

History of a Gene Patent: Tracing the Development and Application of Commercial BRCA Testing

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1. Introduction

The patenting and commercialization of human genetic material raises a host of complex social, ethical, and policy issues, such as the potential for discrimination or stigmatization in access to health care services or employment, the exploitation of minority or indigenous communities in DNA prospecting, and the implications for ongoing biomedical research and access to health care services. But in order to conduct a comprehensive analysis of even one of these issues, it is crucial to first develop a detailed understanding of the particular history and context that have shaped the issue. The objective of this paper is to provide such a description of one particular case, namely the patenting by Myriad Genetics of the two genes (BRCA1 and BRCA2) associated with hereditary breast and ovarian cancer. Following a brief discussion of the aetiology of hereditary breast and ovarian cancer, the founding of Myriad Genetics and its transformation into a biopharmaceutical company is examined as part of the larger context of the international race to discover and patent the BRCA genes. The paper then focuses on Myriad's development and control of public and commercial BRCA testing in the United States, their recent moves to enforce the patents and establish markets in Europe and Canada, and the mounting Canadian and international opposition to Myriad's commercialization and control of BRCA testing.

The Myriad case is a harbinger of an increasing number of instances where gene patents provide companies with monopolies on the development, marketing, and provision of genetic tests and therapeutics. Not surprisingly, this case has become a focal point in Canada and Europe for debates about the social and ethical

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implications of DNA patenting and the commercialization of genetic tests. There have been legal challenges of the BRCA patents in Europe, legislation to require compulsory licensing of diagnostic tests introduced in France, and in Canada an almost nationwide rejection of Myriad's monopoly rights to BRCA testing. There is clearly a need for sustained and comprehensive social, ethical, and policy analysis of the issues arising from this and similar cases. These issues will only be touched on in this paper, as the primary task is to show how a rich description of a specific exemplar – the Myriad case – is essential groundwork for conducting a comprehensive social, ethical, and policy analysis of the commercialization of new genetic technologies.

2. Biotechnology and Gene Patenting

By the early 1990s, enormous amounts of public and private funds were being invested in genetics research and biotechnology development.¹ The U.S. public expenditure on the Human Genome Project is estimated at greater than US\$3 billion. The U.S. biotechnology industry invested US\$11 billion in R&D in 1999² and US\$15.6 billion in 2001.³ In Canada in 1998, federal biotechnology funding reached C\$314 million, of which C\$310 million was devoted to R&D;⁴ Canadian industry invested C\$341 million while not-for-profit institutes invested C\$115 million.⁵ With the creation of Genome Canada in February 2000, the federal government continued its support of biotechnology research by investing a further C\$300 million specifically towards genomics R&D.⁶ Similar funding initiatives have been launched in the United Kingdom⁷ and other European and Asian nations.

While the potential health benefits to be derived from biotechnology were clearly a motivating factor for the substantial public investments, this goal was closely paralleled (if not exceeded) by the conviction that developing a strong

¹ J. Cohen, "The Genomics Gamble" (1997) 275:5301 *Science* 767.

² Ernst & Young, *The Economic Contributions of the Biotechnology Industry to the U.S. Economy* (Biotechnology Industry Organization, May 2000), online: <<http://www.bio.org/news/ernstyoung.pdf>> (date accessed: 7 December 2002) [hereinafter *Economic Contributions*] at 3.

³ Biotechnology Industry Organization, *Biotechnology Industry Statistics*, online: Biotechnology Industry Organization <<http://www.bio.org/er/statistics.asp>> (date accessed: 7 December 2002).

⁴ C. McNiven, *Canadian Biotechnology Statistics: In Support of the Implementation of the Canadian Biotechnology Strategy* (Ottawa: Science and Technology Redesign Project, Statistics Canada, March 1999), online: <http://biotech.gc.ca/archives/graphics/bh/can_biotech_stats_e.pdf> (date accessed: 7 December 2002) at 7.

⁵ Industry Canada, *The 1998 Canadian Biotechnology Strategy: An Ongoing Renewal Process* (Ottawa: Industry Canada, 1998), online: <<http://biotech.gc.ca/docs/engdoc/6889eng.pdf>> (date accessed: 7 December 2002) at 10.

⁶ Genome Canada, *Genome Canada at a Glance*, online: <<http://www.genomecanada.ca>> (date accessed: 7 December 2002).

⁷ U.K. Department of Health, Press Release, "Britain Must Be at the Leading Edge of Genetics - Milburn. New National Network of Genetics Centres Announced" (16 January 2002), online: <<http://www.info.doh.gov.uk/doh/intpress.nsf/page/2002-0025?OpenDocument>> (date accessed: 7 December 2002).

biotechnology industry is essential for stimulating economic growth and building a 'knowledge-based economy.'⁸ Public financial investments in biotechnology were thus also supported by government policies and regulations to facilitate technology transfer and commercialization.⁹

The 1980 U.S. Supreme Court case of *Diamond v. Chakrabarty*¹⁰ was a landmark decision, and significantly influenced Canadian and international patent law.¹¹ This case, which overturned the U.S. Patent and Trademark Office's prior decision not to permit the patenting of a biological organism (a genetically modified bacteria for the bioremediation of oil spills), opened the door for patents on biological organisms and genes.¹² Following the U.S. decision, the 1982 Canadian case of *Re Application of Abitibi Co.*¹³ forced the Canadian Intellectual Property Office to allow the patenting of biological organisms and genes.¹⁴ The permissive nature of U.S. patent policy, as well as international trade and patent harmonization agreements such as the *Agreement on Trade-Related Aspects of Intellectual Property Rights* (TRIPS), the *General Agreement on Trade and Tariffs* (GATT), and the *North American Free Trade Agreement* (NAFTA), have had a major impact on international gene patenting.¹⁵ In developed and developing countries that are signatories to these agreements, genes (including those of human origin) are considered patentable material if they meet general patent criteria and are demon-

⁸D. Kuyek, *The Real Board of Directors: The Construction of Biotechnology Policy in Canada, 1980-2002* (Sorrento, B.C.: The Ram's Horn, May 2002), online: <<http://www.ramshorn.bc.ca/RBOD.html>> (date accessed: 7 December 2002).

⁹R.M. Cook-Deegan, "National Policies Influencing Innovation Based on Human Genetics" in T.A. Caulfield & B. Williams-Jones, eds., *The Commercialization of Genetics Research: Ethical, Legal and Policy Issues* (New York: Kluwer Academic / Plenum Press, 1999) 13.

¹⁰*Diamond, Commissioner of Patents and Trademarks v. Chakrabarty*, 447 U.S. 303, 100 S. Ct. 2204, 65 L. Ed. 2d 144 (1980).

¹¹B.M. Knoppers, "Biotechnology: Sovereignty and Sharing" in Caulfield & Williams-Jones, *supra* note 9, 1 [hereinafter "Biotechnology"].

¹²There is substantial debate in both public forums and academic circles about whether patenting is morally or ethically acceptable. See for example G. McGee, "Gene Patents Can Be Ethical" (1998) 7:4 *Cambridge Quarterly of Healthcare Ethics* 417; A. Caplan, "What's So Special About the Human Genome?" (1998) 7:4 *Cambridge Quarterly of Healthcare Ethics* 422; J.F. Merz & M. Cho, "Disease Genes Are Not Patentable: A Rebuttal of McGee" (1998) 7:4 *Cambridge Quarterly of Healthcare Ethics* 425. This paper does not address the issue of the ethical permissibility of human gene patents per se, but instead lays the groundwork for analysis of the social, ethical, and policy implications of the patenting and commercialization of genetics research and technologies, focusing on the specific case of Myriad Genetics and their BRCA patents. For a broader discussion of the ethical, legal and policy issues of DNA patenting, see Nuffield Council on Bioethics, *The Ethics of Patenting DNA: A Discussion Paper* (London: Nuffield Council on Bioethics, July 2002), online: <<http://www.nuffieldbioethics.org/filelibrary/pdf/theethicsofpatentingdna.pdf>> (date accessed: 7 December 2002).

¹³*Re Application of Abitibi Co.* (1982) 62 C.P.R. (2d) 81 (Patent Appeal Brd. & Commr. of Patents). Similar to the U.S. *Chakrabarty* case, *Abitibi* concerned the patentability of a modified microbial culture, in this case to be used for sewage treatment.

¹⁴E.R. Gold, "Biomedical Patents and Ethics: A Canadian Solution" (2000) 45 *McGill L. J.* 413.

¹⁵Knoppers, "Biotechnology," *supra* note 11; T.A. Caulfield & E.R. Gold, "Whistling in the Wind: Patents on Genetic Research Are a Reality. It's Time to Reframe the Debate" (2000) *Spring Forum for Applied Research and Public Policy* 75.

strated to be new creations (e.g., artificial genes) or are isolated from nature and identified (i.e., cloned and sequenced), and shown to have a particular function and use.¹⁶ In the late 1980s, genetically engineered plants and animals were patented in the U.S. (the Harvard 'Oncomouse' was patented in 1988)¹⁷ and the number of gene and biological patents rapidly increased.¹⁸ Between 1981 and 1995, more than 1,175 human gene patents were granted worldwide,¹⁹ with more than 25,000 DNA-based patents by 2000.²⁰

Biotechnology start-up companies (whose main or only resources were often patents on potential 'disease genes') proliferated in the U.S., growing from 1,231 companies in 1992 to 1,457 in 2002.²¹ Revenues more than doubled between 1993 and 1999 (US\$8 billion to US\$20 billion), and tripled (to US\$27.6 billion) by 2001. The U.S. biotechnology industry, according to one estimate,²² created (directly and indirectly) 437,400 U.S. jobs, generated US\$47 billion in revenues, and provided US\$10 billion in taxes for federal, state and local governments. In Canada, there are more than 500 biotechnology companies with industrial activities generating annual revenues of C\$2 billion and exports of more than C\$750 million.²³

Despite the apparent economic success of this industry (and the government funding and legislation that has supported its development), there has also been a high turnover of biotechnology companies. Only a small percentage of companies remain solvent or independent a few years after start-up – most have either gone bankrupt or been absorbed by large biotechnology or pharmaceutical companies – and even fewer are able to show a profit. There has also been a convergence in markets and research technologies, such that biotechnology companies are consolidating around specific research areas (and not simply a particular gene or technology) and collaborating more closely with pharmaceutical companies to ensure long-term financing for R&D.²⁴

¹⁶ Specifically, the invention must be: novel, inventive or non-obvious, useful or have industrial application, and be fully disclosed in the patent application. There may also be restrictions based on *ordre public* or public morality, as in European patent law.

¹⁷ U.S. Patent 4,736,866. The Canadian case of *The President and Fellows of Harvard College v. Commissioner of Patents* (1998), 79 C.P.R. (3d) 98 (F.C.T.D.), upheld the denial by the Canadian Patent Commissioner of Harvard's claim to a Canadian patent for the 'Oncomouse'. This decision was confirmed by the Supreme Court of Canada (which overturned the Federal Court of Appeal's ruling in favour of Harvard) in *Harvard College v. Canada (Commissioner of Patents)*, 2002 SCC 76.

¹⁸ R.S. Eisenberg, "Patenting the Human Genome" (1990) 39:3 Emory L. J. 721.

¹⁹ Caulfield & Gold, *supra* note 15.

²⁰ R.M. Cook-Deegan & S.J. McCormack, "Intellectual Property: Patents, Secrecy, and DNA" (2001) 293:5528 Science 217 at 217.

²¹ Biotechnology Industry Organization, *supra* note 3.

²² Ernst & Young, *Economic Contributions*, *supra* note 2 at 3.

²³ Industry Canada, *supra* note 5 at 11.

²⁴ Ernst & Young, *Convergence: The Biotechnology Industry Report* (New York: Ernst & Young, 2000), online: <[http://www.ey.com/global/download.nsf/Finland/Convergence_summary/\\$file/Convergence_summary.pdf](http://www.ey.com/global/download.nsf/Finland/Convergence_summary/$file/Convergence_summary.pdf)> (date accessed: 7 December 2002).

One such biotechnology company is Utah-based Myriad Genetics, Inc. Myriad built its reputation and later established itself as a market leader in gene discovery and diagnostics – although they have also expanded into proteomics research – by helping to discover and patent the first genes (BRCA1 and BRCA2) to be associated with susceptibility for hereditary breast and ovarian cancer.²⁵

3. Hereditary Breast Cancer

Breast cancer is one of the most common non-skin cancers affecting women and the second leading cause of death in this group after heart disease; less than 1% of breast cancers occur in men. In 2002, an estimated 20,500 new cases of breast cancer will be diagnosed in Canadian women (a cumulative lifetime risk of 1 in 9), and 5,540 women are predicted to die from the disease.²⁶ Breast cancer is a heterogeneous disease, but approximately 80% of breast cancers are infiltrating ductile carcinomas. Treatment and prevention of further cancers depends on the type and size of cancer involved, and whether it is encapsulated and restricted to one area or has spread to other parts of the breast and body. Treatment options include lumpectomy, partial or total mastectomy, radiation, chemotherapy, and drugs such as tamoxifen and raloxifene.²⁷

Of those women who develop breast and ovarian cancers, current evidence suggests that only 5 to 10% are likely to have inherited a particular allele associated with increased risk of developing the disease.²⁸ To date, the genes BRCA1 and BRCA2 have been strongly associated with hereditary breast cancer. BRCA1 is a large gene on chromosome 17 with 22 exons made up of 5,592 base pairs, and codes for a protein of 1,863 amino acids. The protein is critical for DNA repair and transcription regulation; when the gene is inactivated through mutation and the protein altered, it leads to abnormal cellular gene expression. BRCA2 is located on chromosome 13 and is even larger, with 27 exons, 10,254 base pairs, and codes for a protein of 3,418 amino acids. The functions of the BRCA2 protein appear similar to that of BRCA1, although BRCA2 tumours have different cellular expression.²⁹

Deleterious mutations in these two genes are caused by insertions or deletions of nucleotides (single or multiple), or by large scale deletions or rearrangements. Such mutations may shift the reading frame of triplet codons (the group of three DNA nucleotides that correspond to specific amino acids) during protein synthesis. This results in a premature stop instruction, abrupt termination of protein synthesis,

²⁵ J. Roberts, "US Gene Discovery Leads to Patent War" (1996) 312:7043 *British Med. J.* 1378.

²⁶ Canadian Cancer Society, *Canadian Cancer Statistics* (Toronto: Canadian Cancer Society & National Cancer Institute of Canada, 2002), online: <http://www.cancer.ca/files/stats2002_e.pdf> (date accessed: 7 December 2002), at 20.

²⁷ W. Hofmann & P.M. Schlag, "BRCA1 and BRCA2: Breast Cancer Susceptibility Genes [Review]" (2000) 126:9 *J. Cancer Research & Clinical Oncology* 487.

²⁸ C.I. Szabo & M.C. King, "Population Genetics of BRCA1 and BRCA2" (1997) 60:5 *Am. J. Human Genetics* 1013; *ibid.*

²⁹ Hofmann & Schlag, *supra* note 27.

and a truncated and non-functional protein. BRCA1 and BRCA2 are considered classic tumour-suppressor genes because the associated cancers are believed to result from a 'two-hit' process of gene/protein inactivation. The first hit is due to a mutated (non-functional) gene in the germ line (inherited from a parent), which leaves only one remaining functional copy (allele) of the gene in all cells of the body. A person with a deleterious BRCA mutation is predisposed to breast and ovarian cancer because the second allele may be knocked out (second hit) through random mutation. If this occurs, the tumour-suppressor function is inactivated with resulting loss of control over cellular growth.

Individuals with such mutations are estimated to have a cumulative lifetime risk of 40-85% for developing breast cancer, and 16-40% for developing ovarian cancer, depending on the mutation and family history.³⁰ Mutations in both BRCA genes confer risk in an autosomal dominant manner; in other words, only one such allele is needed for increased risk of developing cancer, although a person with a deleterious mutation may never develop breast or ovarian cancer. The children of BRCA mutation carriers have a 50% chance of inheriting the gene mutation. There is still much scientific uncertainty with respect to the BRCA1 and BRCA2 genes and the functions of the resulting proteins. And only about 20-25% of families meeting stringent entry criteria (e.g., extensive family history or early age of onset) for genetic testing at public cancer clinics will have an identifiable mutation in BRCA1 or BRCA2.³¹ It is likely that there are other genes yet to be discovered that affect breast cancer risk in families negative for BRCA1 or BRCA2 mutations, some of which may be high penetrance genes that confer significantly increased risk such as a putative BRCA3 gene,³² and others that are low-penetrance and confer moderately increased risk such as CHEK2.³³ Social and environmental factors

³⁰R.F. Carter, "BRCA1, BRCA2 and Breast Cancer: A Concise Clinical Review" (2001) 24:3 *Clinical & Investigative Medicine* 147 at 154. Much of the research on the incidence of cancer as a result of mutations in the BRCA1 and BRCA2 genes has been conducted on large families with many affected individuals. There is thus some evidence that these risk figures may be over-estimates that do not accurately reflect levels of risk in families with less extreme incidence of cancer, or the general population. Hofmann & Schlag, *supra* note 27. These risk estimates also raise serious ethical, social and psychological issues about how physicians, counsellors, patients and family members interpret and understand risk information. See A.-M. Codori, "Psychological Opportunities and Hazards in Predictive Genetic Testing for Cancer Risk" (1997) 26:1 *Colorectal Neoplasia, Part II: Diagnosis & Treatment* 19; S.M. Cox & W. McKellin, "'There's This Thing in Our Family': Predictive Testing and the Construction of Risk for Huntington Disease" (1999) 21:5 *Sociology of Health & Illness* 622; N. Press, J. Fishman & B.A. Koenig, "Collective Fear, Individualized Risk: The Social and Cultural Context of Genetic Testing for Breast Cancer" (2000) 7 *Nursing Ethics* 237; J.P. Evans, C. Skrzynia & W. Burke, "The Complexities of Predictive Testing" (2001) 322 *British Med. J.* 1052.

³¹Personal communication from D. Horsman, Hereditary Cancer Program, BC Cancer Agency (8 February 2002).

³²"Breast Cancer Gene Discovered" *BBC News* (8 February 2002), online: <http://news.bbc.co.uk/1/hi/english/health/newsid_1808000/1808908.stm> (date accessed: 7 December 2002).

³³CHEK2-Breast Cancer Consortium, "Low-Penetrance Susceptibility to Breast Cancer Due to Chek2*1100delc in Noncarriers of BRCA1 or BRCA2 Mutations" (2002) 31:1 *Nature Genetics* 55.

clearly also influence the risk of developing breast cancer, as do, in all likelihood, genes at other loci.

4. Myriad Genetics

Myriad Genetics, Inc. is a biopharmaceutical and genomics company based in Salt Lake City, Utah, “specializing in the use of proteomic and genomic technologies to create break-through medical, diagnostic and therapeutic products.”³⁴ It focuses on therapeutic product development, the identification of disease-causing genes as potential drug targets, disease pathway discovery using proteomic technologies, molecular diagnostic testing for inherited risk, and high-throughput DNA sequencing to map the genomes of plants, animals, and microbes.

Founded in 1991, Myriad is a spin-off company from the Center for Cancer Genetics Epidemiology at the University of Utah. The founders were Mark Skolnick (Adjunct Professor in the Department of Medical Informatics at the University of Utah, and Chief Scientific Officer of Myriad), Walter Gilbert (1980 Nobel Laureate in chemistry, Professor in the Department of Molecular and Cellular Biology at Harvard University, and Vice Chairman of the Board of Myriad), and Peter Meldrum (past President and CEO of Agridyne, and current President and CEO of Myriad). Initial start-up capital and funds (e.g., to purchase equipment such as automated DNA sequencers), came from a private stock offering in 1993 that raised US\$10 million, of which \$1 million was equity from pharmaceutical giant Eli Lilly.³⁵ Eli Lilly also provided another \$1.8 million over three years to search for the genes associated with hereditary breast cancer in return for licensing privileges for diagnostic kits and therapeutic products for BRCA1,³⁶ Myriad maintains the rights for therapeutics development on BRCA2.³⁷

Myriad began life as a gene discovery company, “focused on the discovery and commercialization of genes involved in major common disorders including cancer and heart disease.”³⁸ This initial focus was possible because researchers were able to access and link important genealogical and medical databases. The Utah Population Database, developed as part of Skolnick’s Ph.D. research in the early 1970s, contained information on 200,000 Mormon family groups and most of the 1.6 million descendants of the initial 10,000 settlers of Utah.³⁹ This database was

³⁴ Myriad Genetics, Home page, online: <<http://www.myriad.com>> (date accessed: 7 December 2002).

³⁵ S. Parthasarathy, *A Global Genome? Governing Genetic Testing for Breast Cancer in the United States and Britain* (Ph.D. Thesis, Cornell University, 2002) [unpublished].

³⁶ K. Davies & M. White, *Breakthrough: The Race to Find the Breast Cancer Gene* (New York: John Wiley & Sons, 1995).

³⁷ K. Blanton, “Corporate Takeover” *Boston Globe Magazine* (24 February 2002), online: <http://www.boston.com/globe/magazine/2002/0224_patent_part1.htm> (date accessed: 7 December 2002).

³⁸ K.K. Key & D.J. DeNoon, “Researchers Isolate Cause of Inherited Breast Cancer” *Cancer Researcher Weekly* (19 September 1994) 4 at 7.

³⁹ Davies & White, *supra* note 36.

then linked to the Utah Cancer Registry (which contains more than 100,000 entries), and resulted in 40,000 cross-linked entries.⁴⁰ Researchers at Myriad have been involved in discovering various disease susceptibility genes and have developed or are in the process of developing a range of genetic susceptibility tests. Myriad has commercially available genetic tests for hereditary non-polyposis colorectal cancer (*Colaris*), hereditary breast and ovarian cancer (*BRACAnalysis*), cardiovascular disease (*CardiaRisk*), and melanoma (*Melaris*), while their test for prostate cancer (*Prolaris*) is still in development. Myriad is also conducting research into genes associated with lung cancer, obesity, asthma, osteoporosis, and central nervous system disorders such as depression and dementia.

Since its early days, Myriad's mandate has expanded beyond gene discovery and commercial genetic testing – these services are now provided by their diagnostic arm and subsidiary, Myriad Genetics Laboratories – into the field of proteomics. Proteomics involves the systematic analysis of gene expression at the protein level within an organism, in order to better understand disease processes and facilitate the discovery and development of therapeutics. To this end, Myriad has formed a \$185 million joint venture with Hitachi and Oracle to map protein-protein interactions using Myriad's ProNet subscription access database. This project is being conducted through a second subsidiary company, Myriad Proteomics, with the goal of developing a complete map and database of all human proteins in three years, competing head to head with Celera Genomics (collaborating with Compaq) and IBM.⁴¹ Myriad is also involved with the development of compounds to fight prostate cancer, HIV/AIDS, and lymphoma,⁴² and there are another ten cancer drugs in the development pipeline. Collaboration with Bayer using the ProNet database has led to the discovery of six candidate therapeutic targets for dementia, and investigations are expanding into the biological pathways involved in obesity. Myriad has established strategic alliances with pharmaceutical and biotechnology

⁴⁰ It should be noted that the Utah Population Database is not available to commercial entities, except through a very limited, previously reviewed and approved, relationship with a researcher at the University of Utah, online: <<http://www.utah.edu/rge>>. Nevertheless, the correlation of information from large databases of genealogical information, health records, genetic information, or pathological samples has been the source of widespread academic and public debate. Serious research ethics issues arise with respect to patient confidentiality, commercialization, the use of individualized vs. aggregate and anonymous data, banking of genetic material and storage of samples, and the potential for discrimination and stigmatization of visible minorities and ethnic communities. See L. Nielsen, "The Icelandic Health Sector Database: Legal and Ethical Considerations" in Caulfield & Williams-Jones, *supra* note 9, 111; M. Specter, "Decoding Iceland" *The New Yorker* (18 January 1999) 40; B.M. Knoppers, T.A. Caulfield & T.D. Kinsella, eds., *Legal Rights and Human Genetic Material* (Toronto: Emond Montgomery, 1996); W.E. Thurston, M.M. Burgess & C.E. Adair, "Ethical Issues in the Use of Computerized Databases for Epidemiologic and Other Health Research [Commentary]" (1999) 20:3 *Chronic Diseases in Canada* 127, online: <http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/cdic-mcc/20-3/d_e.html> (date accessed: 7 December 2002).

⁴¹ A. Feuerstein, "With Genome Complete, Myriad Allies with Others to Pursue Proteins" *TheStreet.com* (4 April 2001), online: <<http://www.thestreet.com/pf/stocks/biotech/1377314.html>> (date accessed: 7 December 2002).

⁴² T. Clarke, "Myriad Genetics Says Find Potential Cancer Drug" *Reuters* (9 October 2001), online: <http://biz.yahoo.com/rf/011009/n09309248_6.html> (date accessed: 1 November 2001).

giants such as Eli Lilly, Monsanto, Novartis, Roche, Shering AG, and Schering-Plough.⁴³

Myriad employs 275 researchers and business professionals at their University of Utah facilities, in a 20,000 square foot laboratory for genetic testing and a 55,000 square foot gene discovery R&D building. The company has raised over US\$900 million in financing since 1992.⁴⁴ Their revenues for 2001 totalled \$45 million, up from \$34 million in 2000, a 32% increase due primarily to revenue from their genetic testing program (\$17.1 million in 2001 up from \$8.8 million in 2000). In 2001, Myriad saw a 20% increase in R&D investment to \$33.8 million, with particular emphasis on their prostate cancer drug which has finished phase 2 clinical trials. Despite this growth, Myriad still posted a net loss of \$7.2 million for 2001, although this was an improvement over their \$8.7 million losses for 2000.⁴⁵

5. A Race to Discover and Patent the BRCA Genes

The search for a genetic basis for breast and ovarian cancer began in earnest in 1988 with the formation of a U.K. research group that later became the International Breast Cancer Linkage Consortium.⁴⁶ U.S. researchers were conducting similar research, and at the 1990 American Society of Human Genetics Meeting, a team led by Mary-Claire King announced the localization through linkage analysis of a gene associated with increased risk for breast cancer (BRCA1) to the long arm of chromosome 17.⁴⁷ In August 1994, Mark Skolnick and researchers at Myriad, along with colleagues at the University of Utah, the U.S. National Institutes of Health (NIH), and McGill University sequenced BRCA1.⁴⁸ This research was supported in part by funding from the pharmaceutical company Eli Lilly, but also from government agencies such as the NIH which provided Skolnick with more than \$5 million specifically to look for BRCA1. Skolnick and Myriad filed for U.S. 'composition-of-matter' and 'methods-of-use' patents on the whole gene, as well as for a variety of deleterious mutations.⁴⁹

⁴³ Myriad Genetics, Press Release, "Myriad Genetics and Bayer Extend Proteomics Collaboration through December 31, 2002" (13 December 2000), online: <http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=mygn&script=411&layout=9&item_id=212120> (date accessed: 7 December 2002).

⁴⁴ ReCap, *Myriad Genetics: Valuation History* (2001), online: ReCap <<http://www.recap.com>> (date accessed: 26 October 2001).

⁴⁵ Myriad Genetics, Press Release, "Myriad Genetics Reports Fiscal 2001 Year-End Results" (21 August 2001), online: <http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=mygn&script=410&layout=9&item_id=210259> (date accessed: 7 December 2002).

⁴⁶ Breast Cancer Linkage Consortium, *The Breast Cancer Linkage Consortium: Past, Present & Future* (10 June 1999), online: Breast Cancer Linkage Consortium <<http://www.medfac.leidenuniv.nl/lab-devilee/BCLC/history.htm>> (date accessed: 7 December 2002).

⁴⁷ M.-C. King, "Localization of the Early-Onset Breast Cancer Gene" (1991) 26:10 Hospital Practice (Office ed.) 121.

⁴⁸ Y. Miki *et al.*, "A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene BRCA1" (1994) 266:5182 Science 66.

⁴⁹ US patents 5,747,282 and 5,710,001; and 5,693,473 with the Canadian Centre du Recherche du Chul

After the 1990 discovery of BRCA1, it quickly became apparent that at least one other gene was involved in hereditary breast and ovarian cancer, leading researchers to continue their search for BRCA2. The patenting of BRCA1 by Myriad, and the resulting ability of a company to control access to and pricing of the gene for use in research and for susceptibility or diagnostic tests, presented a disturbing scenario to many of the researchers involved in the hunt for BRCA1 and BRCA2.⁵⁰ A race ensued between Skolnick at Myriad, and a consortium of U.K. researchers led by Michael Stratton at the Institute for Cancer Research and the Sanger Centre, to be the first to discover and control (i.e., patent) BRCA2. In September 1994, BRCA2 was localized through linkage analysis to chromosome 13.

On December 22 the following year, the day before it was to publish the sequence for BRCA2 in the journal *Nature*,⁵¹ the U.K. consortium held a press conference to announce their discovery as well as their filing of a U.K. gene patent. Despite opposition to the patent process by many U.K. researchers, it was agreed that a patent was necessary to prevent exclusive control by companies such as Myriad. A patent on BRCA2⁵² was filed by CRC Technology, the commercial arm of the Cancer Research Campaign (CRC), the charity that had funded much of the BRCA research in the U.K. The afternoon of the press conference, Myriad announced that they had also discovered the gene (supposedly at an earlier date than the U.K. researchers) and had filed for a U.S. patent.⁵³

During this period, patents were also filed by other groups. OncorMed, Inc. (another gene discovery company) and the NIH filed competing patents on BRCA1; the NIH withdrew their patent application after two of their researchers were named on a Myriad BRCA1 patent. By the end of 1997, the U.S. Patent and Trademark Office had awarded overlapping and conflicting patents to Myriad and OncorMed for diagnostic and therapeutic applications of the BRCA1 gene. OncorMed's U.S. patent for a non-mutated BRCA1 allele⁵⁴ described a DNA sequence most likely to be found in the majority of the population, only slightly different (due to normal gene polymorphisms) from the DNA sequence described in the Myriad patent.⁵⁵ Patent infringement suits were filed by both companies in 1998 but Myriad settled out of court for an undisclosed fee, purchasing the

and the Cancer Institute in Japan. For a detailed discussion of the science and politics behind the race to discover BRCA1, see Davies & White, *supra* note 36.

⁵⁰J. Murray, "Owning Genes: Disputes Involving DNA Sequence Patents" (1999) 75 *Chicago-Kent L. Rev.* 231; Davies & White, *supra* note 36.

⁵¹R. Wooster *et al.*, "Identification of the Breast Cancer Susceptibility Gene BRCA2" (1995) 378:6559 *Nature* 789.

⁵²U.K. patent GB2307477.

⁵³U.S. patent 5,837,492. J. Meek, "US Firm May Double Cost of UK Cancer Checks" *The Guardian* (17 January 2000), online: <<http://www.guardian.co.uk/Print/0,3858,3951576,00.html>> (date accessed: 7 December 2002).

⁵⁴U.S. patent 5,654,155.

⁵⁵Murray, *supra* note 50.

OncorMed patents.⁵⁶ The U.S. BRCA patents are quite broad, covering a host of deleterious mutations in the BRCA1 and BRCA2 genes, the use of these mutations for diagnosis and prognosis for breast and ovarian cancer, screening for cancer predisposition, and the development of therapeutics to treat cancers with mutations in either gene.⁵⁷ The immediate purpose of these patents was to protect Myriad's new genetic test, as well as to establish control over the U.S. and international markets (and thus be exclusive provider) for genetic testing for hereditary breast cancer.

6. A Patent, a Test, and a Market

A genetic test for hereditary breast and ovarian cancer, based on full DNA sequencing of the BRCA1 and BRCA2 genes to identify deleterious mutations, was developed by Myriad and marketed as *BRCAAnalysis*. In 1996, Myriad initially marketed a BRCA1 test kit for \$900 US,⁵⁸ but this kit was quickly recalled after widespread criticism from the medical community about the lack of genetic counselling support and the potential for public harm as a result of consumers misinterpreting test results. There were also concerns within the company about potential liability should a consumer be harmed by the test. *BRCAAnalysis* was re-released as an 'in-house' laboratory test, requiring a physician to be involved as facilitator or middleman to order the test (thus it is not strictly a direct-to-consumer service). Test results would then be provided to the physician to help increase the likelihood that patients would receive some level of genetic counselling; this may also shift liability for patient harm from the company to the physician to some extent. To further support counselling, Myriad developed and maintains substantial 'educational' resources for both patients and physicians, in the form of free and accessible online and print information about hereditary breast and ovarian cancer. Myriad has also invested in interacting more directly with physicians, and for example has worked with Aetna U.S. Healthcare to distribute information packages to physicians in the Aetna network. Myriad has also sponsored an American Medical Association Continuing Medical Education program for physicians, on genetic testing for breast and ovarian cancer.⁵⁹

The *BRCAAnalysis* test is marketed as three subtests: Single site *BRCAAnalysis* (single mutation analysis for a known family mutation, that is carrier testing) for US\$295 (C\$525); Multisite 3 *BRCAAnalysis* (analysis of the three common

⁵⁶Myriad Genetics, Press Release, "Myriad Genetics Obtains OncorMed's BRCA1/BRCA2 Genetic Testing Program in Patent Settlement" (18 May 1998), online: <<http://www.myriad.com/pr/19980518.html>> (date accessed: 9 September, 2002).

⁵⁷Murray, *supra* note 50.

⁵⁸Roberts, *supra* note 25.

⁵⁹Myriad Genetics, Press Release, "Aetna U.S. Healthcare and Myriad Genetics Distribute American Medical Association Monograph to Educate Physicians on Genetic Testing" (20 October 1999), online: <http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=mygn&script=412&layout=9&item_id=212167> (date accessed: 7 December 2002).

Ashkenazi Jewish mutations – 187delAG, 5385insC, 617delT) for US\$450 (C\$600); and Comprehensive *BRCA*Analysis (full gene sequencing) for US\$2,600 (C\$3,850). Thus patients who have not previously had BRCA testing in their family would undergo full sequencing (as the index case) of both BRCA genes to search for a mutation associated with the hereditary breast cancer in their family. If such a mutation is found, other family members can then be tested (at the reduced rate for single mutation analysis) to determine whether they carry the known family mutation.

In 1999 Myriad introduced its Rapid *BRCA*Analysis testing program, which has a seven day turn-around time and an additional cost of US\$1100 over the price for full sequencing.⁶⁰ Myriad's BRCA testing program is based on the use of large numbers of high-throughput automated DNA sequencers. The method is costly, but Myriad represents it as the 'gold standard' for genetic testing because each base-pair in the coding region of both BRCA genes is checked, and deleterious mutations can be specifically identified.⁶¹ This test will detect missense mutations (single nucleotide alterations that change an amino acid), and most frameshift or nonsense mutations that result in protein truncation.

Before the U.S. patent disputes were resolved, BRCA testing had already become commercially available in 1996; prior to 1996, testing had been available free of charge on a research basis. Myriad, OncorMed, the Genetics and IVF Institute, and the University of Pennsylvania Genetics Diagnostics Laboratory offered commercial genetic testing, but they varied in their methods, the parts of the genes tested, and the populations to which testing was made available.⁶² For example, Dr. Arupa Ganguly at the University of Pennsylvania Laboratory independently developed a BRCA test using conformation-sensitive gel electrophoresis (CSGE) which was offered commercially to patients for US\$1900. This method detects mutations by creating DNA hybrids (a single strand of known wild-type sequence paired with a single strand of test sequence containing a mutation), and then running them through gel electrophoresis where any pairing mismatch that affects DNA migration will be visible.⁶³ In contrast, OncorMed, which only per-

⁶⁰Myriad Genetics, Press Release, "Myriad Genetics Introduces New Breast Cancer Testing Service: Rapid BRCAAnalysis Designed to Provide Results in 7 Days" (4 November 1999), online: <<http://www.myriad.com/pr/19991104.html>> (date accessed: 9 September, 2002) [hereinafter "New Breast Cancer Testing Service"].

⁶¹Myriad Genetics, Press Release, "Myriad Genetics Launches Molecular Diagnostic Testing in Canada - MDS Laboratory Services to Provide BRCAAnalysis Throughout Canada" (9 March 2000), online: <http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=mygn&script=411&layout=9&item_id=212154> (date accessed: 7 December 2002) [hereinafter "Molecular Diagnostic Testing in Canada"].

⁶²H. Greely, B.A. Koenig, & T.A. Raffin, *Genetic Susceptibility Testing for Breast Cancer: A Report of the Stanford Program in Genomics, Ethics, and Society* (Cambridge: Cambridge University Press, in press); D.S. Hilzenrath, "Md. Firm's Gene Test to Intensify Bioethics Debate" *Washington Post* (25 July 1996) D14.

⁶³T. Ganguly *et al.*, "High Throughput Fluorescence-Based Conformation-Sensitive Gel Electrophoresis (F-CSge) Identifies Six Unique BRCA2 Mutations and an Overall Low Incidence of BRCA2 Mutations in High-Risk BRCA1-Negative Breast Cancer Families" (1998) 102:5 *Human Genetics* 549.

formed testing on patients who were part of Institutional Review Board approved research protocols, used protein truncation testing (PTT) – a method that analyses changes in protein length – followed by localized DNA sequencing.⁶⁴ Other laboratories used screening techniques such as single stranded conformational polymorphism (SSCP), which identifies mutations based on alterations in the way that single-stranded DNA folds upon itself and affects mobility on gel electrophoresis.⁶⁵

By the mid 1990s, BRCA testing had also become available through public laboratories, most of which had opted for a less expensive 2-step method that used a screening technique followed by limited gene sequencing. For example, PTT or SSCP would first be used to detect terminating mutations in the coding region of the gene. Once the target gene was isolated (either from DNA or RNA) and amplified using polymerase chain reaction (PCR), this product would then be used as a template for RNA synthesis and translated into a protein. These proteins could then be analysed to detect whether they were shorter than expected, as a result of truncation by mutated alleles. PTT preferentially detects a mutation type (that results in truncation) that is always clinically significant.⁶⁶ This technique can also detect large deletions and re-arrangements that would be missed by full DNA sequencing.⁶⁷ However, as missense mutations will not be detected, any positive result from PTT will have to be confirmed by DNA sequence analysis of the region in question to identify the specific mutation.

Understanding the technical aspects of these different approaches is important because there has been debate in the scientific and medical communities over which testing method should be considered the ‘gold standard.’ Some argue that PTT in conjunction with localized sequencing is equally effective as full DNA sequencing, with neither method being 100% accurate.⁶⁸ A new French method developed at the Institut Curie (using combed DNA colour bar coding) is able to detect large deletions and re-arrangements of BRCA1 and BRCA2 which the full DNA sequencing offered by Myriad misses.⁶⁹ Despite these disagreements about appropriate testing methodology, it is perhaps not surprising that Myriad maintains

⁶⁴ C.L. Carter *et al.*, “The Oncormed Approach to Genetic Testing” (1997) 1:2 Genetic Testing 137.

⁶⁵ GeneTests, Glossary, online: <<http://www.genetests.org>> (date accessed: 7 December 2002).

⁶⁶ Carter, *supra* note 30.

⁶⁷ DNA sequencing, whether automated or performed manually, operates by analysing a collection of short, overlapping pieces of DNA to determine the sequence of nucleotides. If a large portion of a gene has been deleted or re-arranged, particularly if it is in a non-coding region of the gene, this will not be detected.

⁶⁸ Carter, *supra* note 30. J.P. Geisler *et al.*, “Ovarian Cancer BRCA1 Mutation Detection: Protein Truncation Test (PTT) Outperforms Single Strand Conformation Polymorphism Analysis (SSCP)” (2001) 18:4 Human Mutation 337. Many patients will receive inconclusive results from either testing method. Despite being at high risk, no mutation may be found in the patient or their family and thus it remains unclear whether the result is a false-negative, the family history of cancer is the result of another gene, there is a common environmental cause, or the cancer is sporadic.

⁶⁹ S. Gad *et al.*, “Identification of a Large Rearrangement of the BRCA1 Gene Using Colour Bar Code on Combed DNA in an American Breast/Ovarian Cancer Family Previously Studied by Direct Sequencing” (2001) 38:6 J. Med. Genet. 388.

that their full sequencing approach is the gold standard. Due to their numerous U.S. and international patents – Myriad holds patents on the two BRCA genes in the U.S., Europe, Canada, Australia and New Zealand – they have been successful in overcoming their initial commercial competitors.⁷⁰ Commercial laboratories such as OncorMed and the University of Pennsylvania were systematically threatened with litigation until Myriad became the sole commercial provider of BRCA testing in the U.S.⁷¹ Myriad has continued to aggressively enforce its patent rights in the U.S., and is also beginning to do so internationally, most recently in Canada and Europe.

In the U.S., Myriad has entered into agreements with the major Health Management Organizations and insurance companies, such as Kaiser Permanente,⁷² Aetna U.S. Health Care, Blue Cross, and Blue Shield, to provide BRCA testing to their members. By 1999, over 390 health care insurers covered *BRCA*-analysis as part of their insurance plans.⁷³ In December 2001, Myriad announced a partnership with LabCorp, a large U.S. medical diagnostics company, that enlists LabCorp's 600-person U.S. sales force to market and distribute Myriad's predictive medicine products to more than 200,000 physician customers. Myriad will continue marketing its products to oncologists⁷⁴ and in September 2002 launched an extensive public marketing campaign for BRCA testing in two U.S. cities.⁷⁵ Internationally, Myriad has signed licensing agreements with companies in Canada,⁷⁶ the U.K. and Ireland,⁷⁷ Japan,⁷⁸ Germany, Switzerland, and Austria,⁷⁹ for exclusive provision

⁷⁰M. Balter, "Cancer Research: Transatlantic War over *BRCA 1* Patent" (2001) 292:5523 *Science* 118.

⁷¹J. Borger, "Rush to Patent Genes Is Hampering Medical Research" *The Guardian* (15 December 1999), online: <<http://www.purefood.org/Patent/rushpatent.cfm>> (date accessed: 7 December 2002).

⁷²Myriad Genetics, Press Release, "Myriad Genetics and Kaiser Permanente Sign Agreement for Breast Cancer Testing" (15 February 2000), online: <http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=mygn&script=411&layout=9&item_id=212157> (date accessed: 7 December 2002).

⁷³Myriad Genetics, "New Breast Cancer Testing Service" *supra* note 60.

⁷⁴Myriad Genetics, Press Release, "Myriad Genetics and Labcorp Form Exclusive Predictive Medicine Marketing Alliance" (4 December 2001), online: <http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=mygn&script=410&layout=9&item_id=232709> (date accessed: 15 November 2002).

⁷⁵Myriad Genetics, Press Release, "Myriad Genetics Launches Direct to Consumer Advertising Campaign for Breast Cancer Test" (12 September 2002), online: <http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=mygn&script=413&layout=9&item_id=333030> (date accessed: 12 November 2002).

⁷⁶Myriad Genetics, "Molecular Diagnostic Testing in Canada" *supra* note 61.

⁷⁷Myriad Genetics, Press Release, "Myriad Genetics Launches Predictive Medicine Business in the United Kingdom and Ireland" (8 March 2000), online: <http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=mygn&script=411&layout=9&item_id=212155> (date accessed: 7 December 2002) [hereinafter "Predictive Medicine Business"].

⁷⁸Myriad Genetics, Press Release, "Myriad Genetics Launches Genetic Testing in Japan - Falco Biosystems, Ltd. To Promote Myriad's Commercial Products in Japan" (1 February 2000), online: <http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=mygn&script=411&layout=9&item_id=212159> (date accessed: 7 December 2002).

⁷⁹Myriad Genetics, Press Release, "Myriad Genetics Launches Predictive Medicine Testing in Germany, Switzerland, and Austria" (27 June 2001), online: <http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=mygn&script=410&layout=9&item_id=210285> (date accessed: 7 December 2002).

of BRCA testing in those countries. Myriad has also reached agreements with various U.S. research facilities, including the NIH and National Cancer Institutes, to provide at-cost (US\$1,200) DNA sequencing for researchers, as long as the research does not include the provision of clinical services.⁸⁰

A complicating factor for Myriad in launching a genetic testing program in Europe and protecting this program through enforcement of their patents is the Cancer Research Campaign's (CRC) U.K. patent on part of BRCA2. The CRC had licensed its patent to OncorMed with the proviso that the U.K. National Health Service (NHS) be able to use the resulting test without payment of license fees or royalties. When Myriad purchased the OncorMed patents, Myriad then entered into a five year licensing agreement with the Scottish company Rosgen Ltd. to market BRCA testing in the U.K. and Ireland.⁸¹ However, Rosgen was unable to raise sufficient capital investment to stay solvent and folded in 2001. Myriad is still negotiating with the U.K. Department of Health about provision of BRCA testing in the U.K.⁸² Recent E.U. patents on BRCA1 and BRCA2 in 2001 have further strengthened Myriad's legal position in Europe.

7. Reactions Against Commercial Testing

The marketing of commercial BRCA testing and Myriad's subsequent dominance in this area has met with opposition on a variety of fronts, beginning in the U.S. in 1994 through 1996.⁸³ Support groups such as Breast Cancer Action have been critical of Myriad's public education program, charging that it has far more to do with increasing anxiety and convincing women and their physicians of the need for testing, than actually informing people of the facts about breast cancer.⁸⁴ In part due to the issues exemplified by the commercialization of the BRCA genes, the American College of Medical Geneticists has called for a ban on human gene patenting, arguing that it leads to monopolistic licensing and exorbitant user fees.⁸⁵ More recently, in March 2002 hearings were held by the U.S. Federal Trade

⁸⁰T. Reynolds, "NCI-Myriad Agreement Offers BRCA Testing at Reduced Cost [News]" (2000) 92:8 J. National Cancer Institute 596.

⁸¹Myriad Genetics, "Predictive Medicine Business" *supra* note 77.

⁸²R. Sylvester, "NHS Deal on Gene Test for Cancer" *Electronic Telegraph* (26 April 2001), online: <www.telegraph.co.uk> (date accessed: 7 December 2002); Nuffield Council on Bioethics, *supra* note 12 at 39.

⁸³Nature, "U.S. Coalition Counters Breast Gene Patents" (1996) 381:6580 Nature 265; K. Wright, "Patent Medicine" *Discover* (January 1997) 78; Roberts, *supra* note 25.

⁸⁴J. Lauren, "Getting into Our Genes: Myriad Nails the BRCA-1 and 2 Testing Market" (2001) 67 Breast Cancer Action Newsletter, online: <<http://www.bcaction.org/Pages/SearchablePages/2001Newsletters/Newsletter067A.html>> (date accessed: 7 December 2002).

⁸⁵American College of Medical Genetics, *Position Statement on Gene Patents and Accessibility of Gene Testing* (ACMG, 2 August 1999), online: <<http://www.faseb.org/genetics/acmg/pol-34.htm>> (date accessed: 7 December 2002).

Commission⁸⁶ and a subcommittee of the House of Representatives' judiciary committee⁸⁷ to address issues with regards to biotechnology and patent policies; in the same month, a bill was introduced (by Democratic Representative Lynn Rivers) that would require the Director of the Office of Science and Technology Policy to study the impact of government policies on the innovation process for genomic technologies, and would create an exemption from patent infringement for researchers and clinicians who use genetic-based diagnostic tests for non-commercial purposes.⁸⁸ Significant opposition to commercial genetic testing, and particularly the patenting of the BRCA genes, has also developed in Canada and Europe as Myriad has obtained patents and begun licensing testing to local companies.

8.1 Europe

In January and May of 2001, the European Patent Office (EPO) granted Myriad patents on the BRCA1 and BRCA2 genes.⁸⁹ Prior to this decision there had been mounting pressure from the U.K. and French genetics research communities opposing the commercialization of BRCA testing. With the patents granted, opposition has crystallized into opposition proceedings against the E.U. patents by the Institut Curie in Paris and a coalition of 16 other French laboratories.⁹⁰ The BRCA patents are being challenged for not meeting the basic criteria of European patent law. Specifically, it is argued that the patents: 1) lack novelty because predisposition tests were already available prior to the patents being filed; 2) lack inventiveness because Myriad benefited from knowledge gained by a public consortium not acknowledged in the patents; and 3) are insufficiently described, as the protein sequence used in the patents filing is insufficient to produce the diagnostic method covered in the patents.⁹¹

Opposition by the Institut Curie and other European laboratories, however, is grounded in a more expansive rejection of the patentability of the genes. First

⁸⁶ Federal Trade Commission, *Competition and Intellectual Property Law and Policy in the Knowledge-Based Economy*, online: <<http://www.ftc.gov/opp/intellect/index.htm>> (date accessed: 7 December 2002).

⁸⁷ Subcommittee on Courts, the Internet, and Intellectual Property, *Patent Law and Non-Profit Research Collaboration*, online: <<http://www.house.gov/judiciary/78218.PDF>> (date accessed: 7 December 2002).

⁸⁸ *Genomic Research and Diagnostic Accessibility Act of 2002*, H.R.3966, online: <http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=107_cong_bills&docid=f:h3966ih.txt> (date accessed: 7 December 2002).

⁸⁹ R. Watson, "MEPs Add Their Voice to Protest at Patent for Breast Cancer Gene" (2001) 323:7318 *British Med. J.* 888.

⁹⁰ A. Dorozynski, "France Challenges Patent for Genetic Screening of Breast Cancer" (2001) 323 *British Med. J.* 589; M. Rimmer, "Myriad Genetics: Patent Law and Genetic Testing" (2003) 25:1 *Eur. Intellectual Property Rev.* (forthcoming).

⁹¹ Institut Curie, *Against Myriad Genetics's Monopoly on Tests for Predisposition to Breast and Ovarian Cancer* (Paris: Institut Curie, 12 September 2001), online: <http://www.curie.net/frame.cfm?menu=A&smenu=A&content=actualites/myriad/declaration_e.htm> (date accessed: 7 December 2002).

and foremost, the French dispute the legitimacy of Myriad's claim to be providing the 'gold standard' genetic test. The Myriad approach to testing, which involves full DNA sequencing of the two BRCA genes, can only detect small-scale deletions and re-arrangements. However, recent work conducted by researchers at the Institut Curie – using a technique developed (and patented) by the Institut Pasteur in 1994 called combed DNA colour bar coding⁹² – identified a 3 exon deletion in BRCA1 in a patient who had received a negative result (no mutations detected) when tested by Myriad. This and other research suggests that large scale deletions or re-arrangements may be responsible for as much as 36% of BRCA1 mutations in some populations.⁹³ The researchers at the Institut Curie argue that Myriad's testing method misses 10% to 20% of expected mutations, seriously jeopardising the quality of test results and usefulness of this information for patient care.⁹⁴ Their position is that the Curie test for large scale deletions should be used at least as a supplement, if not an alternative, to the full sequencing approach used by Myriad. The broad nature of the European BRCA patents – which cover any diagnostic or therapeutic use of the BRCA1 and BRCA2 genes – means that clinicians using this new technique would be infringing the patents and thus open to legal suits, thereby undermining their ability to provide patient services.

It is further argued that the Myriad patents constitute an unreasonable monopoly that negatively constrains research, preventing the development of better, faster, and more accurate tests and treatments.⁹⁵ The fee demanded by Myriad is too costly to be covered by many public health insurance systems, particularly if the service is paid for out of hospital budgets. In France, BRCA testing performed 'in-house' would cost approximately a third of Myriad's price. Complying with the European patents and paying Myriad for testing would result in an estimated additional cost of 36 million francs (C\$7.6 million) to hospital budgets.⁹⁶ These high costs would result in restrictions in access to needed medical services, and are thus against the public interest.

For these reasons, a number of European nations, e.g., Germany, Sweden, the Netherlands, Spain, and Belgium, have voiced their opposition to the patents (with the Netherlands and Belgium joining the Institut Curie's suits⁹⁷) and intent to continue provision of BRCA testing in defiance of the E.U. patents.⁹⁸ This position has been backed by Members of the European Parliament who adopted a resolution criticizing the decision of the EPO, and warning that these patents would create an

⁹² Gad *et al.*, *supra* note 69.

⁹³ *Ibid.*

⁹⁴ Institut Curie, *supra* note 91.

⁹⁵ J. Henley, "Cancer Unit Fights Us Gene Patent" *The Guardian* (8 September 2001), online: <<http://www.guardian.co.uk/international/story/0,3604,548535,00.html>> (date accessed: 7 December 2002).

⁹⁶ Institut Curie, *supra* note 91.

⁹⁷ S. Warner, "Lawmakers Plan Curbs to Patent Power [News]" (2002) 16:10 *The Scientist* 30.

⁹⁸ S. Benowitz, "French Challenge to BRCA1 Patent Underlies European Discontent [News]" (2002)

94:2 *J. National Cancer Institute* 80.

unfair and harmful monopoly in Europe.⁹⁹ In France, concern about the Myriad patents has caused delays in updating the Biotechnology Patenting Directive and led to a controversial bioethics bill that would broaden compulsory licensing schemes to facilitate access to diagnostic testing services, and even ban the patenting of human genes.¹⁰⁰

8.2 Canada

Genetic testing for mutations in the two BRCA genes was first available in Canada on a research trial basis in 1996 (although linkage testing was in use by 1995). In British Columbia, clinical services have been provided since 1996 through the Hereditary Cancer Program (HCP) at the B.C. Cancer Agency. This capacity was developed in part through funding by the B.C. chapter of the Canadian Breast Cancer Foundation for the purchase of a DNA sequencer to perform BRCA testing, as well as for a pilot study on how best to offer genetic counselling and testing for hereditary breast and ovarian cancer. The HCP's operating budget – which covers provision of genetic testing, patient counselling, and physician and patient education for a range of hereditary cancers – comes from the global budget of the B.C. Cancer Agency, which is in turn funded by the province.

An average of 80 families have entered the HCP each month, with 1500 passing through the program in the past 5 years.¹⁰¹ Similar publicly funded genetic testing programs and laboratories have been set up in Ontario and Alberta. Saskatchewan,¹⁰² Newfoundland, and Nova Scotia provide services but send blood samples out for analysis by other provincial laboratories, usually in Ontario. Manitoba provides screening for the Ashkenazi Jewish and Icelandic mutations only. Québec is the exception in that local laboratories screen for 5 to 7 Ashkenazi and French Canadian mutations, but full DNA sequencing is sent to Myriad and paid for by the provincial government.¹⁰³

⁹⁹Watson, *supra* note 89.

¹⁰⁰The *Projet de loi relatif à la bioéthique*, online:

<<http://www.assemblee-nationale.fr/dossiers/bioethique.asp>> (date accessed: 7 December 2002), passed review by the lower house of the French parliament in February 2002, although a vote by the upper house is not expected until later in the year. ERA-News, "France Votes to Ban DNA Patents" *ERA-News* (14 February 2002), online: <<http://www.gentech.at/pressespiegel/pressespiegel85text.html#2>> (date accessed: 7 December 2002). Interestingly, this move towards compulsory licensing of genetic testing may be permissible under TRIPS agreement, as a legitimate public health measure. World Trade Organization. *Declaration on the TRIPs Agreement and Public Health*, Doc. WT/MIN(01)/Dec/2 (20 November, 2001), online: <http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm> (accessed: 7 December 2002).

¹⁰¹Horsman, *supra* note 31.

¹⁰²E.G. Lemire, "Saskatchewan Continues Breast Cancer Screening [Letters]" (2002) 166:8 C.M.A.J. 1012.

¹⁰³Personal Communication from K. Panabaker, Hereditary Cancer Program, BC Cancer Agency (23 January 2002).

Despite the existence of these provincial programs, the public health care system still has difficulty providing comprehensive and timely genetic testing and counselling for hereditary breast and ovarian cancer, due in part to understaffing of laboratory personnel and genetic counsellors, and a lack of high throughput DNA sequencers. This has resulted in extended waiting lists – more than a year in some centres – for access to genetic testing and counselling. In August 1999, this situation in Ontario led to the case of Fiona Webster, a woman at risk for hereditary breast cancer who successfully challenged the Ontario Health Insurance Plan (OHIP) to cover rapid access to BRCA testing as an essential service. Ms. Webster had not received testing because she was not part of a research protocol and did not meet the testing criteria. OHIP agreed to cover the cost of testing through Myriad in order that Ms. Webster could have quicker access to information with which to make a decision about prophylactic surgery.¹⁰⁴ In March 2000, the Ontario government decided to fund genetic testing for hereditary breast and ovarian cancer as part of the provincial health insurance plan, and thus expanded the number of laboratories providing clinical genetic testing and counselling.

While genetic testing in Canada had been offered publicly in various provinces, it was also available commercially from companies such as Myriad Genetics. In March 2000, Myriad announced an exclusive licensing agreement with MDS Laboratory Services of Toronto, to provide *BRCA* analysis testing across Canada. MDS is one of the largest providers of medical diagnostic testing services in the country. They are offering a turn-around time for BRCA testing of approximately 3 weeks, with easy access to testing facilities through their nation wide collection and logistics facilities. In practice, regional differences in the operation of MDS (there are two branches of the company which operate somewhat independently of each other) mean that in western Canada MDS is establishing laboratory services for single mutation testing, but sending index cases and samples requiring full sequencing to the Myriad laboratory in Utah. In contrast, in eastern Canada MDS has established itself primarily as a broker for patients seeking BRCA testing and is sending all samples to Myriad for analysis. In addition, MDS is expanding their Canadian market for genetic testing by introducing other tests such as Myriad's *Colaris* test for colorectal and uterine cancer.¹⁰⁵ Along with testing, MDS will engage in patient and physician 'education' as a means of facilitating better access and management of the entire testing process.

In October 2000, the first Canadian patent on BRCA1 was granted to Myriad; the BRCA2 patent was granted the following April (for a total of 4 patents).¹⁰⁶

¹⁰⁴C. Abraham, "The Politics of Hope" *The Globe & Mail* (17 July 1998); C. Abraham, "Tenacious Woman Scores Medical Victory" *The Globe & Mail* (27 August 1999) A1.

¹⁰⁵Myriad Genetics, Press Release, "Myriad Genetics Launches Colaris(TM) in Canada: MDS to Market Colaris Colon Cancer Product Throughout Canada" (19 October 2000), online: <http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=mygn&script=411&layout=9&item_id=212127> (date accessed: 7 December 2002).

¹⁰⁶Canadian patents CA 2,239,733, CA 2,196,790, CA 2,196,795, and CA 2,196,797. Canadian Intellec-

Myriad and MDS began notifying public health care institutions that MDS had the exclusive Canadian rights for the use of the BRCA1 and BRCA2 genes for all forms of clinical testing. Public laboratories were therefore sent 'cease and desist' letters to encourage them to comply with the Canadian patents and refer BRCA testing directly to MDS or Myriad,¹⁰⁷ although these letters have yet to be backed by formal legal challenges from either Myriad or MDS.

Among the Canadian provinces offering public BRCA testing, to date only British Columbia complied (temporarily) with the Myriad patents and ceased to provide in-house testing. On July 13 2001, the Hereditary Cancer Program (HCP) at the B.C. Cancer Agency was forced to stop testing by the B.C. Ministry of Health Services,¹⁰⁸ or purchase testing through Myriad or MDS out of the HCP's existing budget. The cost to perform genetic testing (PTT followed by targeted sequencing) at the HCP is approximately C\$1200;¹⁰⁹ purchasing the test from Myriad at a cost of C\$3850 (full DNA sequencing of both genes) would quickly exhaust the HCP's budget. This would undermine the HCP's ability (and mandate) to provide services to patients at-risk for a variety of hereditary cancer syndromes. For patients whose blood samples had been taken and testing begun, the HCP completed the analyses but could not provide follow-up carrier testing for other family members if a mutation was found. For patients whose blood had been collected but testing had not been started, the HCP was no longer performing testing. Patients were informed they would have to pay MDS or Myriad if they wished testing, but the HCP would continue to provide pre- and post-test genetic counselling, as well as facilitating the purchase of testing should it be desired by patients and families.¹¹⁰ Unsatisfied with this situation, the HCP and the BC Cancer Agency began employing "round about methods" to avoid infringing the patents, and brokered patient access to an Ontario run BRCA research project. Those individuals who qualified for the research project received testing (although based on a less comprehensive method than was used by the HCP) and obtained results privately, which they could then share with the HCP staff as part of post-test counselling and interpretation.¹¹¹ In February 2003, the B.C. Ministry of Health Services changed its position (of obeying the Myriad patents) and permitted the HCP and BC Cancer Agency to recommence in-house BRCA testing.¹¹²

tual Property Office patents database, online: <<http://patents1.ic.gc.ca/intro-e.html>> (accessed: 7 December 2002).

¹⁰⁷ Myriad Genetics, "Molecular Diagnostic Testing in Canada" *supra* note 61.

¹⁰⁸ A.J. Coldman, Press Release, "Policy Change for Testing of Breast Cancer Susceptibility Genes: BRCA1 and BRCA2" (24 August 2001).

¹⁰⁹ H. Kent, "Patenting Move Ends BC's Gene-Testing Program" (2001) 165:6 C.M.A.J. 812, online: <<http://www.cmaj.ca/cgi/reprint/165/6/812.pdf>> (date accessed: 7 December 2002), at 812.

¹¹⁰ *Ibid.*

¹¹¹ CBC, "Ontario Doing B.C. Breast Cancer Testing" (18 October 2002) *CBC*, online: <http://vancouver.cbc.ca/template/servlet/View?filename=bc_cancer021018> (date accessed: 12 November 2002).

¹¹² British Columbia Ministry of Health Services, "Federal Leadership Urged as Genetic Testing Resumes" (14 February 2003) *Press Release*, online: <http://www2.news.gov.bc.ca/nrm_news_releases/2003HSER0009-000160.htm> (date accessed: 26 March 2003).

Former Ontario Premier Mike Harris has been most notable in his public opposition to the commercialization of BRCA testing in Canada. In August 2001, Harris raised the issue of gene patenting (and the particular case of Myriad) at the Annual Premiers' Conference in Victoria, B.C.¹¹³ The Harris government took the position that Ontario was not infringing Myriad's patents by paying hospitals to perform BRCA testing, and that public testing should be continued due to its benefit for Canadian women.¹¹⁴ In speeches by Harris¹¹⁵ and Ontario Minister of Health Tony Clement¹¹⁶ to the Ontario Advisory Committee on Predictive Genetic Technology, concerns were raised about the commercialization of genes in general, and Myriad's BRCA patents in particular. Specifically, Harris and Clement questioned the effects of monopoly pricing on the continued provision of publicly funded health care and the extent to which patents facilitate or inhibit continued genetic and medical research. Harris argued that the benefits coming from the Human Genome Project should not be controlled by a few people or companies, as the genetic heritage of humanity belongs to everyone. He said that the federal government should therefore address the 'Wild West' of gene patenting.¹¹⁷ Further, the Ontario Ministry of Health and Long Term Care was tasked with preparing a report for the Premiers' conference, entitled *Genetics and Gene Patenting: Charting New Territory in Health Care*. This report discusses the ethical and policy implications of gene patenting and recommends, amongst other things, the modernization of the Canadian *Patent Act* to improve oversight and transparency, the exclusion of broad-based genetic patents such as those for the BRCA genes, the introduction and use of a strong public morality clause (similar to that present in E.U. patent law), and the establishment of safeguards to protect health care practitioners and researchers from patent infringement for experimental or non-commercial use.¹¹⁸

Finally, the Canadian Cancer Society (CCS) and the National Cancer Institute of Canada (NCIC) have taken the position that the federal government should "take

¹¹³ P. Willcocks, "Canadian Premiers Wade into Gene Patenting Debate" *Reuters News* (3 August 2001).

¹¹⁴ C. Mallan, "Gene Tests for Cancer Won't Stop" *The Toronto Star* (20 September 2001), online: <http://www.thestar.com/NASApp/cs/ContentServer?GXHC_gx_session_id_=1b4efb9da8e66544&pagename=thestar/Layout/Article_PrintFriendly&c=Article&cid=1000936972246> (date accessed: 7 December 2002); Canadian Press, "Ontario Defies U.S. Gene Company over Cancer Test, Arguing Health Care at Risk" *Excite News* (19 September 2001), online: <<http://lists.essential.org/pipermail/ip-health/2001-September/001877.html>> (date accessed: 7 December 2002).

¹¹⁵ M. Harris, "Notes for Remarks by Mike Harris, Ontario's Premier" (Ontario Advisory Committee on Predictive Genetic Technology, Government of Ontario, Toronto, 19 September 2001).

¹¹⁶ T. Clement, "Speech Re: Myriad Gene Patent Issue" (Ontario Advisory Committee on Predictive Genetic Technology, Government of Ontario, Toronto, 19 September 2001), online: <http://www.gov.on.ca/health/english/news/speech/sp_091901_tc.html> (date accessed: 7 December 2002).

¹¹⁷ Harris, *supra* note 115.

¹¹⁸ Ontario Ministry of Health and Long Term Care, *Genetics and Gene Patenting: Charting New Territory in Health Care* (Toronto: Government of Ontario, January 2002), online: <<http://www.gov.on.ca/health/english/pub/ministry/geneticsrep02/genetics.html>> (date accessed: 7 December 2002).

action to ensure that Myriad's patents are not permitted to interfere with Canadian women's access to BRCA1 and BRCA2 testing, carried out with appropriate counselling, or with the expeditious development of new knowledge about genes and health." Moreover, the CCS and NCIC "encourage provincial governments to initiate court challenges of the breadth of the claims contained in these patents and the manner in which the patents are administered."¹¹⁹

9. Conclusion

The race to find, patent, and commercialize the two BRCA genes associated with hereditary breast and ovarian cancer raises significant issues that may affect the way in which genetic testing services will be provided around the world. In the U.S., BRCA testing has been adopted for coverage by many of the major private health insurers, and for groups covered in this way, the commercial nature of the test has largely ceased to be an issue of contention; women outside such group coverage still do not have access to the test unless they can pay the high cost. Nevertheless, as noted above there have been preliminary policy discussions about the implications of biotech patents on access to genetic services, and draft legislation that would constrain broad gene patents and enforce compulsory licensing to guarantee public access to genetics tests.¹²⁰

In Canada and Europe, where there are publicly supported health care systems, the commercial nature of the test and Myriad's attempt to enforce their patent rights is fuelling heated debate. Although initially it was the clinicians and scientists involved in the provision of genetic services who were most concerned about the patenting of the BRCA genes, increasingly it is becoming a concern of patient support and advocacy groups, politicians, and the general public. In Canada, opposition has taken the form of provincial service providers for the most part simply ignoring Myriad's patent claims.¹²¹ In Europe, opposition has led to formal legal challenges of the BRCA patents by the French Institut Curie, backed by other national genetics laboratories. If these challenges are successful, they will have a profound impact on Myriad's ability to function as a commercial provider of genetic services, as the legal costs might well bankrupt the company. A successful European challenge could also galvanize opposition in other countries such as

¹¹⁹ Canadian Cancer Society & National Cancer Institute of Canada, *Canadian Cancer Society (CCS) and National Cancer Institute of Canada (NCIC) Position on the Patenting of BRCA1 and BRCA2 Genes* (Ottawa: Canadian Cancer Society & National Cancer Institute of Canada, 8 March 2002), online: <<http://www.cancer.ca/files/BRCApatents.pdf>> (date accessed: 7 December 2002) at 3.

¹²⁰ See *supra* notes 86, 87, and 88 and accompanying text. There is also a burgeoning social, ethical and policy literature that is beginning to explore the implications of gene patents for the provision of health care and conduct of research in the U.S. See J. Merz, "A Patently Bad Prescription: 'Breaking Bioethics' Argues against Patents for Gene Tests" *MSNBC* (30 August 1999); S.C. Hull & K. Prasad, "Reading between the Lines: Direct-to-Consumer Advertising of Genetic Testing in the USA" (2001) 9:18 *Reproductive Health Matters* 44; M.K. Cho *et al.*, "Commercialization of BRCA1/2 Testing: Practitioner Awareness and Use of a New Genetic Test" (1999) 83 *Am. J. Med. Genet.* 157.

¹²¹ L. Eggertson, "Ontario Defies Us Firm's Genetic Patent, Continues Cancer Screening" (2002) 166:4 *C.M.A.J.* 494; Lemire, *supra* note 102.

Canada. Yet even if the challenges do not succeed but public service providers continue to provide testing, the lack of monopoly control on BRCA testing will effectively dissipate Myriad's market in Europe and Canada. The complete history of the discovery and commercialization of the BRCA genes remains to be written.

In working through the Myriad case study, this paper provides the rich description necessary to lay the groundwork on which to build a comprehensive social and ethical analysis of the issues arising from DNA patenting and commercialization.¹²² The Myriad patent is a forerunner or test case for a host of other gene and biological patents, and has implications for national and international patent law. If the BRCA patents stand, hundreds of other gene patents are likely to follow, exacerbating the current rush to patent genes – what former Premier Harris described as the 'Wild West' situation. This will have a direct impact on the manner in which scientific knowledge and discoveries are commercialized and transformed into clinical practice. Unrestrained DNA patenting could lead to a situation where all genes are patented and new research becomes prohibitively expensive, what Heller and Eisenberg have described as a 'tragedy of the anticommons.'¹²³ Unrestrained gene patenting would also have a significant impact on the provision of genetic services through the public health care system, potentially making genetic tests and therapeutics unaffordable, and thereby raising serious issues of justice in access to medical services. It is thus crucial that health services research begin to address these issues in detail, with particular consideration to if and how genetic services are to operate as part of the Canadian health care system.¹²⁴ The Myriad case touches on a fundamental question for Canadians: how as a society should we go about more coherently deciding what to cover as part of public health insurance and what to leave to private purchase? And if we

¹²²For examples of such analyses, see the author's unpublished dissertation, B. Williams-Jones, *Genetic Testing for Sale: Implications of Commercial BRCA Testing in Canada* (Ph.D. thesis, University of British Columbia, 2002), and two articles in print and in press, "Where There's a Web, There's a Way: Commercial Genetic Testing and the Internet" (2003) 6:1 *Community Genetics* 46; B. Williams-Jones & J. Graham, "Actor-Network Theory: A Tool to Support Ethical Analysis of Commercial Genetic Testing" (in press) *New Genetics and Society*. In these works, an interdisciplinary analysis is presented that draws tools from the social sciences, health law and policy, and moral philosophy. The author also proposes recommendations for government oversight and regulation to minimize the negative aspects of commercialization while maximizing the benefits, in order to improve the ethical and equitable provision of commercial genetic tests. See also L. Sheremeta, E.R. Gold & T.A. Caulfield, "Harmonizing Commercialization and Gene Patent Policy with Other Social Goals" (3rd International DNA Sampling Conference, Montreal, 5-8 September 2002), in B.M. Knoppers, ed., *Proceedings of the 3rd International DNA Sampling Conference*, (forthcoming).

¹²³M.A. Heller & R.S. Eisenberg, "Can Patents Deter Innovation? The Anticommons in Biomedical Research" (1998) 280:5364 *Science* 698.

¹²⁴The Ontario government, through their Provincial Advisory Committee on New Predictive Genetic Technologies, has begun considering these issues in some depth and even provided an evaluative framework (which has yet to be validated) to support policy discussions. Provincial Advisory Committee on New Predictive Genetic Technologies, *Genetic Services in Ontario: Mapping the Future* (Toronto: Provincial Advisory Committee on New Predictive Genetic Technologies, 30 November 2001), online: <http://www.gov.on.ca/health/english/pub/ministry/geneticsrep01/genetic_report.pdf> (date accessed: 7 December 2002). Concrete recommendations have also been made in the Report for the Premiers' conference: Ontario Ministry of Health and Long Term Care, *supra* note 118.

are going to leave some (which?) genetic tests available for private purchase, we must then be prepared to deal with the consequences of less equitable access to public health care services.