

Chapter

4

Case studies

Case studies

4.1 The following five case studies have been chosen because they represent a range of patents that assert rights over DNA sequences and that have implications for healthcare. The case studies concern a gene associated with susceptibility to breast cancer called BRCA1, a receptor that is important in HIV/AIDS called the CCR5 receptor, the DNA sequence of the hepatitis C and hepatitis B viruses, and the DNA sequence of a protein from the malarial parasite. We highlight a range of issues raised by each case study, which inform our discussion in Chapter 5.

Case study 1: BRCA1 - susceptibility to breast cancer

4.2 Two genes have so far been discovered which indicate susceptibility to breast cancer, BRCA1 and BRCA2. In this case study we discuss BRCA1, the first such gene to be discovered, which is located on chromosome 17.¹ The gene and its mutations have been part of numerous patent applications by a range of privately and publicly-funded research groups.

4.3 The original discovery of the BRCA1 gene was reported in 1994 by researchers from the University of Utah and the US company Myriad Genetics. In 1995, two patent applications were filed jointly by Myriad Genetics, the University of Utah Research Foundation and the US Secretary of Health, and were subsequently granted.² The applications asserted rights over the normal BRCA1 gene sequence and various mutations, diagnostic tests for detecting mutations in BRCA1, and methods for screening samples taken from tumours. The same year, Myriad Genetics filed an application with the Centre du Recherche du Chul in Canada and the Cancer Institute in Tokyo, Japan, for a patent that claimed a number of mutations in the BRCA1 gene. This patent was awarded in 1997.³

4.4 In 1996, another US patent application was filed by a company called OncorMed for a 'consensus sequence' of the BRCA1 gene. The patent, which was awarded in 1997, asserts rights over a method of identifying individuals with a normal copy of the gene, and of identifying seven mutations in the gene.⁴ In 1998, after claims and counter-claims of infringement, Myriad Genetics acquired the rights to the genetic testing business of OncorMed. In January 2001, Myriad Genetics was granted a European patent that asserted rights over the diagnostic use of the BRCA1 gene (but did not claim the sequence itself).⁵ As a result of this patent, Myriad Genetics has a temporary monopoly on diagnostic testing for BRCA1 in many European countries.

4.5 In the UK, negotiations between the Department of Health and Myriad Genetics are still in progress regarding the provision of services for genetic testing for BRCA1. Laboratories in the NHS continue to conduct tests on the genes and there is no indication that Myriad Genetics has placed any pressure on the NHS to cease testing, despite their patent.

4.6 In October 2001, an opposition procedure was filed jointly by three French organisations against Myriad Genetics' European patent on BRCA1.⁶ Additional oppositions have also been

¹ Only a small proportion of cases of breast cancer are accounted for by mutations in this gene.

² US patent 5,747,282 and US patent 5,710,001.

³ US patent 5,693,473.

⁴ US patent 5,654,155.

⁵ European patent 699754.

⁶ The organisations involved are the Institut Curie, the Assistance Publique-Hôpitaux de Paris and the Institut Gustave-Roussy.

filed by other organisations including the Belgian Society of Human Genetics and the Danish Society for Medical Genetics. The patent is being challenged on the grounds that it is not inventive and that it does not sufficiently describe the inventions over which it asserts property rights.⁷ The opposition is aimed at curtailing any possible deleterious consequences which might stem from sanctioning the monopoly conferred on Myriad Genetics, including possible threats to the development of research and the identification of new tests and diagnostic methods. It has also been argued that the patent will have a serious impact on equitable access to testing. It is suggested that the monopoly is antithetical to an approach to public health that is based on a commitment to the comprehensive care of patients at high-risk.

4.7 The three French joint opposing parties, and the Belgian and Dutch Centres for Human Genetics, the Belgian Ministers of Health, Social Affairs and Scientific Research, and the Dutch Minister of Health, filed oppositions to a second patent of Myriad Genetics in February 2002. This is a European patent granted in 2001 which covers a method for diagnosing susceptibility to breast and ovarian cancer linked to the BRCA1 gene and covers the use of a further 34 specific mutations of the gene in diagnosis.⁸ The patent was challenged on the grounds that it was not inventive, that it lacked industrial applicability and again that it was excessively broad in its reach, covering all possible diagnostic methods. None of the Oppositions has yet been decided upon.

4.8 The potential impact of Myriad Genetics' monopoly on the diagnosis of a susceptibility to breast cancer prompted the government of France to revise its legal framework to facilitate access to diagnostic testing by broadening compulsory licensing schemes or equivalent measures.⁹ Across Europe, the patents have faced mounting opposition from genetics societies. The European Parliament adopted a resolution in October 2001 opposing the patenting of the BRCA1 gene.

Box 4.1: Case study 1 - Issues

- Is it in the public interest that there is only one diagnostic test available for a particular disease?
- Will patents on diagnostic tests prevent other diagnostic tests from being developed and used? Alternatively, will they stimulate further development?
- Will patents such as those that assert rights over BRCA1 inhibit further research, even in the context of other diseases?

⁷ The opposition contends that the protein sequence used for Myriad's first patent application on a diagnostic test is *per se* insufficient for producing a test for susceptibility to breast cancer.

⁸ European patent 705903.

⁹ In Canada, Myriad Genetics has demanded that all screening tests based on the BRCA1 gene mutations on which it holds patents be done through its own laboratories. Publicly-funded laboratories in Ontario, British Columbia, Quebec and Alberta had been using other tests, and the threat of legal action prompted British Columbia to suspend temporarily the funding of predictive tests based on the patented genes. The province continues to provide counselling services for patients who pay for testing themselves. Quebec has begun sending samples to Myriad Genetics for testing. Only Ontario and Alberta, of the provinces that previously offered the tests, continue to fund predictive screening programmes. Ontario decided that the precedent that they would set by agreeing to Myriad Genetics' request was undesirable. So far, Myriad Genetics has not taken further legal action against Ontario, despite being aware of its position. (See Eggerston L. Ontario defies US firm's genetic patent, continues cancer screening. CMAJ 2002;166(4):494).

Case study 2: The CCR5 Receptor – HIV/AIDS

4.9 In February 2000, Human Genome Sciences Inc (HGS), a US company, was granted a US patent which asserted rights over the gene that codes for the CCR5 receptor.¹⁰ The CCR5 receptor is the route by which the HIV/AIDS virus enters a cell. When HGS originally isolated the gene for this receptor and filed for the patent in June 1995, its estimate of how it would meet the criterion of utility was that the CCR5 protein product would be a cell-surface receptor. Their patent claims did cover a viral receptor, but at the time, they were unaware of the receptor's role in HIV/AIDS. Instead, the researchers expected to exploit the patent primarily for the development of anti-inflammatory therapies. Subsequently, the role of the CCR5 receptor in HIV/AIDS was revealed by other researchers, six months after HGS filed its patent application. Another researcher, Dr M Parmentier, had isolated the gene some years earlier but only filed a patent application in March 1996 when its biological function had been confirmed. His team and a number of other research groups simultaneously published the finding that CCR5 was indeed a critical site for entry of the HIV virus into the cell. Parmentier's patent has not yet been granted.

4.10 HGS has already agreed to several licences for the use of the CCR5 receptor gene in research into new drugs. In one recent example, Praecis Pharmaceuticals was licensed to develop therapies for AIDS, employing the receptor. Future therapeutic interventions will depend on licensing of the HGS patent. At present, it appears that HGS does not plan to prevent academics from undertaking unlicensed research involving CCR5.

Box 4.2: Case study 2 - Issues

- To what extent is it reasonable that an estimate of utility be rewarded?
- Should the established principle that a patent applies even to an unanticipated utility apply in the case of DNA sequences?
- What entitlement should the team which actually identified the role of CCR5 in HIV/AIDS enjoy?
- What would be the impact of patents such as this on research if they were not licensed generously?

Case study 3: Gene-based diagnostic test for hepatitis C

4.11 Appropriate tests for hepatitis A and B were developed in the 1970s, but the hepatitis C virus (HCV) was not identified for a further 12 years, despite substantial research programmes. Scientists from Chiron Corporation in the US cloned HCV in 1987 and identified its role in some forms of hepatitis. This was the first time an infectious agent had been identified by molecular cloning techniques alone and was a fundamental breakthrough in research into infectious diseases. As a result of its groundbreaking research, Chiron was granted a broad UK patent on the viral components of HCV and the use of them in diagnostic tests.¹¹ A European patent was subsequently granted and then opposed.¹² The Opposition Division of the EPO broadly upheld the claims, but on appeal, significant amendments to the claims were

¹⁰ US patent 6,025,154.

¹¹ UK patent 2212511.

¹² European patent 0318216.

made. In effect, the claims in the patent were limited to nucleic acid probes and PCR materials for the detection of HCV. The original claims relating to immunoassays and antigens were held to be unsubstantiated in the form granted.

- 4.12 At present, Chiron has been granted in excess of 100 patents related to HCV in over 20 countries. Its tests have been liberally licensed, widely used and have created considerable income for the company. Chiron has successfully defended its broad patents against a number of legal challenges and has enforced its patent rights against companies who have infringed its patents by producing unlicensed tests, or have sought to develop novel medicines or vaccines without a licence.
- 4.13 Although the case of HCV concerns the patenting of viral, rather than human, genes, it raises issues similar to those in the previous case studies. A key question is whether the patent did meet the necessary legal criteria: was the isolation of the viral components clearly inventive? Chiron's achievement was held to have met the legal requirements for patenting, namely novelty, inventiveness and utility. Others have taken the view that their diagnostic test was not sufficiently inventive. In any case there has been concern expressed over the breadth of the patent granted. When Chiron first sued for infringement of the patent relating to diagnostic tests, the defendants counter-claimed that Chiron's patent be revoked. To the extent that the patent explicitly asserted rights over vaccines against HCV, it was held invalid, because the patent did not contain enough instructions on how to make a vaccine (indeed, no vaccines yet exist). However, the company was still left with a patent covering a DNA sequence which is relevant to such a vaccine. Arguably, if others produce a vaccine, it will have to be based on Chiron's work and the sequence patented by them, although it may be possible to produce a so-called 'anti-idiotypic' vaccine which gives rise to an immune response against the patented protein but does not contain it.

Box 4.3: Case study 3 - Issues

- Should groundbreaking research be rewarded with broad patents, for example patents conferring the exclusive use of DNA sequences in diagnostic tests?
- How far should claims in a product patent that cover the use of sequence in one area extend to other uses such as medicines and vaccines?

Case study 4: Hepatitis B

- 4.14 The US company Biogen filed an initial patent application in the UK in 1978. It asserted rights over the development of hepatitis B virus (HBV) antigens using recombinant technology. Biogen subsequently filed a European patent one year later. In 1992, Biogen claimed that another company, Medeva, had infringed its patent by producing a vaccine for hepatitis B called 'Hepagene'. Medeva also used technology based on recombinant DNA techniques but used a different method. Biogen commenced legal proceedings against Medeva. In response, Medeva counter-claimed that Biogen's patent was invalid. The question to be resolved was whether Biogen's original patent justified rights over a monopoly over any recombinant method of making antigens.
- 4.15 In the decision in the House of Lords, Lord Hoffmann held that the claims in Biogen's patent were too broad and that the company did not have a monopoly on all recombinant methods of making antigens. Its breadth was excessive due to the fact that the same results could be produced by different means. In fact, once the DNA in question had been

sequenced, no one would choose to use the route set out in the initial patent. Lord Hoffman said that 'care is needed not to stifle further research and healthy competition by allowing the first person who has found a way of achieving an obviously desirable goal to monopolise every other way of doing so'.¹³ The House of Lords found that since Biogen's invention had been obvious by the time its European patent application had been filed in 1979, the patent was invalid.

Box 4.4: Case study 4 - Issues

- Are there sufficient safeguards to enable the patent system to be corrected where patents that assert property rights over DNA sequences are too broad?

Case Study 5: Malaria – MSP-1 protein

- 4.16 The development of vaccines and medicines for diseases prevalent in the developing world is often subsidised by the public sector because the markets for healthcare products are too poorly developed or too diffuse to attract commercial investment. There have, however, been a number of recent initiatives which have brought publicly-funded and privately-funded organisations together to try and address some of the more urgent health needs of developing countries. The Malaria Vaccine Initiative (MVI) is one such initiative which aims to develop vaccines for malaria. MVI is part of the Programme for Appropriate Technology in Health (PATH), an international charitable organisation, dedicated to improving health in developing countries. PATH has been considering whether to provide support for the development and commercialisation of various candidates for a malaria vaccine.
- 4.17 Some potential vaccines against malaria currently being considered for development and commercial use are likely to rely on a particular antigenic protein produced by the malaria parasite called MSP-1.¹⁴ PATH discovered that the group of different patents which related to MSP-1 was complex, in part because many of the patents were very similar. This is attributable both to the fact that the protein was not well-defined in the early stages of research and the lack of effort shown by patent applicants and to a lesser extent, examiners to more fully appraise themselves of existing patents before filing or granting patents respectively.
- 4.18 In the US, five core patents relating to MSP-1 were identified, with about a dozen other patents relating to 'add-on' technologies, which generally concerned specialised antigens and nucleic acid sequences of potential utility in constructing a vaccine. A further five patents specifically related to the production of MSP-1 vaccines. In general, there was a lack of reference to previous, relevant patents in almost all the MSP-1 patents. Before investing in the development and commercial use of a vaccine based on MSP-1, it was necessary to establish:
- whether there were patents that were pending or granted which asserted rights over the MSP protein and the DNA encoding it, the methods of producing the protein, and its use in malaria vaccines, and;
 - which of these patents were likely to be of most relevance to the commercial use of the vaccine in question.

¹³ *Biogen Inc v Medeva Plc* [1997] RPC 1 House of Lords.

¹⁴ MSP-1 is the merozoite surface protein.

It took considerable time and resources for PATH to negotiate with individual owners of the patents to obtain the necessary agreements to proceed with its research.

Box 4.5: **Case study 5 - Issues**

- Do complex and contradictory patents on research tools serve the public interest if they hinder the development of products related to healthcare?