like to thank the scientists and clinicians who kindly agreed to be interviewed, and the participants of the 'BRCA Gene Research and Medical Practices: A Comparative Transnational Social Science Workshop' (Brocher Foundation, Geneva, 5–7 December, 2011) for their comments and suggestions.

2. HBOC accounts for less than 10 per cent of all breast and ovarian cancer cases; moreover, only a subset of HBOC involves BRCA mutations. As for the alleged reasons for the focus on BRCA, critics mention biomedical 'reductionism' and the unwillingness to tackle alternative (including environmental) causes (Klawiter 2008, McCormick *et al.* 2012).
3. See also Nelson *et al.* (2013) for a discussion on the shift from risk to actionability in recent oncology.
4. The title is a clear reference to a celebrated paper (almost 10,000 citations by October 2012) published in 2000 by Hanahan and Weinberg under the title 'The hallmarks of cancer'.
5. While somatic BRCA mutations surfaced in ovarian cancer, they remained exceedingly rare.
6. See, for instance, the guidelines jointly designed by the American Society of Clinical Oncology and the College of American Pathologists for ER and PR testing (Hammond *et al.* 2010) and for HER2 testing (Wolff *et al.* 2007). For more on the debates surrounding these pronouncements, see, for example, Allison (2010) and Schmidt (2011)
7. This is an extremely simplified description, as many other factors are involved in these processes. But for our present purpose it should suffice.
8. It could be argued that Figure 9.3 shows a dichotomous rather than a translational domain, but this is due to the fact that co-citation maps display a more conservative view of the field – one based on the contributions authors consider key to their domain. An inter-citation map of the same domain (not shown), which displays a more comprehensive view of the relations between the field and its subfields, shows a densely interconnected network with no clear subdivisions. The two approaches are, in fact, complementary; nonetheless, we have opted for the co-citation map because it allows for a clearer identification of the subfields concerned in the article by Farmer *et al.* For a discussion on these methodological issues, see Jones *et al.* (2011).
9. Hartwell *et al.* (1997) did not cite the original Dobzhansky article; instead they cited a review from 1995 by Doye and Hurt, also unrelated to cancer. A recent article by Bernards (2012) has repackaged the synthetic lethality approach as a general strategy for overcoming drug resistance in the case of targeted therapies.

References

Allemani, C., Sant, M., Berrino, F. et al. (2004) 'Prognostic value of morphology and hormone receptor status in breast cancer – a population-based study', *British Journal of Cancer*, 9: 1263–68.

Allison, M. (2010) 'The HER2 testing conundrum', *Nature Biotechnology,* 28: 117–19.

Amin, A. and Cohendet, P. (2004) *Architectures of Knowledge. Firms, Capabilities, and Communities.* Oxford: Oxford University Press.

Bazell, R. (1998). *Her-2: The Making of Herceptin, a Revolutionary Treatment for Breast Cancer.* New York: Random House.

Bernards, R. (2012) 'A missing link in genotype-directed cancer therapy', *Cell,* 151: 465–68.

Boltanski, L. and Thévenot, L. (1999) 'The sociology of critical capacity', *European Journal of Social Theory,* 2: 359–77.

Bourret, P. (2005) 'BRCA patients and clinical collectives. New configurations of action in cancer genetics practices', *Social Studies of Science,* 35: 41–68.

Bourret, P., Mogoutov, A., Julian-Reynier, C., Cambrosio, A. (2006) 'A new clinical collective for French cancer genetics: a heterogeneous mapping analysis', *Science, Technology, and Human Values*, 31: 431–64.

Bourret, P., Keating, P. and Cambrosio, A. (2011) 'Regulating diagnosis in post-genomic medicine: re-aligning clinical judgment?' *Social Science and Medicine,* 73: 816–24.

Boyd, J. (1995) 'BRCA1: more than just a hereditary breast cancer gene?' *Nature Genetics,* 9: 335–36.

Brown, H. (2007) 'Translational cancer research in the USA', *Molecular Oncology,* 1: 11–13.

Bryant, H.E., Schultz, N., Thomas, H. D. et al.(2005) 'Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase', *Nature*, 434: 913-17.

Butler, D. (2008) 'Crossing the valley of death', *Nature,* 453: 840–2.

Callon, M. (2012) 'Les sciences sociales confrontées aux nouvelles pratiques de recherche et d'innovation' (manuscript submitted for publication).

Carey, L., Winer, E., Viale, G. et al. (2010) 'Triple-negative breast cancer: disease entity or title of convenience?' *Nature Reviews Clinical Oncology*, 7: 683–92.

Cambrosio, A., Keating, P. and Mogoutov, A. (2012) 'What's in a pill? On the informational enrichment of anti-cancer drugs'. In Gaudillière, J. P. and Hess, V. (eds) *Ways of Regulating Drugs in the 19th and 20th Centuries.* Houndmills: Palgrave, 181–205.

Catteau, A., Harris, W. H., Xu, C. F. and Solomon, E. (1999) 'Methylation of the BRCA1 promoter region in sporadic breast and ovarian cancer: Correlation with disease characteristics', *Oncogene*, 18: 1957–65.

Chambon, P., Weill, J. D. and Mandel, P. (1963) 'Nicotinamide mononucleotide activation of new DNA-dependent polyadenylic acid synthesizing nuclear enzyme', *Biochemical and Biophysical Research Communications,* 11: 39–43.

Cressey, D. (2010) 'Talking up translation', *Nature,* 463: 422–3.

Dobzhansky, T. (1946) 'Genetics of natural populations: XIII. Recombination and variability in populations of Drosophila Pseudoobscura', *Genetics,* 31: 269–90.

Domchek, S. M., Mitchell, G., Lindeman, G. J. et al. (2011) 'Challenges to the development of new agents for molecularly defined patient subsets: lessons from BRCA1/2-associated breast cancer', *Journal of Clinical Oncology*, 29: 4224–6.

Doye, V. and Hurt, E. C. (1995) 'Genetic approaches to nuclear pore structure and function', *Trends in Genetics,* 11: 235–41.

Durkacz, B. W., Omidiji, O., Gray, D. A. and Shall, S. (1980) '(ADP-ribose)n participates in DNA excision repair', *Nature*, 283: 593–96.

Eiermann, W., Bergh, J., Cardoso, F. et al. (2012) 'Triple negative breast cancer: Proposals for a pragmatic definition and implications for patient management and trial design', *Breast*, 21: 20–26.

Essioux, L. and Bonaïti-Pellié, C. (1997) 'Epidémiologie des prédispositions héréditaires aux cancers et évaluation du risque héréditaire en oncologie'. In Bignon, Y. J. (ed.) Oncogénétique. Vers une médecine de présomption/prédiction. Paris: Lavoisier, 33–47.

Esteller, M., Silva, J. M., Dominguez, G. et al. (2000) 'Promoter hypermethylation and BRCA1 inactivation in sporadic breast and ovarian tumours', *Journal of the National Cancer Institute*, 92: 564–69.

Evans, D. G., Howell, A., Ward, D. et al. (2011) 'Prevalence of BRCA1 and BRCA2 mutations in triple negative breast cancer', *Journal of Medical Genetics*, 48: 520–2.

Farmer, H., McCabe N., Lord, C. J. et al. (2005) 'Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy', *Nature*, 434: 917–21.

Ferraris, D. V. (2010) 'Evolution of Poly(ADP-ribose) Polymerase-1 (PARP-1) inhibitors. From concept to clinic', *Journal of Medicinal Chemistry,* 53: 4561–84.

Gibbon, S. (2007) *Breast Cancer Genes and the Gendering of Knowledge. Science and Citizenship in the Cultural Context of the 'New' Genetics,* Houndsmills: Palgrave.

Grushko, T. A. Dignam, J. J., Das, S. et al. (2004) '*MYC* is amplified in *BRCA1*-associated breast cancers', *Clinical Cancer Research*, 10: 499–507.

Guha, M. (2011) 'PARP inhibitors stumble in breast cancer', *Nature Biotechnology,* 29: 373–4.

Hammond, M.E.H., Hayes, D. F., Dowsett, M. et al. (2010) 'American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer', *Journal of Clinical Oncology*, 28: 2784–95.

Hartwell, L. H., Szankasi, P., Roberts, C. J. et al. (1997) 'Integrating genetic approaches into the discovery of anticancer drugs', *Science*, 278: 1064–68.

Hedenfalk, I. Duggan, D., Chen Y. et al. (2001) 'Gene expression profiles in hereditary breast cancer', *NEJM*, 344: 539–48.

Jazaeri, A. A., Yee, S. J., Sotiriou, C. et al. (2002) 'Gene expression profiles of BRCA1-linked, BRCA2-linked, and sporadic ovarian cancers', *Journal of the National Cancer Institute*, 94: 990–1000.

Jones, D., Cambrosio, A. and Mogoutov, A. (2011) 'Detection and characterization of translational research in cancer and cardiovascular medicine', *Journal of Translational Medicine,* 9: 57.

Keating, P. and Cambrosio, A. (2001) 'The new genetics and cancer. The contributions of clinical medicine in the era of biomedicine', *Journal of the History of Medicine and Allied Sciences,* 56: 321–52.

Kepler, T. B., Crossman, C. and Cook-Deegan, R. (2010) 'Metastazing patent claims on BRCA1', *Genomics,* 95: 312–14.

Klawiter, M. (2008) *The Biopolitics of Cancer. Changing Cultures of Disease and Activism,* Minneapolis: University of Minnesota Press.

Kohli-Laven, N., Bourret, P., Keating, P. and Cambrosio, A. (2011) 'Cancer clinical trials in the era of genomic signatures: biomedical innovation, clinical utility, and regulatory-scientific hybrids', *Social Studies of Science,* 41: 487–513.

Konstantinopoulos, P. A. Spentzos, D., Karlan, B. Y. et al. (2010) 'Gene expression profile of BRCAness that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer', *Journal of Clinical Oncology*, 28: 3555–61.

Löwy, I. and Gaudillière, J. P. (2008) 'Localizing the global: testing for hereditary risks of breast cancer', *Science Technology and Human Values,* 33: 299–325.

Lynch, M. (1982) 'Technical work and critical inquiry: investigations in a scientific laboratory', *Social Studies of Science,* 12: 499–533.

Magdinier, F., Ribieras, S., Lenoir, G. M. et al. (1998) 'Down-regulation of BRCA1 in human sporadic breast cancer; analysis of DNA methylation patterns of the putative promoter region', *Oncogene*, 17: 3169–76.

Maxwell, K. N. and Domcheck, S. M. (2012) 'Cancer treatment according to BRCA1 and BRCA2 mutations', *Nature Reviews Clinical Oncology,* 9: 520–8.

McCormick, S., Brown, P., Zavestoksi, S. and Cordner, A. (2012) 'The personal is scientific, the scientific is political. The public paradigm of the environmental breast cancer movement'. In P. Brown, R. Morello-Frosch and S. Zavestoksi (eds) *Contested Illnesses. Citizens, Science, and Health Social Movements*, Berkeley: University of California Press.

Morange, M. (1997) 'From the regulatory vision of cancer to the oncogene paradigm, 1975–1985', *Journal of the History of Biology,* 30: 1–29.

Narod, S.A. (2012) 'Should all women with breast cancer be tested for BRCA mutations at the time of diagnosis?' *Journal of Clinical Oncology,* 30: 2–3.

Nelson, N., Keating, P. and Cambrosio, A. (2013) 'On being "actionable": clinical sequencing and the emerging contours of a regime of genomic medicine in oncology', *New Genetics and Society,* 32: 405–28.

Ong, M.B.H. (2012) 'Senate increases NIH funding for 2013, rejects President's $200+ million increase for program evaluation activities,' *The Cancer Letter,* 38, 25: 1, 7–9.

Parthasarathy, S. (2007) *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care.* Cambridge, MA: MIT Press.

Perou, C.M., Sorlie, T., Eisen, M.B. et al. (2000) 'Molecular portraits of human breast tumours', *Nature*, 406: 747–52.

Rabeharisoa, V. and Bourret, P. (2009) 'Staging and weighting evidence in biomedicine: comparing clinical practices in cancer genetics and psychiatric genetics', *Social Studies of Science,* 39: 691–715.

Reis-Filho, J. and Pusztai, L. (2011) 'Gene expression profile in breast cancer: classification, prognostication and prediction', *Lancet,* 378: 1812–23.

Rice, J.C., Massey-Brown, K.S. and Futscher, B.W. (1998) 'Aberrant methylation of the BRCA1 CpG island promoter is associated with decreased BRCA1 mRNA in sporadic breast cancer cells', *Oncogene,* 17: 1807–12.

Rios, J. and Puhalla, S. (2011) 'PARP inhibitors in breast cancer: BRCA and beyond', *Oncology,* 25: 1014–25.

Roop, R. P, Ma, C.X. and Ellis, M.J.C. (2011) 'PARP inhibitors and their evolving role in breast cancer', *Oncology,* 25: 1033–34.

Schmidt, C. (2011) 'How do you tell whether a breast cancer is HER2 positive? Ongoing studies keep debate in high gear', *Journal of the National Cancer Institute,* 103: 87–9.

Sorlie, T., Perou, C.M., Tibshirani, R. et al. (2001) 'Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications', *Proceedings of the National Academy of Sciences USA*, 98: 10869–74.

Turner, N., Tutt, A. and Ashworth, A. (2004). 'Hallmarks of "BRCAness" in sporadic cancers', *Nature Reviews Cancer,* 4: 814–19.

van't Veer, L.J., Dai, H., van de Vijver, M.J. et al. (2002) 'Gene expression profiling predicts clinical outcome of breast cancer', *Nature*, 415: 530–36.

Wolff, A.C., Hammond, M.E.H., Schwartz, J.N. et al. (2007) 'American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer', *Archives of Pathology and Laboratory Medicine*, 131: 18–43.

10 Ethical analysis of PGD for BRCA

Attending to more than risks and benefits

Lisa R. Rubin and Inmaculada de Melo-Martín

Introduction

Among the supposed benefits of BRCA gene mutation testing is that individuals, particularly women, identified as carrying a BRCA mutation can then take steps to manage the risk of, and possibly even prevent, the development of breast and ovarian cancer. However, until recently, there were few options available for BRCA carriers to manage or prevent transmission of this inherited gene mutation to their biogenetically related children. BRCA mutations are autosomal dominant, and men and women who carry a BRCA1 or BRCA2 mutation confront a 50 per cent chance that their children will inherit the mutation. Although it is not clear that BRCA has shifted childbearing decisions for the majority of carriers (Van Asperen *et al.* 2002), this has nonetheless been identified as a significant concern for many carriers and their parents (Claes *et al.* 2004).

Until the clinical implementation of preimplantation genetic diagnoses (PGD), options for individuals wishing to avoid the risk of transmitting a BRCA mutation were limited to remaining child-free, or adoption. The use of PGD in combination with *in vitro* fertilization (IVF), however, currently allows determination of whether an embryo carries genetic mutations or chromosomal abnormalities that can cause disability or might increase a future child's risk of suffering from a particular disease (Geraedts and De Wert 2009, Simpson 2010). With that information, prospective parents can make decisions about whether to prevent certain embryos from being implanted.

As is the case with most technological developments, these new abilities raise important ethical challenges. In general, these challenges tend to be evaluated within the framework of risks and benefits (Noble *et al.* 2008). The use of PGD for BRCA, as well as for other gene mutations associated with inherited risk of adult-onset cancer, is not an exception. This risk–benefit framework has been used to inform policy making, and even outside of policy making, it has the potential to influence medical practice. However, much of the literature about the ethics of using PGD for BRCA focuses on a limited range of questions about the risks and benefits of the use of this technology. Although, of course, risk assessments are an important component of an ethical evaluation, an ethical analysis packaged entirely within a traditional risk–benefit framework may provide too narrow a lens

through which to locate the ethical issues at stake in the use of PGD for BRCA1/2. In this chapter, we call attention to several ethical concerns regarding the use of PGD for BRCA that extend beyond risk–benefit considerations.

The benefits of PGD seem clear to most people: it allows the identification and elimination of a variety of diseases and impairments, thus promoting the goal of having healthy children (Bredenoord *et al.* 2008, Esplen *et al.* 2007, Harper and SenGupta, 2012, Malek and Daar 2012, Mansour 2004, Savulescu 2001, SenGupta *et al.* 2012). The potential harm most often discussed has centred on matters of eugenics, which is particularly relevant in light of recent and cross-national histories of eugenic practices (Baum 2006; King, D. S. 1999; McCabe and McCabe 2011, Parens and Asch 1999). Ethical assessments of PGD thus usually attempt to determine how to balance the potential benefits of this technology with a variety of harms, including the eugenic harms that it might cause. Such balance is thought to be attained by providing parameters and criterion that presumably help minimize the risks of using PGD and maximize its possible benefits, thus demarcating ethically appropriate from inappropriate uses of PGD. For example, the 'seriousness of the genetic condition' is supposed to provide us with such a criterion. However, what counts as 'serious' when evaluating diseases and impairments has turned out to be – unsurprisingly – not an easy matter. Indeed, when attending to factors such as the impact of the condition on health, the severity of symptoms, degree of penetrance of the genetic mutation, the existence of a cure or treatment, the rate of progression and the age of onset, all make determinations of seriousness fraught with challenges. A significant amount of debate has thus centred on trying to examine, probe, refine and dispute this criterion as a guide for the moral acceptability of PGD (Camporesi 2010, Clancy 2010, Krahn 2009, Mansour 2004, Oster *et al.* 2008, Robertson 2003, Scott *et al.* 2007, SenGupta *et al.* 2012, Snelling 2008).

Dilemmas of line-drawing around seriousness have taken centre stage in critiques using a risk–benefit framework of ethical evaluation, foreclosing the examination of other limitations of this framework. Because evaluations of risks and benefits are not value-neutral, focusing ethical concerns exclusively on identifying and balancing risks and benefits can draw attention away from the need to consider the values underlying risk–benefit analysis. For example, values are implicated in evaluations of what counts as a risk or a benefit, when is a risk considered too risky (or not risky enough) and what is an acceptable level of risk. Determination of the relevant time frame for investigating risks, the manageability of the proposed risks or the standards with which to judge whether unmanageable risks are not present are all value-laden judgments, as are evaluations of how compelling the benefits are. The value-laden nature of risk–benefit analyses is underscored by the considerable cross-national variability in the regulation of PGD across the globe – from all out bans on this technology in countries such as Germany, Austria, and Italy, to regulatory systems in the UK and Canada, and the use of professional guidelines within the US and Japan (King 2008). To the extent that this is the case, it seems important to evaluate the value judgments that play a role in determinations about the risks and benefits.

Another related drawback of the risk-benefit framework is that it conceals other concerns that are morally relevant when evaluating technologies in general and PGD in particular. Indeed, general questions such as (1) how the practices and values of knowledge production influence the types of technologies that we choose to develop, (2) how these affect the technologies that are found desirable or even feasible and (3) how new technologies that promote or challenge particular values fail to find a place in these types of evaluations. However, even more specific questions about the desirability of the goals that PGD presumably helps us achieve, or the appropriateness of PGD as a means to such goals, also become clouded when limiting the evaluation of PGD to an assessment of risks and benefits. The purpose of this chapter is to uncover some of those aspects. In particular, we focus here on relevant concerns, such as the constraints that the availability of PGD for BRCA puts on prospective parent's choices, the emphasis on PGD as a solution to breast and ovarian cancer risks at the expense of other possible solutions, the construction of health and disease in reductionist ways and the value assumptions about good parenting that are presupposed by the use of PGD. Although these concerns fit uneasily within a risk–benefit framework and thus tend to be ignored in bioethical evaluations within academic medicine and by those involved in direct clinical care, they are nonetheless essential to a robust ethical analysis of this technology.

This chapter is the product of an ongoing collaboration between a philosopher (de Melo-Martín) and a psychologist (Rubin). We explore ways of integrating normative ethical analysis with qualitative research to deepen our understanding of ethical, social and psychological issues involved in repro-genetic technologies (Rubin and de Melo-Martín 2012). For de Melo-Martín, this includes a programme of research that examines the often neglected and unacknowledged role of values within scientific and bioethical evaluations. Within the field of philosophy, the empirical investigation of patient stakeholders' attitudes and values may not always be relevant to a normative ethical analysis (i.e. analysis of what 'ought to be'), but they certainly can be. This became apparent to Rubin when she noticed how de Melo-Martín's work of drawing out the unspoken values at stake in the practice of PGD often mapped the concerns of women and men she interviewed who carried a BRCA1/2 mutation as they weighed the option of PGD. To this end, this chapter draws on interviews conducted as part of a larger study exploring attitudes toward using PGD to prevent the transmission of inherited breast and ovarian cancer risk associated with BRCA1 and BRCA2 mutations among reproductive-age mutation carriers living in the US. The normative conclusions about the failures of the risk–benefit analysis of PGD for BRCA made here are illustrated by the experiences of BRCA1/2 mutation carriers as they contemplated the possibility of PGD. Our aim here is not to advocate for or against the use of PGD for BRCA1/2, or for any other condition. Instead, by drawing from interviews with BRCA1/2 mutation carriers considering the possibility of PGD, we illuminate some of ethical issues that are not readily locatable within a traditional risk–benefit framework but are deeply relevant to the experiences of individuals navigating these technologies in their everyday lives.

Methods

As part of the aforementioned study led by Rubin and colleagues (Rubin 2008–2011), thirty-three reproductive-age women and men who had undergone genetic screening for a BRCA mutation and tested positive for a BRCA1 or BRCA2 mutation were recruited from the Clinical Genetic Service (CGS) of a private, comprehensive cancer centre in New York City to participate in an interview study about their views regarding PGD for BRCA. Inclusion criteria required that participants (1) were identified as carriers of a deleterious BRCA mutation documented by CGS, (2) were of 'reproductive age' defined as under the age of 43 for women and under the age of 50 for men and (3) had not undergone hysterectomy or risk-reducing oophorectomy. In addition, a second sample comprised of six individuals seeking consultation for PGD to screen embryos for a BRCA gene mutation were recruited through the Center for Reproductive Medicine (CRM) in New York City. Eligibility criteria were the same, with the exception that female partners of male BRCA carriers were also eligible to participate.

A total of 39 interviews were conducted, with 34 female and 5 male participants. The majority were white (92 per cent), married (76.9 per cent), working full-time (59 per cent) and affluent (nearly 70 per cent reported annual incomes greater than $100,000). Just over half of the sample had children (56.4 per cent), and nearly 80 per cent reported they were not finished (or not sure they were finished) with plans for having children. In addition, 61.5 per cent identified as Jewish with a range of identifications from secular to Orthodox. All participants were BRCA mutation positive except one female participant who was undergoing PGD to identify and screen out a BRCA gene mutation carried by her husband.

After providing informed consent and completing a brief survey of background demographics as well as prior knowledge of and experience with repro-genetic technologies, participants viewed a brief, standardized educational tutorial, developed in collaboration with a doctoral-level genetic counsellor and CGS genetic counsellors, reviewing risk and inheritance patterns associated with BRCA gene mutations, defining preimplantation genetic diagnosis and prenatal genetic diagnosis and describing the procedures and associated features (including cost) for each. This ensured that all participants were exposed to the same basic knowledge regarding patterns of cancer risk and inheritance associated with a BRCA gene mutation, the procedures involved with PGD as well as the costs and alternatives. Following the educational presentation, participants completed a brief knowledge assessment to ensure comprehension of the key points of the educational presentation.

Participants then took part in an in-depth, semi-structured interview with a clinical psychologist or social worker, both of whom were experienced in qualitative interviewing and were knowledgeable about hereditary cancer risk. Interviews lasted approximately one hour and explored experiences of familial cancer and genetic testing, screening and/or surveillance options for BRCA mutation carriers, the impact of a BRCA mutation on family planning, attitudes toward the use of PGD as well as prenatal diagnosis to screen for BRCA. Concerns relating to religion, family views and costs were also explored.

All interviews were audio-recorded and transcribed verbatim by a professional transcription service. As part of the larger study, data were analysed using a grounded theory approach (Charmaz 2000), which identified key tensions expressed between and among participants in relation to their attitude toward and interest in PGD for BRCA. With an *a priori* framework of thinking beyond risk–benefit analysis in mind, we reviewed interviews and coded data to examine ways in which participants' interviews expanded our understanding of the ethical issues involved in PGD for BRCA beyond the risk–benefit framework.

The limits of risk–benefit evaluations of PGD for BRCA

Interview findings shed light on several ethical concerns raised by participants that go beyond a risk–benefit framework. We believe that these deserve consideration when providing ethical analysis of PGD for BRCA. Our goal is not to ascertain how ethical concerns of PGD for BRCA *ought* to be evaluated. We simply aim to reveal some ethical factors that are typically neglected when the main focus of an evaluation of PGD is the determination and assessment of the risks and potential benefits of PGD for BRCA. We illustrate such concerns by presenting the voices of individuals who are confronted with the use of this technology.

Constraints on choice

The introduction of new technological developments is normally hailed as a way to increase people's choices. The use of PGD for BRCA is no exception. Prospective parents at risk of transmitting BRCA mutations to their biogenetic offspring now have the choice to use the technology, so as not to pass on such mutations. Expanded choices are usually seen as benefiting people, as more choices usually increase the chances that people will be able to satisfy their own particular desires or address their own concerns. And yet this increase in choices often comes at a cost, and such a cost is rarely acknowledged. For instance, because PGD requires the use of IVF, the existence of this choice can constrain BRCA carriers' desires to become pregnant without the help of technologies. In the words of one participant, a 30-year-old woman who originally heard about PGD from her uncle and tried to become pregnant several times using PGD but failed:

> I had heard about it, my uncle is a doctor . . . and he had heard about it. He had mentioned it to me. And initially I was very upset about it. Like, I was very upset that I *had to,* like, go through this process. I was twenty-seven years old and I wanted to just have kids! I wanted to, like, be normal! Like all my friends who were getting pregnant. And I really didn't, I really thought pregnancy was, like, oh, you tried and you got pregnant.
>
> (emphasis added)

Of course, BRCA carriers are not prevented from choosing to become pregnant without the use of IVF and PGD. The concern is that the existence of this choice might decrease the likelihood that one can exercise previous choices that one

would have preferred, such as trying to conceive naturally. Once this participant learned about PGD, she felt she no longer had the choice to become pregnant naturally. Rather, she felt that after hearing about it, she *had to* use PGD.

The concern expressed by this participant – that being presented with the choice of using PGD actually constrained the possibility of choosing alternate options – was also experienced by other participants in various ways that illustrate the often neglected costs of introducing technological choices. For instance, one 36-year-old male participant, who had a daughter before learning about PGD for BRCA and was trying to decide whether to use PGD as he and his wife planned for their next pregnancy, was conflicted about this choice. He wished that he had never been presented with what Kenen (1996) has described as the 'diagnostic invitation and the "gift" of knowing' about PGD for BRCA, while he reluctantly acknowledged that the invitation now could not be ignored.

> [The doctor] probably also almost certainly regarded it as giving me a choice, you know, giving me an opportunity . . . I'm sure I take it for granted and have the childish approach to it, complaining about having the opportunity. It is an opportunity, and – you know, no one would really in the end rather be ignorant, I don't think . . . it's nobody's fault that we were then presented with all the information.

This cost of increased technological choice – that the availability of PGD necessitated its use (Dumit and Davis-Floyd 1998) – was raised by several participants, a few of whom also discussed the consequent constraints on other previously available choices. Others experienced the 'invitation' as a burden of responsibility. Indeed, having a choice, and being aware of it, raised the issue of responsibility. A failure to choose could now be used to hold someone, and oneself, responsible and to judge them, and oneself, blameworthy. Indeed, some participants who opted for not using PGD expressed trepidation that the decision not to do so could be construed as being irresponsible. As one participant, a 38-year-old woman who was pregnant at the time of the interview put it:

> It's a little irresponsible. I think my husband feels differently. He's like, you know, you could just, you could get rid of this thing and you know, instead of having her live a life of, you know like you might have to, I don't know.

With responsibility also comes the need to justify that one has made responsible choices. For instance, another participant – a 34-year-old woman who unexpectedly became pregnant naturally after several failed IVF attempts – regarded the fact that she used IVF and PGD, even if unsuccessfully, as sufficient to fulfil her responsibilities of not transmitting the BRCA mutation to her child, and therefore saw herself as not blameworthy:

> I've done my part, right. I've been responsible, I've done my part and now I just have to leave it up to whatever's going to happen. And I'm okay with letting go, as long as I've done my part.

Limiting solutions to BRCA risks

An aspect of technological innovation that risk–benefit analyses often fail to consider is the way that they frame solutions to a particular problem. In this respect, the use of PGD for BRCA is certainly a blunt solution to the problem of reducing the transmission of cancer risks associated with BRCA mutations. After all, this technology allows for such reduction by selecting against embryos that carry such mutations. The elimination of the increased cancer risks is thus inseparable from the elimination of the embryo.

However, an emphasis on PGD as a solution to increased cancer risk associated with BRCA mutations might also limit the solutions offered to address such risk by directing research efforts in particular ways at the expense of others. Thus, if a technology is available that limits the chances of having offspring with BRCA mutations, efforts directed at understanding the ways in which such mutations contribute to cancer, or addressing the environmental contributors to breast and ovarian cancer in this population, might be reduced. As a 35-year-old participant who was undecided about having children but confident that she would not use PGD for BRCA if she did, emphatically put it:

> We're the sickest country. We have disease rates that are climbing astronomically. And, you know, even with BRCA1 and BRCA2 it's not 100% of the people that come down with a cancer. Genetics plays a part, but I think that if more effort could be – what is the secret of the people that don't get it? . . . . And that's where I focus . . . good genetics can take you pretty far, and it can compensate for a lot of problems. . . . But I don't think – it doesn't concern me as much as it used to.

Moreover, the emphasis that underlies the use of PGD for reducing the risk of passing on BRCA mutations also obscures the ways in which such cancer risks might be managed in other ways. For instance, one 30-year-old cancer survivor, who also lost her mother to cancer, called attention to this concern in a poignant way:

> You know, if my mom were alive, would she be blaming herself for giving me breast cancer? Maybe, but do you think that would've stopped her from having me? I don't think so. You know, so it's almost like, yeah, I think I might feel guilty if I did pass that down . . ., but I also think I might be knowledgeable enough, and I feel like in the times that we're living in now, like there's so much care that's available, and it's – you know, it could be cured at that point in time. . . . I don't think that [BRCA] would ever stop me from having kids.

Indeed, most participants felt optimistic that better options than PGD would develop by the time their children would begin to face an increased cancer risk, assuming they had inherited their parents' mutation. For example, a 40-year-old breast cancer survivor who was diagnosed in the middle of IVF treatment and who

was not interested in PGD, stated: 'They're doing a lot of research in this area so eventually they're going to find what to do to correct the mutation. So I felt that in my child's lifetime, that correction would be done.'

Health and values

The main goal of PGD is to produce healthy children. The risk–benefit analyses of PGD take for granted the ethical appropriateness of such a goal. However, health and disease are not simply descriptive concepts; they involve normative considerations. Because of such normative considerations, health and disease states are not always easy to determine, at least in part. Moreover, health is one among many other goods that human beings value dearly, and at times, those goods can conflict. Conflicts between goods and the value-laden nature of the concepts of health and disease are also aspects that fit uneasily within the risk–benefit framework normally used to evaluate PGD. Indeed, one of the ethical concerns obscured by risk–benefit analysis is the fact that the use of PGD solves these conflicts between goods in a particular way. Thus, because PGD is aimed exclusively at limiting the possibility that prospective parents will pass on their BRCA mutations to their offspring, this technology in fact prioritizes concerns about health, and in particular a future child's health, over other aspects of human existence. This concern was expressed over and over by participants who were forced to face the existential question (Ormondroyd *et al.* 2012): Would I have been born if my parents had had the option of using PGD?

For instance, one 35-year-old woman who was using PGD for another condition but did not feel it was necessary for BRCA, wondered:

> Why would I? If my mother had this opportunity I wouldn't be here maybe. I don't know. I mean, that's just the way I was thinking. . . . I'm fine, I'm here. . . . When I look at my daughter, who could have the BRCA gene. . . . It doesn't make – it's not – I mean, would I not want her? That's what it comes down to.

Similarly, another participant who was 41 years old at the time of the interview had cancer a few years earlier and had frozen eggs just before her cancer treatment. However, despite the fact that she would need to undergo IVF to have biogenetically related children, she was nonetheless uninterested in PGD. She explained:

> . . . now that I have eggs frozen on First Avenue waiting for me – I've thought about it a lot and I don't think I would do the PGD because [pause]. Believe me this sucks – would I say my life hasn't been worth living because of it? No. Would my mother say, 'I wish I never had kids?' No.

Or, as another 38-year-old woman who participated simply stated: 'Would I have chosen never to be born? No, obviously.'

The emphasis on health at the expense of other aspects of human existence is also voiced by a 35-year-old cancer survivor with seven children, all daughters, who notes:

> I think most people walking around, I think if they tested corpses you would find that most people walking around are predisposed to many things. It's not a reason not to live. And it's not a reason not to have kids. This is not – I don't know. It's not guaranteed to be a terminal – you know, this isn't, you know, I don't know, maybe if it was a worse cancer.

Risk–benefit analyses fail to attend to the fact that the use of PGD presents a particular solution to the conflicts between goods, and they thus ignore the ethical consequences of the weighing of such goods. Moreover, such analyses also neglect considerations about how the use of PGD actually alters the boundaries between health and disease and encourages a particular construction of health, one that reduces health to the absence of genetic risks. Indeed, to the extent that PGD is thought of as an appropriate means to achieve the goal of having healthy children, its use for BRCA implies that people with such mutations are not healthy. This concern was clearly expressed by some of our participants, who challenged this view of health and disease. For instance, as one 35-year-old participant, whose mother and grandmother were both breast cancer survivors, explained: 'I just, I look at somebody with BRCA as healthy.' Another participant, a 30-year-old breast cancer survivor quoted earlier, explained that 'just because you have the gene doesn't mean you're gonna get cancer. It's not a sure thing. And I mean I'm healthy, I'm fine.'

She thus echoed the previous participant's challenge to equating risk with disease. However, as a cancer survivor, she takes this statement further to say that, even after having been through a cancer diagnosis and cancer treatment, she still views herself as healthy – a statement that was not uncommon among participants who had been diagnosed with early-stage breast cancer. Still another participant, a 34-year-old woman who had already undergone a prophylactic mastectomy and viewed this decision not as a signifier of illness but as a way to preserve her status as a healthy individual, explained: 'I'm still a healthy person and I'm still able to make decisions that preserve my health, so it feels different from having something where you're just not healthy.'

The boundaries between health and disease are often contested and unstable (Greene 2007). To the extent that PGD involves value-laden understandings of health and disease, such values must be open to scrutiny and critical evaluation. However, in taking such values for granted, risk–benefit analysis prevents just such an evaluation.

Conceptions of good parenting

PGD for BRCA is aimed at the selection of particular children – i.e. children who are not carriers of BRCA mutations. It is thus important that its use is grounded in particular assumptions about what it means to be a good parent. One such

assumption is that good parenting is compatible with making decisions about a child's characteristics, even when such characteristics are unlikely to make the life of the child not worth living. However, such a conception conflicts with other widely accepted notions of good parenting that call for parents to love whatever child comes along (Herissone-Kelly 2007a, Herissone-Kelly 2007b, McDougall 2005). Indeed, some participants regard the use of PGD for BRCA as being at odds with this understanding of parenting. For instance, a 29-year-old Orthodox Jewish woman hoping to have children in the near future says about the likelihood of her using PGD:

> Probably not because in general I really do feel you get the lot that you get and you make the most of what you have. And if you start playing with – and again, let's say, I'll just have to teach my child how to deal with it. Medicine in general is going to help you deal with what you're genetically predisposed to.

Similarly, a 27-year-old participant – Catholic, Latina, and a cancer survivor – challenged the use of PGD for BRCA, which she viewed as conflicting with her own understanding of good parenting. In her words:

> Me personally – and this is coming from a girl who's never had a kid. I mean I don't know, I can theoretically think about the responsibility and the awesome, you know, burden on a parent's shoulder when they have a child with any condition, whether it's cancer or Down Syndrome. I would like to think that I would welcome any child, you know? And that when I become a parent I'm accepting to become a parent no matter what that child has, whether it's an emotional condition or psychological or – you know, I'd like to – I would hope that that would be my case. But I know that I haven't been a parent. I don't know what it is to walk into a doctor's office and have a doctor tell you your child is almost certain to have cancer one day, or that your child will have Down Syndrome, or . . .

This is not to say that the conception of good parenting that calls for parents to love whatever child comes along is a better conception than the one underlying the defence of PGD for BRCA. It is to say that such a defence actually presupposes a particular conception of good parents. Thus, while the use of PGD might have an important effect on our understanding of what it means to be a good parent, such considerations are ignored when we use a risk–benefit framework as a sufficient way to provide ourselves with a robust ethical analysis of PGD for BRCA mutations.

Conclusion

There is little doubt that, when evaluating medical technologies such as PGD for BRCA, paying attention to risks and benefits is often necessary and helpful. Although it is not emphasized in this chapter, participants in the study from which

our data were derived certainly discussed matters that fall within a traditional risk–benefit analysis, including matters of eugenics and concerns about 'drawing lines', as well as the potential medical risks of IVF for women and children. However, as our paper illustrates, they raised further issues that are generally not recognized within this traditional analytic framework. While acknowledging the importance of the risk–benefit analysis, we contend that its use as the primary and exclusive strategy for engaging with an ethical analysis of PGD can direct and delimit how we understand the value and limitations of this technology. For example, if the central and primary concern is eugenics, debates will centre on whether PGD for hereditary cancer risk is a eugenic practice and on how to mitigate potential eugenic harms by establishing limitations and parameters on its use. However, while a variety of other ethical concerns are also relevant, these are disregarded by a risk–benefit framework as traditionally understood. These include questions about the cost of increased choices, the limitations that an emphasis on PGD as a solution to breast and ovarian cancer risks can introduce when considering solutions to such risks, the meaning of the goal of creating healthy children, and with it, the construction of health and disease in reductionist ways as well as the value assumptions about good parenting that are presupposed by the use of PGD.

Moving beyond a risk–benefit framework engages many issues that are raised throughout this volume, including matters of temporality, subjectivity, empowerment and prevention. When considering PGD, interview participants often engaged with the past – particularly their mother's, aunts' or grandmothers' experiences of cancer – to weigh concerns about their (future) children's lives. PGD gives BRCA mutation carriers hope that they can halt devastating intergenerational legacies of cancer. However, the discourse of empowerment that supported their decision to undergo BRCA testing already made BRCA feel less devastating. Thus, participants could be observed weighing decisions about PGD in a context in which the meaning of BRCA itself is continually shifting and 'mutating' (Gibbon 2007: 74). Indeed, some participants resisted the geneticization of identity that has accompanied predictive genetic testing (Novas and Rose 2000), refusing ways of reformulating risk as disease (Fosket 2010) and reconceptualizing the category 'at risk' as 'chronically ill'.

As we noted earlier, when considering disease prevention, PGD – while halting a particular BRCA mutation within a family line – is a 'blunt instrument' that is a limited strategy for cancer prevention. Several participants felt that the option of PGD (as well as the other preventive measures available, such as preventive surgery and chemoprevention) was an overly individualized and unsatisfactory strategy for prevention. It is noteworthy that our data were collected within the US health care context. Indeed, a risk–benefit framework sits comfortably within the US neoliberal health care context, which emphasizes such individualized solutions. However, as a handful of participants highlighted, it also limits our imagination regarding the kind of solutions that are sought in relation to cancer prevention.

Through the voices of people who are carriers of BRCA mutations – people living in the US who were invited to discuss the use of PGD – we have illustrated

several important ethical considerations here that fit uneasily within the risk–benefit framework. To the extent that attention to these concerns is arguably relevant to be able to adequately evaluate PGD, exclusively focusing on the assessment of the risks and benefits of PGD – which is the primary approach taken within academic medicine and which informs everyday practice – will fall short of providing a compelling ethical evaluation of this technique.

References

Baum, M. (2006) 'Pre-implantation genetic diagnosis (PGD): the spectre of eugenics or a "no brainer"', *International Journal of Surgery,* 4: 144–5.

Bredenoord, A.L., Dondorp, W., Pennings, G., De Die-Smulders, C.E. and De Wert, G. (2008) 'PGD to reduce reproductive risk: the case of mitochondrial DNA disorders', *Human Reproduction,* 23: 2392–401.

Camporesi, S. (2010) 'Choosing deafness with preimplantation genetic diagnosis: an ethical way to carry on a cultural bloodline?' *Cambridge Quarterly of Healthcare Ethics,* 19: 86–96.

Charmaz, K. (2000) 'Grounded theory: objectivist and constructivist methods'. In Denzin, N.K. and Lincoln, Y.S. (eds) *Handbook of Qualitative Research,* 2nd ed. Thousand Oaks, CA: Sage Publications.

Claes, E., Evers-Kiebooms, G., Boogaerts, A., Decruyenaere, M., Denayer, L. and Legius, E. (2004) 'Diagnostic genetic testing for hereditary breast and ovarian cancer in cancer patients: women's looking back on the pre-test period and a psychological evaluation', *Genetic Testing,* 8: 13–21.

Clancy, T. (2010) 'A clinical perspective on ethical arguments around prenatal diagnosis and preimplantation genetic diagnosis for later onset inherited cancer predispositions', *Familial Cancer,* 9: 9–14.

Dumit, J. and Davis-Floyd, R. (1998) 'Cyborg babies: children of the third millennium'. In J. Dumit and R. Davis-Floyd (eds) *Cyborg Babies: From Techno-Sex to Techno-Tots.* New York, NY: Routledge.

Esplen, M.J., Madlensky, L., Aronson, M. et al. (2007) 'Colorectal cancer survivors undergoing genetic testing for hereditary non-polyposis colorectal cancer: motivational factors and psychosocial functioning', *Clinical Genetics,* 72: 394–401.

Fosket, J.R. (2010) 'Breast cancer risk as disease: biomedicalizing risk'. In Clarke, A.E., Mamo, L., Fosket, J.R., Fishman, J.F. and Shim, J.K. (eds) *Biomedicalization: Technoscience, Health, and the Illness in the U.S.* Durham, NC: Duke University Press.

Geraedts, J.P. and De Wert, G.M. (2009) 'Preimplantation genetic diagnosis', *Clinical Genetics,* 76: 315–25.

Gibbon, S. (2007) *Breast Cancer Genes and the Gendering of Knowledge: Science and Citizenship in the Cultural Context of the 'New' Genetics.* New York: Palgrave MacMillan.

Greene, J.A. (2007) *Prescribing by Numbers: Drugs and the Definition of Disease.* Baltimore: Johns Hopkins University Press.

Harper, J.C. and SenGupta, S.B. (2012) 'Preimplantation genetic diagnosis: state of the art 2011', *Human Genetics,* 131: 175–86.

Herissone-Kelly, P. (2007a) 'Parental love and the ethics of sex selection', *Cambridge Quarterly of Healthcare Ethics,* 16: 326–35.

———. (2007b) 'The "parental love" objection to nonmedical sex selection: deepening the argument', *Cambridge Quarterly of Healthcare Ethics,* 16: 446–55.

Kenen, R. H. (1996) 'The at-risk health status and technology: a diagnostic invitation and the "gift" of knowing.' *Social Science and Medicine,* 42: 1545–53.

King, D. S. (1999) 'Preimplantation genetic diagnosis and the "new" eugenics', *Journal of Medical Ethics,* 25: 176–82.

King, J. (2008) 'Predicting probability: regulating the future of preimplantation genetic screening', *Yale Journal of Health Policy, Law, and Ethics,* 8: 283–358.

Krahn, T. (2009) 'Preimplantation genetic diagnosis: does age of onset matter (anymore)?' *Medicine, Health Care and Philosophy,* 12: 187–202.

Malek, J. and Daar, J. (2012) 'The case for a parental duty to use preimplantation genetic diagnosis for medical benefit', *American Journal of Bioethics,* 12: 3–11.

Mansour, R. (2004) 'Preimplantation genetic diagnosis for Y-linked diseases: why not?' *Reproductive Biomedicine Online,* 8: 144–5.

McCabe, L. L. and McCabe, E. R. (2011) Down syndrome: coercion and eugenics', *Genetics in Medicine,* 13: 708–10.

Mcdougall, R. (2005) 'Acting parentally: an argument against sex selection', *Journal of Medical Ethics,* 31: 601–5.

Noble, R., Bahadur, G., Iqbal, M. and Sanyal, A. (2008) 'Pandora's box: ethics of PGD for inherited risk of late-onset disorders', *Reproductive Biomedicine Online,* 17 Suppl. 3: 55–60.

Novas, C. and Rose, N. (2000) 'Genetic risk and the birth of the somatic individual', *Economy and Society,* 29: 485–513.

Ormondroyd, E., Donnelly, L., Moynihan, C. et al. (2012) 'Attitudes to reproductive genetic testing in women who had a positive BRCA test before having children: a qualitative analysis', *European Journal of Human Genetics,* 20: 4–10.

Oster, E., Dorsey, E. R., Bausch, J. et al. and Huntington Study Group PHAROS Investigators (2008) 'Fear of health insurance loss among individuals at risk for Huntington disease', *American Journal of Medical Genetics Part A,* 146A: 2070–7.

Parens, E. and Asch, A. (1999) 'The disability rights critique of prenatal genetic testing: reflections and recommendations', *The Hastings Center Report,* 29: 40–47.

Robertson, J. A. (2003) 'Extending preimplantation genetic diagnosis: the ethical debate. Ethical issues in new uses of preimplantation genetic diagnosis', *Human Reproduction,* 18: 465–71.

Rubin, L. (2008–2011) 'Awareness and attitudes regarding prenatal and preimplantation genetic diagnosis for inherited breast-ovarian cancer risk'. Online. http://projectreporter.nih.gov/project_info_description.cfm?aid=7533877&icde=18536649&ddparam=&ddvalue=&ddsub=&cr=2&csb=default&cs=ASC

Rubin, L. and de Melo-Martín, I. (2012) ' "Dilemmas of choice": exploring how oocyte recipients manage information about prospective donors', paper presented at the conference Selective Reproductive Technologies – Routes of Routinisation and Globalisation, University of Copenhagen, Denmark, 13–15 December.

Savulescu, J. (2001) 'Procreative beneficence: why we should select the best children', *Bioethics,* 15: 413–26.

Scott, R., Williams, C., Ehrich, K. and Farsides, B. (2007) 'The appropriate extent of pre-implantation genetic diagnosis: health professionals' and scientists' views on the requirement for a "significant risk of a serious genetic condition" ', *Medical Law Review,* 15: 320–56.

SenGupta, S. B., Vadaparampil, S. T. and Menon, U. (2012) 'Preimplantation genetic diagnosis for hereditary cancers', *Advances in Experimental Medicine and Biology,* 732: 103–13.

Simpson, J. L. (2010) 'Preimplantation genetic diagnosis at 20 years', *Prenatal Diagnostics,* 30: 682–95.

Snelling, J. (2008) 'Preimplantation genetic diagnosis for susceptibility conditions: a new frontier or a logical extension?' *Journal of Law and Medicine,* 16: 263–78.

Van Asperen, C. J., Van Dijk, S., Zoeteweij, M. W. et al. (2002) 'What do women really want to know? Motives for attending familial breast cancer clinics', *Journal of Medical Genetics,* 39: 410–414.