GENETIC TESTING FOR SALE:
IMPLICATIONS OF COMMERCIAL BRCA TESTING IN CANADA

by

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Abstract

Ongoing research in the fields of genetics and biotechnology hold the promise of improved diagnosis and treatment of genetic diseases, and potentially the development of individually tailored pharmaceuticals and gene therapies. Difficulty, however, arises in determining how these services are to be evaluated and integrated equitably into public health care systems such as Canada's. The current context is one of increasing fiscal restraint on the part of governments, limited financial resources being dedicated to health care, and rising costs for new health care services and technologies. This has led to increasing public debate in the last few years about how to reform public health care, and whether we should prohibit, permit or perhaps even encourage private purchase of health care services.

In Canada, some of these concerns have crystallized around the issue of gene patents and commercial genetic testing, in particular as illustrated by the case of Myriad Genetics' patented *BRACAnalysis* test for hereditary breast and ovarian cancer. While most Canadians who currently access genetic services do so through the public health care system, for those with the means, private purchase is becoming an option. This situation raises serious concerns – about justice in access to health care; about continued access to safe and reliable genetic testing supported by unbiased patient information; and about the broader effects of commercialization for ongoing research and the Canadian public health care system. Commercial genetic testing presents a challenge to health care professionals, policy analysts, and academics concerned with the social, ethical and policy implications of new genetic technologies. Using the Myriad case as an exemplar, tools from moral philosophy, the social sciences, and health policy and law will be brought to bear on the larger issues of how as a society we should regulate commercial research and product development, and more coherently decide which services to cover under public health insurance and which to leave to private purchase. Generally, the thesis is concerned with the question of "how best to bring capital, morality, and knowledge into a productive and ethical relationship" (Rabinow 1999, 20).

Table of Contents

List of Figures

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Chapter 1

General Introduction

Introduction

The last decade has seen a phenomenal growth in new medical technologies, particularly in the area of genetics and biotechnology. Pre-natal genetic testing is now being used to detect a host of conditions such as Down syndrome, myotonic and muscular dystrophy, cystic fibrosis, or hypercholesterolemia, in order to provide parents with information about the health status of their future offspring, possible treatment options, and the opportunity to make decisions about the continuation of a pregnancy. Genetic testing is also becoming useful for obtaining information about adult-onset disorders such as Huntington disease, Alzheimer's disease, polycystic kidney disease, and for the single gene forms of an increasing number of common hereditary cancers such as colon, breast and ovarian cancer.[1]

The development of and access to these new genetic technologies is set within a context of slowing economic development and calls for fiscal restraint, deficit fighting, and the 'need' to re-evaluate public expenditures. Mounting pressures on the health care system in Canada have led to criticism by some groups and renewed debate about how to reform health care. In particular, discussion has focused on the politically charged questions of determining which services should be funded, how they ought to be delivered, and whether

[1] For the purposes of this thesis, 'genetic testing' will be defined as "the analysis of a particular gene in order to provide 'predictive' or 'pre-symptomatic' information – usually for high penetrance genes – about the nature or time of disease onset; or 'susceptibility' information – for genotypes of low penetrance – about the potential or risk of developing a particular disease." This is a modification of the 1998 WHO definition (WHO Programme in Human Genetics 1998), and does not explicitly include multiplex or genomic testing, which will likely become more important as a result of information arising from the Human Genome Project.

the system should move towards more private purchase of services. At the Premiers Health Care Summit in Vancouver (January 24-25, 2002), for example, a variety of approaches to health care reform were discussed, especially the need to re-evaluate the *Canada Health Act.* The premiers agreed to work towards better inter-provincial co-operation to increase efficiency and reduce duplication of services; they also agreed on the importance of presenting a united front in negotiations with the federal government about increased health care funding (Joyce 2002; Thomson and Ovenden 2002). Provincial governments have commissioned reports, such as the Alberta Mazankowski Report *A Framework for Reform* (Mazankowski 2001), to make recommendations for rationalizing health care provision in order to improve delivery and quality of services while reducing the costs. At the national level, the federal government has launched the Romanow Commission on the Future of Health Care in Canada. Tasked with making recommendations on how to sustain the public health care system, the Commission is holding public consultations in all ten provinces and three territories, with a process that it is hoped will be objective, transparent, comprehensive, evidence-based, inclusive and respectful (www.healthcarecommission.ca).

The integration of new genetic technologies into health care systems, and coverage under public health insurance, will be an ongoing challenge for policy makers. In an ideal world, every needed and beneficial health care service would be supported by a health care system, and provided in a timely and equitable manner to the entire population (Daniels 1985, 2001). The current political reality is one of limited resources being put towards health care and the need to fund other important sectors such as social services, education, or transportation that may be as or even more effective at producing health (Evans, Barer, and Marmor 1994; Mechanic 1999). Determining how best to allocate health care resources is a

difficult task that is further complicated by the rapid development of new and often expensive medical technologies, and pressures from a variety of interests to cover particular services under public health insurance. Short of devoting the majority of a nation's economic resources to the funding of health care, not all useful and desired health care services will be affordable – priority-setting decisions will be required (Evans 1992; Burgess 1996).

In evaluating new and existing health care technologies and services for coverage under public health insurance, medical and scientific criteria will first be applied to ensure that services meet basic levels of safety and efficacy before being made available to patients and health care professionals. But technology assessment will be only one of many factors involved in determining whether a technology or service will receive public funding; other criteria, such as whether a service is considered 'medically necessary' will often play an important role in such determinations. However, this particular concept is ambiguous and while it may be widely used, e.g., in the *Canada Health Act*, it is rarely defined. Added to these difficulties is the fact that decisions about which services to fund are not usually based on rational or coherent decision-making frameworks. Instead, decisions have and continue to be made in an *ad hoc* manner influenced by public, private, and professional interests (Evans 1992; Flood 1999). Those services or technologies that are popular, innovative, or favoured by public or professional interest groups may become funded even when the usefulness of the service remains unclear. Similarly, other services that are less in the public focus and not demanded by influential groups, but are nonetheless demonstrably useful, may not be covered by public health insurance.

Health care insurance, originally developed to cover the costs of treating catastrophic injuries that would otherwise bankrupt individuals and families, has developed into a broad

plan that covers a host of acute, chronic, and preventative health care services. These additions were not made in a coherent manner with a clear vision of the purpose or goal of health care, so the resulting system is a conglomeration of different services added on over the last fifty years (Evans 1992; Flood 1999). This situation raises serious concerns about the efficient use of limited funds and justice in the allocation of and access to health care services. It points towards the need for a more fair and coherent method of decision-making, one that better evaluates the costs and benefits of services while considering the larger goals of public health care (Daniels 2001).

Some questions that need to be addressed (but which are extremely controversial) include determining what proportion of health care should be aimed at improving population health in comparison to the proportion for treating chronic or acute illness. For specific services, what is the service supposed to achieve in terms of information, benefits, or treatment options? How and to whom should the service be accessible? Who defines 'utility' and 'benefit' of the service and whether it is 'medically necessary'? Where does the service fit in terms of importance relative to other health care services? What are the role of patents and commercial providers in developing and implementing services? Should the service be supported as part of public health care insurance? Should it be permitted to be offered for private purchase?

Answering these questions is an ongoing challenge for fields as diverse as health economics, policy and law, moral and political philosophy, and medical sociology and anthropology, and therefore clearly too broad to be addressed within the scope of one dissertation. The thesis will instead focus on a particular exemplar of the issues, namely the development and marketing by Myriad Genetics of *BRACAnalysis*, a commercial genetic

susceptibility test for hereditary breast and ovarian cancer. This case study traces the development of a new genetic technology and its integration (or lack thereof) into public and for-profit health care, and serves as a specific concrete example on which to ground an analysis of the social, ethical and policy implications of commercial genetic testing. With such a detailed analysis, it is then possible to make recommendations about how to address the concerns raised by patenting and commercialization, and how best to integrate commercial genetic services with the public health care system in order to maximize the benefits while minimizing the harms of this new technology.

A Case Study: Myriad Genetics and BRCA Testing

Some private purchase of genetic testing is already a possibility. With increasing use of and access to the Internet, Canadians can purchase a range of genetic tests online from a host of international providers, send in blood or tissue samples by mail for analysis, and receive test results in the privacy of their homes (Williams-Jones 1999). However, for a few genetic tests, Canadians need not go abroad or online as these services are now commercially available in Canada. In 2000, the Utah-based biopharmaceutical company Myriad Genetics, Inc., signed an agreement with MDS Laboratory Services (headquartered in Toronto), granting MDS the exclusive right in Canada to provide Myriad's patented *BRACAnalysis* test for hereditary breast and ovarian cancer (Myriad Genetics 2000e).

This commercial genetic test is the result of a hunt in the late 1980s and early 1990s for the hereditary components associated with common cancers. Hundreds of U.S., Canadian and European researchers were involved in the hunt, but two groups were prominent: a U.K. team led by Michael Stratton at the Institute for Cancer Research, and a U.S. team headed by

Mark Skolnick at the University of Utah. The first gene to be discovered (BRCA1) was localized by Mary-Claire King in 1990, and sequenced and patented in 1994 by Skolnick and his newly formed spin-off company Myriad Genetics. In 1995, following a heated race, Skolnick and Stratton both claimed to have been the first to sequence the BRCA2 gene and thus filed competing patents, Skolnick in the U.S. and Stratton in U.K. (Davies and White 1995).

The patenting of genes and other biological materials became possible in the early 1980s following the U.S. case of *Diamond v. Chakrabarty* (447 U.S. 303, 1980); in the next two decades, thousands of gene and DNA-based patents were awarded (Caulfield and Gold 2000a; Cook-Deegan and McCormack 2001). In the case of BRCA1 and BRCA2, patents on these genes enabled the development and marketing by Myriad of a commercial genetic test for hereditary breast cancer. While initially there were competing patent claims within the U.S., Myriad was ultimately successful at obtaining control of the two BRCA genes, and subsequently of the U.S. market for BRCA testing. Myriad has also received Canadian and European patents and signed agreements with various governments, e.g., Ireland and Japan, to be the exclusive provider of BRCA testing in those countries (Myriad Genetics 2000d, f).

Patents have little value as tools for protecting intellectual property if they are not enforced by their owner through the legal system. Thus in Canada, Myriad and their licensee MDS Laboratory Services have begun a campaign to convince (through 'cease and desist' letters) all public health care institutions providing BRCA testing that they must refer testing to MDS or Myriad. Apart from British Columbia where the Ministry of Health Services has complied with the patents and ceased testing, the provinces have rejected Myriad's claim and continue to provide testing and counselling services; Québec performs some mutation testing

locally but sends index testing to Myriad for full analysis (Canadian Press 2001; Eggertson 2002). In Europe, Myriad's efforts to enforce their patents have been met with strong opposition from clinicians, genetics laboratories, and public action groups, and have led to a European patent challenge (Wadman 2001; Benowitz 2002).

This case has implications for national and international patent law, the manner in which scientific knowledge and discoveries are commercialized, the transformation of research tools into clinical practice, public and for-profit health care, and issues of justice in access to medical services. It is a harbinger of an increasing number of instances where gene patents give biotechnology companies monopolies on the development, marketing and provision of genetic tests and therapeutics. The Myriad case can therefore serve as an exemplar of the social, ethical, and policy issues associated with the commercialization of new genetic technologies, and the effects on a public health care system such as Canada's. This case will be localized to the Canadian health care context within one provincial jurisdiction, by referring to the situation in British Columbia and the termination of BRCA testing at the Hereditary Cancer Program of the B.C. Cancer Agency. A comprehensive comparison between B.C. and the other provinces (and other countries) would be very useful, but of a scale beyond what is possible in a dissertation. Focused analysis of the situation in B.C. nonetheless provides important information with which to better understand and address the social, ethical, and policy issues of commercial genetic testing.

The Hereditary Cancer Program

Located at the Vancouver Cancer Centre, the Hereditary Cancer Program (HCP) of the B.C. Cancer Agency was formed in 1996 as a joint initiative of the B.C. Cancer Agency

and the B.C. Provincial Medical Genetics Program, to provide individuals and families with a strong history of cancer with information and genetic counselling. The HCP is an interdisciplinary group with a core staff of pathologists, oncologists, medical geneticists, genetic counsellors, and nurse educators. Supporting this group are a range of other medical professionals at the B.C. Cancer Agency, as well as a medical anthropologist and a bioethicist. The HCP maintains a comprehensive program that includes research into the clinical, social, and ethical aspects of genetic testing for hereditary cancer, patient and clinician education, and genetic testing and counselling for a variety of hereditary cancers.

While the HCP is involved with providing genetic testing, counselling, and clinical care for a wide range of conditions, a major focus of their practice and research has been hereditary breast and ovarian cancer. Through publicly raised funding from the B.C. chapter of the Canadian Breast Cancer Foundation, the HCP was able to purchase a DNA sequencer so they could then offer genetic testing of the two BRCA genes for women at-risk for hereditary breast and ovarian cancer. This funding also permitted the establishment of a pilot study to evaluate how best to offer genetic counselling and testing. Clinical service has been available since 1996, with an average of 80 families entering the program each month and 1500 passing through the program in the past 5 years (Horsman 2002). The HCP also provides genetic counselling for members of high risk families through the B.C. Cancer Agency's Regional Clinics and outreach programs on Vancouver Island, in the Fraser Valley, and in the southern interior of British Columbia.

In July 2001, the HCP's ability to provide BRCA testing changed dramatically. Following receipt of legal notice asserting the patent rights of Myriad Genetics (and their licensee MDS Laboratory Services) to test for BRCA1 and BRCA2, the B.C. Ministry of

Health Services directed the B.C. Cancer Agency to suspend new BRCA testing until further notice. Should the HCP wish to continue offering testing, they would have to purchase these services from Myriad or MDS and pay for it out of the HCP's existing budget. Covering the increased costs would consume the HCP's budget and not permit the provision of other genetic services. As a result, the HCP has ceased genetic testing of BRCA1 and BRCA2, although testing for other cancer syndromes continues. The HCP is still providing counselling to individuals and families who meet the referral criteria, so those patients who are eligible, able, and willing to pay for BRCA testing will receive pre- and post-test genetic counselling and be assisted with arranging testing through MDS or Myriad. The cost of purchasing genetic testing is: $3850Cdn for complete testing of both genes; $600Cdn for testing of the three mutations that are commonly found in Ashkenazi Jewish families; and $525Cdn for a specific family mutation in either BRCA1 or BRCA2 (Coldman 2001).

Method

The ethical analysis in this thesis is based on several perspectives drawn from a range of disciplines including the social sciences, philosophy, health law and policy. A metaphor that may be useful in understanding this interdisciplinary approach is to imagine using a variety of different lenses or tools to visualise an object, such as using visual light as well as radio telescopes to detect distant celestial objects. Each lens or tool can illuminate particular aspects of the object under investigation that would not be visible through another lens; the resulting images, if integrated, then provide a more detailed and comprehensive picture of the object. This thesis takes a similar approach, but does not go to the full extent of providing a unified image that seamlessly blends the various disciplines together; such an endeavour is

beyond the scope of one doctoral thesis. Instead, the objective of the thesis is to demonstrate that different theoretical tools drawn from social science, moral philosophy, and health law and policy can contribute to developing the rich and detailed picture needed to conduct effective social and ethical analysis of the commercialization of genetic technologies.

A review of non-academic literature, in particular news stories in the popular press and business reports, serves to build a chronology of recent events in Canada, the U.S., and Europe, as well as helping to develop a clearer understanding of the public debates for and against commercial BRCA testing. Press releases from Myriad Genetics and content from their website provide a picture of the company's background, their goals in developing BRCA testing, and where this particular technology fits into their larger business plan. This understanding clarifies why public action groups, professional associations, and public genetics laboratories are reacting so strongly against Myriad's move to establish a market for commercial genetic testing in Canada and internationally.

This history must also be supported by an understanding of the wider social, political, legal and ethical contexts in which genetic material has become patentable (a problematic issue in itself), and where companies are moving to the forefront of biotechnology and genomics research. Thus the majority of the analysis in the thesis will be based on a review of academic literature in the social sciences, ethics, health law and policy. This literature will support enquiry into questions such as: What scientific and research processes led to the development of genetic testing for mutations in genes associated with hereditary forms of cancer? How did biological materials become patentable inventions, allowing companies such as Myriad to obtain patents for specific genes? What or who are the driving forces or influences that are moving genetics research towards greater commercialization?

Thesis Outline

The thesis is composed of four main sections (chapters 2-5) written in article format for publication in peer-reviewed journals; Chapter 1 is this introduction, and Chapter 6 the conclusion. Each of the four principle chapters is written as a free-standing document that deals with a particular approach to address the issue of commercial genetic testing. The case study of Myriad's commercial BRCA test (described in Chapter 2) is the primary example under investigation, and will serve as a unifying element throughout the thesis. Conceptualising the thesis as a set of papers means there will be some overlap between chapters in terms of introductory material and discussion of the Myriad case. The repetition is minimized as much as possible by concise and efficient writing, and this approach will facilitate a more rapid transfer of the thesis material into the academic literature.

Chapter 2 – History of a Gene Patent

Chapter 2 is primarily descriptive, aimed at laying out in detail the history of the race to discover and commercialize the two genes, BRCA1 and BRCA2, associated with hereditary breast and ovarian cancer. Beginning with a brief description of the aetiology of breast cancer and the genetic components of the hereditary form of the disease, this chapter then describes Myriad Genetics and their evolution from a company focused on gene discovery, to a biopharmaceutical company increasingly involved in genomics and proteomics research. With this background, the chapter moves on to explore how Myriad, through national and international patents, has established control of BRCA testing in the U.S. and begun attempting to exert similar influence in Canada and Europe. Most Canadian

provinces and European countries have rejected Myriad's patent claim and continue to provide in-house BRCA testing, and the Institut Curie (a prestigious French laboratory) has launched a challenge to the European patents. The description provided in Chapter 2 serves as the central case study for Chapters 3, 4 and 5, and sets the stage for an analysis of the social, ethical and policy implications of commercial genetic testing, and recommendations for how to address some of these complex issues.

Chapter 3 – Actor-Network Theory

Chapter 3 argues that science and technology studies, and Actor-Network Theory (ANT) in particular, can provide useful theoretical tools for analysing the development of genetic technologies. Moreover, for the purposes of social, ethical and policy critique, ANT provides a method for gathering empirical evidence to support a better understanding of the complex social and technical relations that underpin the ethical issues. Three concepts are explored in this chapter: 1) actor-networks: networks of human and non-human actors that constitute all institutions, groups, and technologies; 2) translation: the process whereby the interests of various actors in networks are attempted to be aligned in order to stabilize networks and reduce complexity; and 3) drift: the process whereby a technology is transformed as it is translated into new contexts and used in ways not previously conceptualised by the actors involved in the initial technology development. Applying these tools to the Myriad case will map the actor-networks and trace the relations between actors, allowing better understanding of these multifaceted interactions. In particular, by treating technologies such as BRCA testing as active participants in actor-networks, ANT clarifies the extent to which technologies interact with, shape and are shaped by people, other

technologies, and institutions. This information then supports more sophisticated and nuanced technology assessment, as well as academic analysis and public debate about the social, ethical and policy implications of the commercialization of new genetic technologies.

Chapter 4 – Moral Philosophy and Just Decision-Making

Chapter 4 applies tools from moral philosophy to the issue of just decision-making about the allocation and funding of health care services. The existing *ad hoc* manner in which decisions are made, within a context of limited economic resources being allocated for supporting health care, leads to an unjust situation. It will be argued that in applying consequentialist and cost-effectiveness analyses, social contract theory, and public deliberation to the case of commercial BRCA testing, these theories can contribute to a more just decision-making framework for evaluating services for coverage under public health insurance. There is no guarantee that a more just framework will be used – what will be used will depend on whose interests dominate, and not necessarily on what is just – but this should not undermine the value of creating a just framework and seeking to influence policy makers.

These theories provide useful tools, both for exploring how one would go about determining the overall goals for health care, as well as for evaluating the importance of access to genetic tests, especially in comparison to other beneficial services within a public health care system. For example, in evaluating a service such as BRCA testing, it will be important to determine the extent to which a disease such as breast cancer affects a person's range of opportunities and the benefit that genetic testing provides to patients and families. But the complexity of genetic information and how patients and families use it will mean that determinations will need direct participation from a range of stakeholders, e.g., patients,

family members, advocacy groups, and clinicians. At the level of public health care reform, there may be 'public good' reasons for prohibiting or limiting private purchase, e.g., because private purchase has cost or other negative implications for the health care system. In order to make progress in determining what services should be funded as part of public health insurance, and which if any, should be left to private purchase, it will be critical to engage the public in a reflective process, supported by tools from moral philosophy, scientific and empirical evidence, and conducted in an open and transparent manner.

Chapter 5 – Regulating Gene Patents and Commercial Genetic Testing

Chapter 5 builds on the previous two chapters and seeks to demonstrate how tools drawn from ANT and moral philosophy can in practice support a more comprehensive and coherent approach to technology assessment and priority-setting about health care funding. The chapter begins by exploring the *ad hoc* nature of current approaches to decisions about funding of health care services, followed by a discussion of the problems raised by gene patents and commercialization for research, development and application of new genetic technologies, and the provision of health care. Actor-Network Theory, Consequentialism, Social Contract Theory, and Public Deliberation are briefly outlined and then applied to the specific case of how to regulate gene patents and commercial genetic testing in Canada. It will be argued that effective technology assessment and decision-making will be needed to practically address these complex social, ethical and policy issues. Specifically, changes must be made in the scope of patents and the way they are administered, and licensing mechanisms introduced to facilitate research and application in the public system. Efforts must also be made to further develop collaboration between the federal and provincial governments on the

issue of patents, and in particular the use of the buying power of provincial health care insurance plans to shape the ethical behaviour of commercial developers and providers.

Conclusion

The thesis investigates the case of provision of commercial genetic testing services by companies such as Myriad Genetics, the ability of Canadian patients and consumers to purchase genetic testing, and the social and ethical consequences of such access on the public health care system. As private purchase of genetic tests in Canada is relatively new, and by most accounts not many people are embracing this opportunity (although there are no studies evaluating uptake in Canada), it is difficult to draw firm conclusions about the probability of there being serious social or systemic harms. However, it may be possible to generalize and learn from the effects of provision of other services for private purchase. The current situation with respect to genetic testing provides a unique opportunity to analyse the social, ethical and policy implications of these new technologies as they move from the early stage of development, through to implementation, regulation, and public acceptance or rejection.

Commercial investment in health care research and private provision of services is a reality, but this does not mean that companies should be given a free license to develop a market for all health care services. In working through the case study of Myriad and their patented *BRACAnalysis* test for hereditary breast cancer, the thesis aims to shed light on the larger issue of how, as a society, we should go about more coherently deciding what to cover as part of public health insurance, what to leave to private purchase, and if and how private purchase has implications that mean there is less equitable access to public health care services. Further, recommendations are proposed for government oversight and regulation

and modifications to the patent system, to minimize the negative aspects of commercialization while maximizing the benefits, and thereby improve the ethical and equitable provision of commercial genetic tests. Generally, the underlying concern for this thesis is a pragmatic one – "how best to bring capital, morality, and knowledge into a productive and ethical relationship" (Rabinow 1999, 20).

Chapter 2

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

Submitted to the *Health Law Journal*

Abstract

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 gene prospecting, and the implications for ongoing biomedical research and access to health care services. The primary objective of this chapter is to explore the history and context of one instance of gene patenting – the race to discover and commercialize the two genes (BRCA1 and BRCA2) associated with hereditary breast and ovarian cancer – and thus the chapter will only point towards some of the many complex social and ethical issues. A description of how Myriad Genetics came to patent the BRCA genes and establish control of genetic susceptibility testing in the U.S. will, for example, support a better understanding of why Myriad is having such difficulty exerting similar control in Canada and Europe. This understanding provides the necessary groundwork for developing a comprehensive social, ethical and policy analysis of the implications of gene patenting and commercial genetic testing.

Introduction

The 1980 U.S. Supreme Court case of *Diamond v. Chakrabarty* (447 U.S. 303, 1980) was a landmark decision for U.S., Canadian, and international patent law. 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 designed for the bioremediation of oil spills), opened the door for patents on biological organisms and genes.[2] Following the U.S. decision, the 1982 Canadian case of *Re Application of Abitibi Co.* (62 C.P.R. (2d) 81) forced the Canadian Intellectual Property Office to allow the patenting of biological organisms and genes – although this policy has yet to be reviewed by a senior Canadian court (Gold 2000). The permissive nature of U.S. patent policy, as well as international trade and patent harmonization agreements such as the *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 patenting of human genes (Knoppers 1999; Caulfield and Gold 2000b). In Canada, Europe, Australia, etc., genes (including those of human origin) may be patented if they meet general patent criteria (novel, useful, and inventive) and are new creations (e.g., artificial genes), or isolated from nature and identified (i.e., cloned and sequenced) and shown to have a particular function and use (Canadian Patent Office 1998, s. 16.05).[3] In the late 1980s,

[2] There is substantial debate in both public forums and academic circles about whether patenting is morally or ethically acceptable (McGee 1998; Caplan 1998; Merz and Cho 1998). This thesis will not address the issue of the ethical permissibility of human gene patents, but instead lays the groundwork for analysis of the social, ethical, and policy implications of the patenting and commercialization of genetics research and technologies.

[3] Genes and other biological materials are considered patentable when they are isolated from nature (sequenced and described), shown to have a particular application (e.g., for a diagnostic test), and to be inventive (new discoveries or creations). Occasionally, an older product whose patent has expired may receive a new patent as a result of a novel use for the product. For example, the antibiotic drug dapsone, which has been used for more than 50 years to treat leprosy, was discovered to have anti-inflammatory effects that may be useful in treating Alzheimer's disease and dementia (Jones 2000). This novel use allowed for a U.S. Patent (no.5,532,219) by Patrick McGeer and the University of British Columbia.

genetically engineered plants and animals were patented in the U.S. (the Harvard 'Oncomouse' was patented in 1988, U.S. Patent no. 4,736,866)[4] and the number of gene and biological patents rapidly increased (Eisenberg 1990). Between 1981 and 1995, more than 1,175 human gene patents were granted worldwide (Caulfield and Gold 2000b), with more than 25,000 DNA-based patents by 2000 (Cook-Deegan and McCormack 2001).

By the early 1990s, enormous amounts of public and private funds were being invested in genetics research and biotechnology (Cohen 1997). For example, the U.S. biotechnology industry invested $5.6 billion in R&D in 1997; the pharmaceutical industry invested $21.1 billion in biotech related R&D in 1998; while the overall public expenditure on the Human Genome Project is estimated at greater than $3 billion (Malinowski and Littlefield 1999). In Canada, there are more than 500 biotechnology companies with industrial activities generating annual revenues of $2 billion and exports of more than $750 million. By 1998, the federal government was spending $314 million a year on biotechnology R&D, while industry invested $341 million and not-for-profit institutes invested $115 million (Industry Canada 1998). These financial investments in biotechnology were supported by government regulations (both in the U.S. and Canada) that facilitated technology transfer and commercialization (Cook-Deegan 1999). During the same period, biotechnology start-up companies (whose main or only resources were often patents on potential 'disease genes') proliferated in the U.S. (Marshall 1997). One of these companies, Utah-based Myriad Genetics, Inc., built its reputation and later established itself as a market leader in gene discovery and diagnostics, by helping to discover and later patent the first gene

[4] 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 rejection by the Canadian Patent Commissioner of Harvard's claim to a patent for the 'Oncomouse'.

(BRCA1) to be associated with susceptibility for hereditary breast and ovarian cancer (Roberts 1996).

This chapter first outlines information on the aetiology of hereditary breast and ovarian cancer, followed by the founding of Myriad and its transformation into a biopharmaceutical company. The international race to discover and patent the BRCA genes is then discussed to set the context for an analysis of Myriad's development and control of public and commercial BRCA testing in the U.S. and its recent moves to enforce the patents and establish markets in Europe and Canada. The chapter closes by discussing the mounting Canadian and international opposition to Myriad's attempt to control the provision of BRCA testing.

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 2001, an estimated 19,500 Canadian women were diagnosed with breast cancer (a cumulative lifetime risk of 1 in 9, or 10%) and 5,500 women (1 in 26 or 3.9%) are predicted to die from the disease (National Cancer Institute of Canada 2001). Breast cancer is a heterogeneous disease, but approximately 80% of cancers are infiltrating ductile carcinomas. Treatment for breast cancer (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 (Hofmann and Schlag 2000).

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 (Szabo and King 1997; Hofmann and Schlag 2000). 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 and made up of 5,592 base pairs, that codes for a protein of 1,863 amino acids. The resulting protein is critical for DNA repair and transcription regulation; when the gene is inactivated through mutation, 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 (Hofmann and Schlag 2000).

Deleterious mutations in these two genes are caused by insertions or deletions of nucleotides (single or multiple), or from large scale deletions or re-arrangements. 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, and a truncated and non-functional protein. BRCA1 and BRCA2 are considered classic tumour-suppresser 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) though random mutation.

If this occurs, the tumour-suppresser function is inactivated with resulting loss of control over cellular growth.

Individuals with such mutations are considered to have a cumulative lifetime risk of between 40-85% for developing breast cancer, and 16-40% for developing ovarian cancer, depending on the mutation and family history (Carter 2001).[5] 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; only about 20-25% of families meeting stringent entry criteria (e.g., extensive family history) for testing will be found to have an identifiable mutation in BRCA1 or BRCA2 (Horsman 2002). It is likely that there are other yet to be discovered genes affecting 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 (BBC News 2002), and others that are low-penetrance and confer moderately increased risk such as CHEK2 (CHEK2-Breast Cancer Consortium 2002). Social and environmental factors clearly also influence the risk of developing breast cancer.

[5] 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 and Schlag 2000). These risk estimates also raise serious ethical, social and psychological issues about how physicians, counsellors, patients and family members interpret and understand risk information (Codori 1997; Cox and McKellin 1999; Press, Fishman, and Koenig 2000; Evans, Skrzynia, and Burke 2001).

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" (www.myriad.com). They focus on therapeutic products 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 $10 million US, of which $1 million was equity from pharmaceutical giant Eli Lilly. 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 on BRCA1 (Davies and White 1995); Myriad maintains the rights for therapeutics development on BRCA2 (Blanton 2002).

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" (Key and DeNoon 1994, 7). This initial focus was possible because researchers were able to access and link important genealogical and medical databases. The Utah Genealogy 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 (Davies and White 1995). This database was then linked to the Utah Cancer Registry (which contains more than 100,000 entries), and resulted in 40,000 cross-linked entries; Myriad currently has a database of more than 8 million patient records (University of Utah 2001).[6] 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 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. It is hoped that the isolation, separation, identification and functional characterization of proteins will

[6] The combination of information drawn from large population databases of 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 (Nielsen 1999; Specter 1999; Knoppers, Caulfield, and Kinsella 1996; Thurston, Burgess, and Adair 1999).

provide a better understanding of disease processes, facilitating the discovery and development of therapeutic proteins, drug targets and diagnostics. 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 (Feuerstein 2001). Myriad is also involved with the development of compounds to fight prostate cancer, AIDS/HIV, and lymphoma (Clarke 2001), 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 giants such as Eli Lilly, Monsanto, Novartis, Roche, Shering AG and Schering-Plough (Myriad Genetics 2000a).

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 $900 million in financing since 1992 (ReCap 2001). 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 (Myriad Genetics 2001d).

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 (Breast Cancer Linkage Consortium 1999). 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 (King 1991). 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 (Miki *et al.* 1994). 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.[7]

After the 1990 discovery of BRCA1, it quickly became apparent that at least one other gene was associated with cases of 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

[7] For a detailed discussion of the science and politics behind the race to discover BRCA1, see *Breakthrough: The Race to Find the Breast Cancer Gene* (Davies and White 1995).

researchers involved in the hunt for BRCA1 and BRCA2 (Murray 1999; Davies and White 1995). A race ensued between Skolnick at Myriad, and a consortium of U.K. researchers led by Michael Stratton at the Institute for Cancer Research, to be the first to discover and control (i.e., patent) BRCA2. In September 1994, BRCA2 was localized to chromosome 13 using linkage analysis.

On December 22nd the following year, the day before it was to publish the sequence for BRCA2 in the journal *Nature* (Wooster *et al.* 1995), 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 (no. GB2307477) on BRCA2 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[8]) and had filed for a U.S. patent (no. 5,837,492) (Meek 2000).

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 the Myriad BRCA1 patent (Davies and White 1995). By the end of 1997, the U.S. Patent and Trademark Office had awarded overlapping and conflicting patents to Myriad and OncorMed for

[8] An important difference between U.S. and U.K. or E.U. patent laws are the criteria for determining patent rights on new discoveries when there are competing claims. In the U.S., the rule is 'first to invent' based on proof from laboratory notebooks, for example; by contrast, in Europe and most of the rest of the world the rule is 'first to file', i.e., the first patent received by the Patent Office, if awarded (Murray 1999). This complicates matters significantly when competing international teams are filing similar patents in different jurisdictions under different rules.

diagnostic and therapeutic applications of the BRCA1 gene. OncorMed's U.S. patent (no. 5,654,155) for a non-mutated BRCA1 allele, described a DNA sequence most likely to be found in the majority of the population, which was only slightly different (due to natural gene polymorphisms) from the DNA sequence described in the Myriad patent (Murray 1999). Patent infringement suits were filed by both companies in 1998, but Myriad was ultimately successful in this dispute and settled out of court for an undisclosed fee, purchasing the OncorMed patents (Myriad Genetics 1998b). 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 (Murray 1999). The likely purpose of these patents were to protect Myriad's new genetic test, as well as to establish control over the entire U.S. and international market for genetic testing for hereditary breast cancer.

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 *BRACAnalysis*. In 1996, Myriad initially marketed a BRCA1 test kit for $900 (Roberts 1996), 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. *BRACAnalysis* was re-released as an in-house laboratory test requiring that a physician be

involved in the process to serve as facilitator or middleman and order the test (thus not strictly a direct-to-consumer service). Test results would then be provided to a physician to help increase the likelihood that patients would receive some level of genetic counselling; this also to some extent shifts liability for patient harm from the company to the physician. 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 (Aetna U.S. Health Care 1999).

BRACAnalysis is marketed as three subtests: Single site *BRACAnalysis* (single mutation analysis for a known family mutation, that is carrier testing) for $295 ($525Cdn); Multisite 3 *BRACAnalysis* (analysis of the three common Ashkenazi Jewish mutations – 187delAG, 5385insC, 617delT) for $450 ($600Cdn); and Comprehensive *BRACAnalysis* (full gene sequencing) for $2,600 ($3,850Cdn). Thus patients who have not previously had BRCA testing in their family undergo full sequencing (as the index case) of both BRCA genes to search for mutations associated with hereditary breast cancer. 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 Rapid *BRACAnalysis*, a testing program with a seven day turn-around time and at a cost of an additional $1100 to the price for full sequencing (Myriad Genetics 1999). Myriad's 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 (Myriad Genetics 2000e). 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 in Myriad's favour, 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 (Koenig, Greely, and Raffin in press; Hilzenrath 1996). For example, Arupa Ganguly at the University of Pennsylvania Laboratory independently developed a BRCA1 and BRCA2 test using conformation-sensitive gel electrophoresis (CSGE) which was offered commercially to patients for $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 (Ganguly *et al.* 1998). In contrast, OncorMed, which only performed 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 (Carter *et al.* 1997). 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 (www.genetests.org).

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 sequencing parts of the gene. 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, that is the result of truncation by mutated alleles. PTT preferentially detects a mutation type (that results in truncation) that is always clinically significant (Carter 2001); this technique can also detect large deletions and re-arrangements that would be missed by full DNA sequencing.[9] 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.

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 (Carter 2001; Geisler *et al.* 2001).[10] A new French method developed at the Institut Curie (DNA colour bar coding) is able to detect large deletions and re-arrangements

[9] 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.

[10] 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 (Carter 2001).

of BRCA1 and BRCA2 which the full DNA sequencing offered by Myriad misses (Gad *et al.* 2001). Despite these disagreements about appropriate testing methodology, it is perhaps not surprising that Myriad maintains 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 (Balter 2001). Commercial laboratories such as OncorMed and the University of Pennsylvania were systematically challenged with litigation until Myriad became the sole U.S. commercial provider of BRCA testing (Borger 1999). 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 (Myriad Genetics 2000b), 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 *BRACAnalysis* as part of their insurance plans (Myriad Genetics 1999). In December 2001, Myriad announced a partnership with LabCorp, a large U.S. medical diagnostics company, that enrols 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 oncologists (Myriad Genetics 2001a). Internationally, Myriad has signed licensing agreements with companies in Canada (Myriad Genetics 2000e), the U.K. and Ireland (Myriad Genetics 2000f), Japan (Myriad Genetics 2000d), Germany, Switzerland and Austria (Myriad Genetics 2001c), for exclusive provision 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 ($1,200) DNA sequencing for researchers, as long as the research does not include the provision of clinical services (Reynolds 2000).

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 (Myriad Genetics 2000f). However, Rosgen was unable to raise sufficient capital investment to stay solvent and folded in 2001. Myriad is negotiating with the U.K. Department of Health about provision of BRCA testing in the U.K. (Sylvester 2001). Recent E.U. patents on BRCA1 and BRCA2 in 2001 have further strengthened Myriad's legal position in Europe.

Reactions Against Commercial Testing

The expansion of a market for 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 (Nature 1996; Roberts 1996; Wright 1997). 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 (Lauren 2001). 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 (American College of Medical Genetics 1999). More recently, significant opposition to commercial BRCA testing has developed in Canada and Europe as Myriad has sought and obtained patents, and begun licensing testing to local companies.

Europe

In January and May of 2001, the European Patent Office (EPO) granted Myriad patents on the BRCA1 and BRCA2 genes (Watson 2001). 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 a challenge of the E.U. patents by the Institute Curie in Paris and a coalition of 16 other French laboratories (Balter 2001; Dorozynski 2001). 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 unfair and harmful monopoly in Europe (Watson 2001). Other European nations, e.g., Germany, Sweden, the Netherlands, Spain, and Belgium, have voiced their opposition and intent to continue provision of BRCA testing in defiance of the E.U. patents (Benowitz 2002).

The patent challenge by the Institut Curie is based on a few key arguments. First 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

coding (Balter 2001) – 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 (Gad *et al.* 2001). 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 (Institut Curie 2001). 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 Myriad test.[11] However, due to the broad nature of the European BRCA patents – which cover any diagnostic or therapeutic use of the BRCA1 and BRCA2 genes – it would be illegal for clinicians to use this new technique without first reaching an agreement with Myriad.

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 (Henley 2001). 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 ($7.6 million Cdn) to hospital budgets (Institut Curie 2001). These high costs would result in restrictions in access to needed medical services, and are thus against the public interest. Finally, 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

[11] See Chapter 3 for a discussion of technology assessment and the variation in sensitivity and specificity of the various BRCA testing methods.

already available prior to the patent being filed; 2) lack inventiveness because Myriad benefited from knowledge gained by a public consortium not acknowledged in the patent; and 3) are insufficiently described, as the protein sequence used in the patent filing is insufficient to produce the diagnostic method covered in the patents (Institut Curie 2001).

Canada

Genetic testing for mutations in the two BRCA genes was first available on a research trial basis in 1996 (although linkage testing was in use by 1995) in various Canadian provinces. 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 to purchase a DNA sequencer to perform BRCA testing, as well funding for a pilot study on how best to offer genetic counselling and testing for hereditary breast and ovarian cancer. The HCP's operating budget – to provide genetic testing, counselling, and physician and patient education for a range of hereditary cancers – comes out of 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 in the past 5 years (Horsman 2002). Similar publicly funded genetic testing programs and laboratories have been set-up in Ontario and Alberta. Saskatchewan (Lemire 2002), Newfoundland and Nova Scotia provide services but send the 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 they not only screen for 5 to 7 Ashkenazi and French Canadian mutations themselves, but also send

samples to Myriad for full sequencing paid for by the provincial government (Panabaker 2002).

Despite the existence of these various 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 of 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 (Abraham 1998, 1999). In March 2000, the Ontario government decided to fund genetic testing for hereditary breast and ovarian cancer as part of provincial health insurance, and in order to do so 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 *BRACAnalysis* 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 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 (Myriad Genetics 2000c). 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 gene patent was granted the following April (for a total of 4 patents). Myriad, and their Canadian licensee MDS began notifying public health care institutions that Myriad had the exclusive rights to the use of the BRCA1 and BRCA2 genes for all forms of clinical testing, and that the public laboratories should comply with the Canadian patents and refer BRCA testing directly to MDS or Myriad (Myriad Genetics 2000e). Among the Canadian provinces offering public BRCA testing, to date only British Columbia has complied with the Myriad patents and ceased to provide in-house testing. As of 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, or purchase it through Myriad or MDS out of the HCP's existing budget. The cost to perform genetic testing at the HCP is approximately $1200Cdn per test, and purchasing the more expensive testing at a cost of $3850Cdn for full sequencing, would

quickly exhaust the HCP's budget. This would undermine their ability to provide services to patients at-risk for a variety of hereditary cancer syndromes, which is their mandate. For patients whose blood samples had been taken and testing begun, the HCP has completed the analyses but it cannot provide follow-up carrier testing for other family members if a mutation is found. For patients whose blood had been collected but testing had not been started, the HCP is no longer performing testing. Patients have been informed they will have to pay MDS or Myriad if they wish testing, but the HCP will continue to provide pre- and post-test genetic counselling, and will facilitate the purchase of testing should it be desired by patients and families (Coldman 2001).

Former Ontario Premier Mike Harris has been most notable in his public opposition to the commercialization of BRCA testing in Canada. In August 2001, Premier Harris raised the issue of gene patenting (and the particular case of Myriad) at the Annual Premiers' Conference in Victoria, B.C. (Willcocks 2001). 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 who need this service (Mallan 2001; Canadian Press 2001). In speeches by Harris (Harris 2001) and Ontario Minister of Health Tony Clement (Clement 2001), 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. Premier 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 (Harris 2001). The Ontario Ministry of Health and Long Term Care has prepared a draft report, 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, and the need to put in place safeguards to protect health care, medical practitioners and researchers (Ontario Ministry of Health and Long Term Care 2002).

Finally, the Canadian Cancer Society (CCS) and the National Cancer Institute of Canada (NCIC) have taken the position that the federal government should "take 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" (Canadian Cancer Society and National Cancer Institute of Canada 2002, 3).

Conclusion

The race to find, patent, and market 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 most 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.

However, women outside such group coverage do not have access to the test unless they can pay the high cost. By contrast, in Canada and European countries with publicly supported health care systems, the commercial nature of the test and Myriad's attempt to enforce their patent rights is fuelling heated debate. This issue embodies a particular instance of a broader concern, namely fair access to needed health care services. This concern is intensified by the mounting costs of new health care technologies (especially pharmaceuticals), and the costs and benefits of medical and biological patents.

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 continuing with business as usual and ignoring Myriad's patent claim (Lemire 2002; Eggertson 2002). In Europe, opposition has led to formal legal challenges of the European patents by the French Institut Curie, backed by other national genetics laboratories. If this challenge is successful, it 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. Even if the challenge does not succeed, the lack of monopoly control on BRCA testing will effectively dissipate Myriad's market in Europe. A successful European challenge could galvanize opposition in other countries such as Canada and lead to the overturning of local patents. But more importantly, the Myriad patent is the forerunner or test case for a host of other gene and biological patents. If the BRCA patents stand, hundreds of other gene patents are likely to follow, exacerbating the current rush to patent genes that former Premier Harris described as the 'Wild West'. This could potentially

lead to a situation where all genes are patented and new research becomes unaffordable, what Heller and Eisenberg have described as a 'tragedy of the anticommons' (Heller and Eisenberg 1998). The complete history of the discovery and commercialization of the BRCA genes in Canada remains to be written.

Linking Statement

Chapter 2 was largely a descriptive endeavour and only briefly touched on a few examples of what are in fact a host of important social, ethical and policy implications of gene patenting and commercial genetic testing. These issues, and in particular the effects of gene patents on research and access to health care services, will be addressed in detail in Chapters 4 and 5. The following chapter (Chapter 3) builds on the context and history of Chapter 2 and applies Actor-Network Theory (ANT) as a means of 'unpacking' the complex networks involved. It will be demonstrated that ANT is a useful method for elucidating important empirical information and understanding the flow of power and control through the networks involved in the development of BRCA testing, and thus can enable more comprehensive social and ethical analysis.

Chapter 3

Actor-Network Theory: A Tool to Support Ethical Analysis of Commercial Genetic Testing

Submitted to *New Genetics and Society*

Abstract

Social, ethical and policy analysis of the issues arising from gene patenting and commercial genetic testing is enhanced by the addition of science and technology studies, and Actor-Network Theory (ANT) in particular. This theory provides tools for gathering empirical information and for analysing the complex networks involved in the development of genetic technologies. Three concepts are explored in this chapter: 1) actor-networks: networks of human and non-human actors that constitute all institutions, groups, and technologies; 2) translation: the process whereby the interests of various actors are attempted to be aligned in order to stabilize networks; and 3) drift: the process whereby a technology is transformed as it is translated into new contexts and used in ways not previously conceptualised. These tools are applied to the case of Myriad Genetics and their commercial genetic test for hereditary breast cancer (*BRACAnalysis*). Treating this test as an active participant clarifies the extent to which it interacts with, shapes and is shaped by people, other technologies, and institutions. Such an understanding then enables more sophisticated and nuanced technology assessment, and academic analysis and public debate about the social, ethical and policy implications of the commercialization of new genetic technologies.

Introduction

The commercialization of genetic testing services presents a challenge to health care professionals, policy analysts, and academics concerned with the social, ethical and policy implications of new genetic technologies. They are faced with questions about the role of science and medicine in developing novel technologies; the effect of private sector provision of medical technologies on public health care systems; the need for government policy, regulation and oversight of commercial services; and evaluations of the proper scope for personal management of health care. Analysis of these difficult questions, it will be argued, benefits from an application of Actor-Network Theory (ANT) which aims to explore the taken for granted nature of technology and trace the social and technical relations involved in the development and implementation of new technologies (Law and Callon 1992; Callon 1986).

The chapter will begin by describing three concepts: 1) actor-networks, which are made up of human and non-human actors that constitute all institutions, groups, and technologies; 2) translation, the process whereby the interests of various actors in networks are aligned through change and their roles solidified,[12] resulting in network stabilisation (or not) and reduction in complexity; and 3) drift, the transformation of a technology as it is translated into new contexts and used in ways not previously conceptualised by the actors involved in its initial development. These concepts will then be applied to the case study of Myriad Genetics' *BRACAnalysis* genetic test for hereditary breast cancer, as a means of demonstrating that ANT can provide both the empirical and critical conceptual tools necessary to support practical, evidence-based ethics research that advances discussion of the

[12] This process, which Callon calls 'interessement', is "the group of actions by which an entity...attempts to impose and stabilize the identity of other actors it defines through problematization" (Callon 1986, 208).

social, ethical and policy issues associated with the commercialization of genetic technologies.

Actor-Network Theory

In the early 1980s, Bruno Latour and Michel Callon at the École des Mines in Paris, later joined by John Law of Lancaster University, developed Actor-Network Theory (ANT) with the aim of explaining complex networks in scientific research settings. Arising out of the larger domain of science and technology studies (Hess 1997), ANT shares the conviction that greater critical attention and empirical study should be conducted into the actual practice of science. Initially, the focus was on the laboratory setting (Latour and Woolgar 1979; Latour 1988), but more recent ANT analyses have expanded to include investigations of science and technology development outside the laboratory in the public and private sectors (Law and Callon 1992; de Laet and Mol 2000).

ANT challenges some common epistemological convictions by rejecting essential subject/object, culture/nature, or society/technology distinctions. Entities, whether people, objects, or technologies, are not fixed and do not have significance in and of themselves. Instead, entities achieve significance or meaning by being in relation with other entities, and according to Law, "if differences exist it is because they are generated in the relations that produce them. Not because they exist, as it were, in the order of things" (Law 2001, 3). Humans and non-humans (e.g., technology, objects, institutions, corporations) are thus treated as epistemologically equivalent or symmetrical for the purpose of critical analysis, and are 'actors' inasmuch as they have the ability to act and be acted upon.

This ability to be independent actors is largely non-controversial for people, although it can become an issue when, for example, people's independence is constrained by mental illness or differential power relations such as class or gender (Evans, Barer, and Marmor 1994). It may nonetheless seem odd for objects, technologies, or organisations to be also treated as actors. Closer examination of object-human interactions, however, demonstrates that objects and other non-human entities do affect human behaviour. For example, while a telephone may appear to be an ordinary, entirely passive technology, this impression quickly changes when the telephone rings and I run to answer it; I want to get the call, I want the ringing to stop, and the appropriate behaviour is to pick up the telephone. The caller is acting on the telephone which is acting on me, and I in return act on my telephone, and thus the caller and their telephone. Even if I decide to ignore the call and let it ring, the telephone has still provoked a decision making process and elicited a response (Callon and Law 1995).

Actors create meaning through their interactions with other actors. This meaning is not fixed but shifts over time and with different interactions. Actors are necessarily heterogeneous, embodying compromises at the social, political, psychological or economic levels, and have varying degrees of commitment, skill, prejudice, and constraints associated with them – they are often hybrids of the 'social', 'technical' and 'personal' (Latour 1993). At the technical level, a genetic test for hereditary breast cancer (BRCA testing) may involve the full sequencing of the two associated genes, BRCA1 and BRCA2, or analysis of the resulting proteins to search for early truncation (Hofmann and Schlag 2000). The accuracy (sensitivity and specificity[13]) of these tests is determined and disputed by scientists,

[13] Sensitivity is the degree to which a test will provide a true positive result such that a person tested positive in fact has the mutation for which she is being tested. Specificity is the degree to which a test will return a negative result for persons who do not have the mutation.

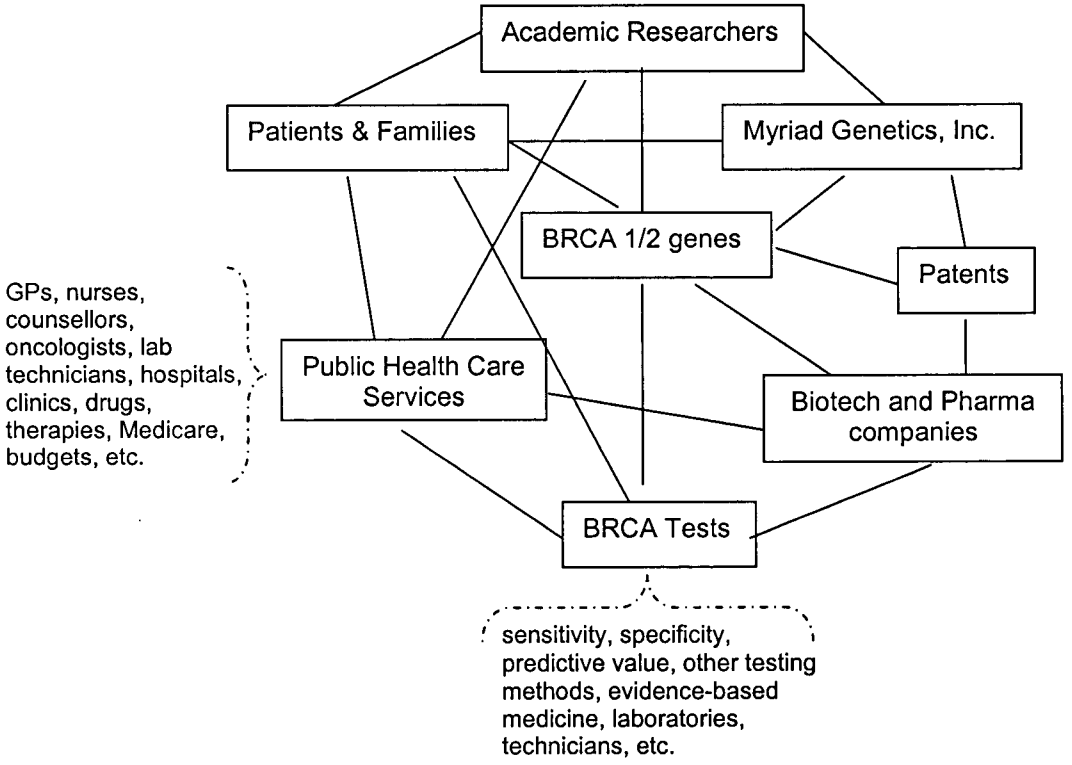
clinicians, and epidemiologists, and there may be better or worse tests for detecting known mutations or others yet to be discovered (Evans, Skrzynia, and Burke 2001). Access by patients to genetic testing may be restricted to certain individuals and families based on professional standards in the medical community, which may nevertheless vary both provincially and internationally (Goel and Crossroads 99 Group 2001; Carter 2001). In order to understand how these relations create meaning and describe the various actors (e.g., the disease, genetic test, patients, clinicians, scientists, the general public, policy makers), it is useful to think in terms of networks of relations, or more specifically, actor-networks.

Actor-Networks

Actor-networks are shifting systems of alliances, 'performed' into existence by the actors involved, and necessarily include human and non-human elements. These networks are inherently unstable over-time, have to be continually maintained through the engagement (enrolment) of the actors involved, and may fail and be replaced by other networks. Of interest are the actions of actors and networks, and the interactions between social institutions, individuals, groups and techno-science. If we wish to know the origins of power and structure in a network, that is, what drives the network or brings it into being, then we need to consider all the components that collaborate, co-operate, compete, and lead to proliferation, persistence, or perishing of that network. The challenge of ANT, then, is to "unpack the dynamic, socio-technical process unfolding over time" (Monteiro 2000, 72) to better understand the underlying processes and components of actors and networks that may not be readily apparent.

To start following actor interactions, it is necessary to first develop a preliminary sketch of the network. For example, Figure 1 maps some of the central actors involved in the development of BRCA testing, one of the networks in which they are engaged, and some of the connections.

Figure 1: Development of BRCA Testing



But this task is complicated by the fact that actors participate in many networks that may or may not overlap with the network under investigation (Busch 1997). One might think of an actor-network as expanding out infinitely (or the inverse, being fractal and infinitely dense), with each actor a node in another network (Law 1999). Given this density, separating foreground from background becomes difficult; an ever expanding network would quickly become an unwieldy, complex web, all but useless for coherent analysis.

Actor-networks can still be scalable. A useful concept that simplifies actor-networks is 'punctualization' or the creation of 'black boxes' (Akrich 1992). As networks become stronger and more stable, they can for the purpose of analysis be treated as points in a larger network – the supporting network disappears into a black box. For example, political maps of a country represent cities as points, but a street plan of a particular city requires a different scale and serves a different purpose (Law and Singleton 2000).[14] In Figure 1, each of the boxes could also be expanded to produce their own complex networks, as illustrated for *BRCA Tests* and *Public Health Care Services*. In no way should this compartmentalisation process be seen to reduce a network to a monad or essential capturing of the whole. The complexity of the network remains but is moved to the background for the purpose of analysis. As is the case for many other fields of research, the focus of inquiry to some extent drives the choice of the most appropriate scale of analysis. While the network illustrated in Figure 1 may be only one of many networks that could usefully contribute to the study of the social, ethical and policy implications of commercial BRCA testing, it is nonetheless a discrete and manageable focus of analysis and an important locus for further investigation.

Punctualization is more than simply an analytic tool but is also essential for everyday life and interactions with technology, organisations, communities, i.e., networks. As Monteiro notes, "ANT is a strategy for unpacking the complexity of our everyday life. Abbreviations, short-circuits and simplifications are always *produced*. They are the (up till [sic] now, successful) result of a mobilization process with black-boxing effects" (Monteiro 2000, 82). For example, it would be simply impractical to always consider the various networks that underlie a technology. A device such as a telephone stands in for (and is

[14] But this metaphor only goes so far – actor-networks are not limited by the restrictions of distance and time inherent in spatial metaphors because they are active, fluid, and ever changing. What is important are the connections – networks are longer or more intensely connected (Latour 1996).

backed by) a network and performs that network over time and in diverse places – the origin of the device and details of its network are not of immediate interest, and in fact would be distracting for everyday use (Latour 1991).

ANT is also focused on the performative or process aspect of alignment that links together the influencing factors that affect an actor and establish a network. But it does not take for granted that an actor or network has to be a certain way. In the case of technology development, for example, a technology could always have been different (Bijker and Law 1992). It might not serve the purpose of its target audience and be resisted; in other circumstances, such as if the social, political or economic climate were more hospitable, the technology might have a better chance of succeeding – we might now be using Beta instead of VHS (Cusumano, Mylonadis, and Rosenbloom 1992). A "technology is stabilized if and only if the heterogeneous relations in which it is implicated, and of which it forms a part, are themselves stabilized" (Bijker and Law 1992, 10). But what is it that brings actors together in a network and keeps them participating if they have competing interests? How is it that a technology becomes either accepted or rejected?

Translation

Every actor in a network is essentially independent and capable of resistance, so there must be some 'glue' that keeps them involved in a network – this glue is translation. Each actor (whether a person, group, company, machine, nation) has its own diverse set of interests, thus a network's stability will result from the continual negotiation, re-interpretation, appropriation, i.e., the translation of interests. The same issue will likely be presented differently to different actors in order to mobilize support. Between humans,

translation is analogous to negotiation of common interests; between humans and non-humans, the interaction will be through design of scripts (to be discussed below). Policies, behaviours, motivations, and goals are translated from one actor to another; and actors are themselves translated and changed through their interactions with others (Callon 1986).

Callon proposes a set of 'moments' in translation: problematization, interessement, enrolment, and mobilization. For our purposes 'interessement', which Callon describes as "the group of actions by which an entity...attempts to impose and stabilize the identity of other actors it defines through problematization" (Callon 1986, 208), is a useful concept for seeing how a group of actors can be brought together around a particular goal or purpose, and the resulting network stabilized. There is often resistance to social change, so translation is about the re-organizing of relations in actor-networks. Disagreement or counter-claims on actors in a network may arise that threaten ongoing stability. Competing claims will require strengthening ties (interests) to the actors, while also weakening links between these actors and other entities. Such actions may involve the use of force, seduction, or simple solicitation, and if this process is successful, then the actors are 'enrolled' in the network.

Interactions between actors are the building blocks of networks, and translation is also the process that enables networks to be black boxed and so be seen as actors themselves. Ongoing translation at a variety of levels is a key source of social order – it is what generates institutions, governments, organisations and agents that exist over time.[15] But control by any given actor – or even by the author of a network – is necessarily limited because power is diffused amongst the actors (Latour 1986). Networks metamorphose in ways likely not predicted by the authors as they are translated by the elements and actors within. There may

[15] Translation is a sufficiently important concept for ANT that the theory is often described as a 'sociology of translation' (Callon 1986; Brown and Capdevila 1999).

nevertheless be various degrees of control in the network, so it is important to recognise the influence and contribution of controlling elements to how a network functions. This helps expose power relations behind technology development. For example, why did Myriad Genetics focus on one particular genetic testing technology, e.g., full DNA sequencing instead of protein analysis, and who's interests were involved?

Technology development is inherently a process of translation. In aligning the goals of the designer with those of the manufacturer, marketer, and end user, the technology will necessarily change. Technologies are not simply passive, to be acted upon and changed by others. During the design phase, objects are given and have embedded within them a 'script', a set of instructions that determine how the technology will function and the extent to which it may interact with, shape, and be shaped by other actors. There are technical and normative values built into the technology (and its supporting documents, advertising, etc.) that attempt to prescribe specific patterns of use while restricting others (Prout 1996). A passenger elevator in a hotel, for example, has embedded within it a set of principles about distributive justice that determine how and in what order passengers are transported between floors. The elevator might respond to the first call and go to the requested destination, wait for a pre-determined number of calls and then proceed to pick up passengers in order, or respond to the first call and ignore all others – the underlying rules according to which elevators do (or should) operate are non-trivial (MacDonald in press). Yet while scripts may affect human behaviour as well as a range of other social and technical interactions, the scripts are not necessarily fixed. Scripts may be translated by other actors so that the technology comes to be used in ways not intended by the designers, i.e., the technology may drift (Martin 1999).

Technology Drift

The concept of 'drift' originates in the field of evolutionary biology – specifically as genetic drift[16] – but has been adapted to other fields such as health services research[17] and corporate information technology.[18] For present purposes, drift is useful for thinking about one aspect of translation, that is the situation in which a technology is used differently from the designer's intent. The purpose or function of a given technology, from the design perspective, will be embedded in the initial script. But the script may not succeed, the technology may be used in unanticipated ways, or its implementation may give rise to a competing script that makes the technology a failure from the point of view of the designers.

There are numerous examples of drift in the computer hardware and software industries where technologies have been 'hacked' by knowledgeable users. In one notable case, Netpliance developed a small user-friendly computer called the *i-opener*, designed solely for e-mail access and marketed to non-technical customers. Sold for a nominal fee ($99US), the intent was for users to subscribe and pay a monthly fee to access their e-mail. Technophiles quickly discovered that they were under no obligation to subscribe to the e-mail service, and that with some simple hardware modifications (e.g., adding a small hard drive and cabling to override the built-in security) they could gain full access to a stripped down, but extremely cheap Internet-ready Pentium computer (Tseng 2000).

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[16] Genetic drift refers to random changes in the allele frequency of a particular gene where the frequency fluctuates from generation to generation, especially in small populations. Drift applies to both the establishment of new mutant alleles in a population and the formation of small subpopulations through isolation from an original, larger population (Thompson, McInnes, and Willard 1991, 158-160).

[17] As medical technologies become diffused, they are used for a widening variety of indications not originally envisaged. For example, some pharmaceuticals will be used 'off-label' to treat unrelated conditions, such as the antibiotic dapsone, originally developed to treat leprosy, now being used for its anti-inflammatory properties to treat Alzheimer's disease and dementia (Jones 2000).

[18] An example of drift in the area of information technology is the Internet. Originally developed in the late 1960s for the U.S. military as a diffused communication network (ARPANET) that would be less susceptible to breakdown in the event of nuclear war, it has expanded beyond the confines and control of military or university systems to become an anarchic, globe spanning public network (Kristula 1997).

The *i-opener* was an abject failure from a marketing perspective as the costs of the hardware (which suppliers could not keep on their shelves) quickly outpaced subscription revenue – after a few failed attempts to regain control of the product, Netpliance terminated production. The initial script for a user-friendly e-mail service designed for the general public was transformed and a competing script developed that re-created the technology as a cheap Internet-ready computer for technophiles – the purpose or use of the technology drifted from what was intended by the designers to something desired by a certain group of users. Thus as Lehoux notes, the "meaning of an innovation is not entirely given a priori, but rather, progressively constructed through social practices" (Lehoux, Sicotte, and Denis 1999, 440). Technology drifts during implementation because of decisions made by many different actors, and the need for the technology to be incorporated into pre-existing social and technological contexts (Holmström and Stalder 2001).

An example of where drift works in concert with the broader intentions of the designer is the Zimbabwe Bush Pump (de Laet and Mol 2000). Designed in Europe to be transferred (but not translated) to the developing world, this technology has been re-created and re-envisioned by a Zimbabwean scientist/engineer. Now produced locally with available materials, it is a strikingly flexible and adaptable technology. It not only allows ready access to water (the initial script), but the modified pump also greatly reduces the possibility of well contamination, thus serving a new and extremely important function (a new script). This new purpose is made possible in part through installation instructions that describe how to lay a secure well-head; but more importantly, the instructions emphasize the need to enrol the community and the local shaman in finding and digging the well to ensure community acceptance. The technology was not simply transferred, but was also translated by the local

users who modified, fixed, or operated the pump while missing supposedly essential parts. The need for translation was built into a script that encouraged the technology to drift, to the extent that based on user experiences and input, the pump has and continues to be regularly re-designed and improved (de Laet and Mol 2000).

Positioning of ANT

To understand how technology is developed and implemented, it is important to move beyond a linear model of technology diffusion or transfer – a simple binary model of technology-push and market-pull is insufficient. There is a complex interaction between the social and the technological such that the two are often inseparable. In implementing a new technology, it may be necessary to allow it to drift into existing and unexpected situations because "rather than [being] unidirectional and fully controlled, technological development itself is part of a wider dynamic in which it is as much shaping as being shaped" (Holmström and Stalder 2001, 200). If the technology is going to 'work', it and all the actors in the network must be open to change. Innovations configure the user, defining who may use it and how, but they also modify existing social structures and create new ones.

The power structures present in a network will affect the ability of actors and end-users to contest the initial problematization of a technology. For example, Myriad's U.S., Canadian and European patents on the BRCA1 and BRCA2 genes are sufficiently broad that they allow Myriad to control any use of the BRCA genes for testing and research, including the development or evaluation of different testing methods. As Gold notes, "Patent laws prohibit patients from obtaining access to their own medical information without agreeing to conditions imposed by a patent holder, and prevent such patients from being able to choose

which diagnostic procedure to use" (Gold 2001, 2). Other BRCA testing methods that may (or may not) compliment or provide different information than Myriad's *BRACAnalysis* test are not legally available to patients from other providers, without prior agreement from Myriad. Nevertheless, while the choice of testing methodology may be restricted, this does not constrain the way in which patients may actually use the test; as will be discussed below, patients will likely use BRCA testing for reasons not anticipated by the designers.

If there is insufficient translation the network or technology may fail (Lehoux, Sicotte, and Denis 1999), and it is in these failures of technology and of the networks underlying them, that the norms and values built into a technology are often best revealed (Law and Callon 1992; Lehoux, Sicotte, and Denis 1999; Holmström and Stalder 2001). For example, the initial success of Myriad in dominating the U.S. market for BRCA testing (and receiving coverage under private health insurance) likely made company executives confident that they would have similar success in Canada and Europe. The failure of most Canadian provinces or European countries' health insurance plans to adopt Myriad's *BRACAnalysis* test, along with the mounting widespread public and professional opposition, must have come as surprise to Myriad executives. One reason for the failure of these networks may be due to insufficient translation that incorporated differences in the social and political contexts in Canada and Europe, such as the existence of universal public health care systems and re-actions against what may be viewed as American capitalist 'imperialism' in enforcing patents that dictate how a health care service should be provided.

Critique

The ANT approach to evaluating technology development and its effects and interactions with other complex networks has also been strongly criticized. Of particular concern is the apparent value-free and overly neutral nature of the theory. By focusing on empirical case studies that provide a rich description of networks and their internal operations, ANT may pay insufficient attention to the larger social and political context, and be unable to support effective social, ethical and political critique. According to Fuller, ANT is overly concerned with the consequences of networks and technology development, while ignoring the means of production. This perpetuates a functionalist, problem-solving description of networks that results in collusion with dominant ideologies, such as industry, government, or patriarchy (Star 1991; Fuller 2000). Fuller sees this as being due in part to ANT's origins, and in particular Latour and Callon's presence at the École des Mines in Paris, an academic institution with a strong engineering focus that has relied heavily on financial support from industry. He is therefore concerned that ANT, a "*seemingly radical innovation that quickly acquires widespread currency probably serves some well-established interests that remain hidden in the context of reception*" (Italics in original, Fuller 2000, 18).

To begin with Fuller's last point, to argue that there is an inherent and overwhelming conflict of interest in researchers pursuing critical research while working in a corporately funded institution amounts to little more than an *ad homonym* attack. Were one to take this argument seriously and apply it uniformly, the vast majority of research in both private and academic institutions would be suspect. There are a wide variety of influences besides corporate funding, such as academic reputation, salaries, administrative pressure, etc., that necessarily have an affect on researchers, but we do not thus condemn all resulting research

as flawed. The reasonable approach is to evaluate research on a case by case basis to see if there are in fact conflicts that jeopardise academic credibility and independence.

With regards to Fuller's first criticism, an ANT based analysis of the networks involved in commercial genetic testing might indicate why a particular implementation scheme failed and so provide the information necessary for commercial interests to improve or stabilize their networks and expand their market. In the Myriad case, an ANT analysis of the company's failure to capture the Canadian and European markets might, for example, highlight the negative response in Canada and Europe to a competitive market approach (as was successful in the U.S.), and point to the need to work more closely with clinicians and administrators to lobby governments for coverage of BRCA testing as part of public health insurance. This information could be extremely useful for Myriad in the event that they decide to re-frame their approach to these markets. In this case, the ANT analysis would have failed to critique the appropriateness of private provision of health care services, the potential negative effects of two-tiered health care, or the manner in which the patent system is being used to control the implementation of health care technologies.

Nevertheless, if we accept that every description is to some extent performative, then there is always a risk of collusion, of bringing into being that which is under study (Law 2001); this is a concern not only for ANT, but for any descriptive project. Yet ANT also introduces the idea of translation – a potentially subversive concept that Law describes as 'betrayal' – which points towards the inevitable change in technologies, actors and networks. If one also takes seriously the relational and hybrid nature of networks proposed by Latour and Callon, then there is no one 'right' way for a network to be stable, nor is there only one network. Instead, there are a multiplicity of networks making up a technological actor and

different visions of how this actor should function or behave. As will be discussed below, while it is sometimes useful to think of the 'BRCA test' as a specific technology or actor, there are in fact many different tests (e.g., family pedigree analysis, PTT, SSCP, CSGE, full DNA sequencing) that are used to determine risk for hereditary breast cancer. It is difficult to support a functionalist, problem-solving approach to technology development if the device in question may be present in many different forms, be situated in very different social and political contexts (which in Myriad's case may lead to patent challenges), or drift in unexpected directions beyond the control of the designers.

ANT is also an approach that is interested in the tensions between actor, network and technology, and how they manifest in practice (Law 1999; Latour 1996). The locations or targets most fruitful for study are those where networks have failed, for example, because the various actors would not stay enrolled, or the technology was not accepted by the end-user or consumer. It is here that the actor-networks reveal themselves, that black boxes are opened, and the norms and values built into technologies are made apparent. Science can be seen as inextricably linked to politics; human and non-human actors are necessary parts of networks; and technologies are inherently value-laden – these insights can be used to support comprehensive ethical analysis and social critique. The more recent literature by ANT scholars such as Law, Callon, Latour, and Mol (Law and Hassard 1999) – working 'after' actor-network theory – has begun to explore more explicitly the place critical social and political analysis. Mol, for example, discusses the important role for ANT in addressing political questions once one accepts a world in which there are multiple ways that an object can manifest. ANT makes explicit that choices will have to be made about how a technology should be developed, who the potential actors should be, and how to deal with a clash

between different, co-existing visions of reality (Mol 1999). ANT could be used for a strictly functionalist analysis, but it can also be used as a way of undermining the functionalist and determinist models of network building (Law 1999).

Another challenge levelled against ANT is aimed at the radical symmetry between human and non-human actors that treats both as essentially equivalent for the study of networks (Pickering 1992; Lee and Brown 1994; Murdoch 2001). Surely, it is argued, humans have different (superior) moral status from machines or corporations, and thus are due special regard? To be fair to ANT, the purpose of treating humans and non-humans as symmetrical is to aid in a detailed description of the network, and not for the purpose of critical social or moral analysis. The theory does not imply or require that all entities be treated as identical for all purposes, nor that the various relations between actors be egalitarian; in fact, part of laying out a network will be tracing the types of relations between actors and determining the flow of power and control. While the theory does not explicitly deal with ethical analysis of particular institutions, technologies, or actors, such an analysis is not precluded.

Myriad Genetics and Commercial Genetic Testing

How does Actor-Network Theory support practical and useful analysis of the social, ethical and policy implications of commercial genetic testing? In the preceding sections, three concepts – actor-networks, translation, and drift – were explored to see how they could contribute to an understanding of the various interactions between individuals, groups, organizations, and technology. In the following, Myriad Genetics' *BRACAnalysis* test for hereditary breast cancer will serve as the focal point for elucidating what is occurring in

actor-networks, specifically the networks which led to the technology being developed and later integrated (or failing in this task) as part of public and for-profit health care in Canada and internationally. Tracing the path of this technological actor highlights the numerous, complex social and ethical issues associated with commercial genetic testing.

Technological Actors

In order to see how an actor such as *BRACAnalysis* interacts with other actors in a network (including other testing methods), it will be necessary to first understand what the technology is and does – the black box that is the technology must be opened in order to examine the underlying actor-network. Genetic testing for hereditary breast cancer involves the analysis of two genes, BRCA1 and BRCA2, to search for mutations (e.g., individual base-pair or large-scale deletions or re-arrangements) which have been associated with an increased risk of developing cancer. The particular testing methodology, however, will vary greatly depending on the laboratory conducting the test. Many European and Canadian laboratories use a 2-step method. The protein truncation test (PTT), for example, may be used as an initial screen to see whether the BRCA proteins are shorter than expected (i.e., truncated by mutated alleles), followed by sequencing of specific regions of the gene to detect individual mutations. Other laboratories may use techniques such as conformation sensitive gel electrophoresis (CSGE) or single stranded conformational polymorphism (SSCP), which locate mutations by evaluating the structure of paired single-stranded DNA moving in gel electrophoresis (www.genetests.org). Myriad's *BRACAnalysis* test, by contrast, is a single-step approach based on full DNA sequencing of the two BRCA genes. A DNA sample is amplified using polymerase chain reaction (PCR) so that each base-pair in

the gene can be checked for deleterious mutations, e.g., frameshift, nonsense or splice-site mutations that result in protein truncations. While more expensive than PTT, Myriad can perform their test more rapidly – usually in a few weeks, but as fast as 7 days with the Rapid *BRACAnalysis* process (Myriad Genetics 1999) – because they use numerous automated high-throughput DNA sequencers (Hofmann and Schlag 2000).

BRCA testing does not have to involve only one approach. There may be real advantages for laboratories in terms of costs and time involved but also with regards to accuracy, in using a particular testing method that may be better suited for certain types of investigation, e.g., using SSCP to detect 3 common Ashkenazi Jewish mutations (Tian *et al.* 2000). The sensitivity and specificity of the test, that is its ability to differentiate between those people who have BRCA mutations and those who do not, will depend in large part on the technology used, but also on the skills and experience of the technicians and geneticists in the laboratories providing testing (Geisler *et al.* 2001). There is significant debate, particularly between those researchers (and Myriad) who favour the full sequencing approach and those using other less expensive approaches such as PTT or SSCP, about which method is more accurate. None of these various methods is 100% accurate, and interpretation of test results will be closely tied to a detailed evaluation of the patient's family history, without which the technical results are not considered informative.

While full DNA sequencing has been evaluated as having a diagnostic sensitivity of approximately 85% (Carter 2001), Myriad states on their website[19] that their *BRACAnalysis* test "has greater than 99% analytical sensitivity and greater than 99% analytical specificity" and thus should be considered the 'gold standard'. It is important to note, however, that in the context of genetic testing, *analytic* sensitivity and specificity refer to whether the test is

[19] http://www.myriad.com/med/brac/physician/08.html

positive when the gene or genetic variant being tested for is actually present and whether the test is negative when the gene or genetic variant is absent. This is different from *clinical* or *diagnostic* sensitivity and specificity, which is the probability that the test will be positive in people with or who will get the disease, and the probability that the test will be negative in people without or who will not get the disease (Holtzman and Watson 1997). Other testing methods in development may have similar or better accuracy than full DNA sequencing. For example, a new approach to using SSCP (which has been historically criticized for having a analytic specificity below 80%) in combination with other technical advances such as capillary electrophoresis, may reach 95% analytic sensitivity in BRCA mutation detection (Kozlowski and Krzyzosiak 2001). Finally, even for very accurate testing methods, no more than 20-25% of patients with a strong family history will have a positive mutation detected – the cause of cancer in their family remains unknown (Carter 2001).

The technology 'BRCA testing' is comprised of complex actor-networks that include technicians, geneticists, counsellors, patients, families, reagents, sequencers, accuracy of measuring instruments, laboratories, etc. The changing nature of each of these actors, e.g., through the discovery of new mutations (Gad *et al.* 2001) or novel approaches to genetic testing and counselling, will mean that the technology itself will continue to change, both regionally and over time. A technology assessment of BRCA testing (e.g., in order to decide which is best for a particular group of patients, or which should be funded as part of public health insurance), would thus need to involve an evaluation of the full range of actors and networks, and the pros and cons of the various testing methods in terms of sensitivity, sensitivity, positive predictive value, cost, difficulty, etc. When thinking of a particular

BRCA test such as *BRACAnalysis* as an actor, and evaluating how it will effect and interact with other actors, it is essential to remember that it is itself a complex actor-network.

Context and History

The development of BRCA testing also has a history, a larger context that continues to shape the actions and effects of this actor-network in the broader health care setting. In the hunt for the BRCA genes, hundreds of scientists from across the U.S., Europe, Japan and Canada were involved in many years of research. This work was supported financially by funding from both national agencies such as the U.S. National Institutes of Health (NIH) – which provided $5 million to the University of Utah team – as well as from investments by the private sector. This research would not have been possible without the participation of many thousands of individuals and families at risk for hereditary breast and ovarian cancer who donated blood samples and family histories (Davies and White 1995).

A few central figures emerge who had a major influence. One was Mark Skolnick, a researcher at the University of Utah's Center for Cancer Genetics Epidemiology who led a consortium of U.S. researchers to isolate and sequence the BRCA genes. Skolnick helped launch Myriad Genetics, was instrumental in obtaining the gene patents, and is currently the company's Chief Scientific Officer (University of Utah 2001). In the U.K., Michael Stratton at the Institute for Cancer Research led another group (part of the Breast Cancer Linkage Consortium) also searching for BRCA1 and BRCA2, and is named on various U.K. and E.U. patents for BRCA2. The race to discover BRCA1 became heated (particularly in the case of BRCA2) with the involvement of commercial interests such as Myriad and pharmaceutical giant Eli Lilly (Davies and White 1995). Skolnick's group was the first to sequence BRCA1

(and later part of BRCA2) which they then patented for Myriad. But gene patenting presented a disturbing scenario to many of the researchers involved in the hunt for the BRCA genes (Murray 1999). Researchers were concerned by the ability of a company to 'own' genes and the resulting susceptibility or diagnostic tests, when the genes had been discovered as a result of many years of international collaborative research.[20] This concern also manifested in national differences (between the U.S. and the U.K.), both in researcher attitudes and government policy about the extent to which the results of academic research should be commercialized (Davies and White 1995; Watson 2001).[21] While there was opposition from many U.K. researchers to patenting, it was agreed that a patent was nonetheless necessary to prevent Myriad from also gaining control of BRCA2. A U.K. patent was filed by CRC Technology, the commercial arm of the Cancer Research Campaign (CRC) charity that had funded much of the U.K. BRCA research. The patent on BRCA2 was then licensed free of charge to the U.K.'s National Health Service for genetic testing. This weakened somewhat Myriad's control over the two genes in Europe (Meek 2000).

Myriad's U.S. patents on BRCA1 and BRCA2 (filed in 1994 and 1995) provided the company with the resources to leverage increased venture capital and continue gene

[20] As the discovery and sequencing of the genes was the result of a larger scientific endeavour with detailed information about the genes published in a range of academic journals, BRCA tests could be developed and provided by many different public and private laboratories. BRCA testing is thus made up of a complex set of actor-networks.

[21] Another example of the consequences of ideological differences for the pursuit of scientific research is presented in *French DNA: Trouble in Purgatory*. Paul Rabinow tells the story of a struggle between France's premiere genomics laboratory, the Centre d'Etude du Polymorphisme Humain (CEPH) and Millennium Pharmaceuticals, an American start-up biotechnology company, to establish a collaborative research project that would sample DNA from the French population for the study of diabetes. Controversy arose over American venture capital investment in and control of Millennium, financial difficulties and mismanagement at CEPH, and issues of identity and nationalism with respect to the control of DNA from the French population (Rabinow 1999).

discovery research (Davies and White 1995).[22] Once a genetic test was produced (first marketed in 1996), the monopoly granted by their patents – which Myriad has vigorously protected – permitted the company to stop other commercial laboratories from providing BRCA testing in the U.S. More recently, Myriad has made similar moves in Canada and Europe with the objective of controlling the provision of all testing, including those which had previously been offered through public laboratories (Myriad Genetics 1998a, 2000b).

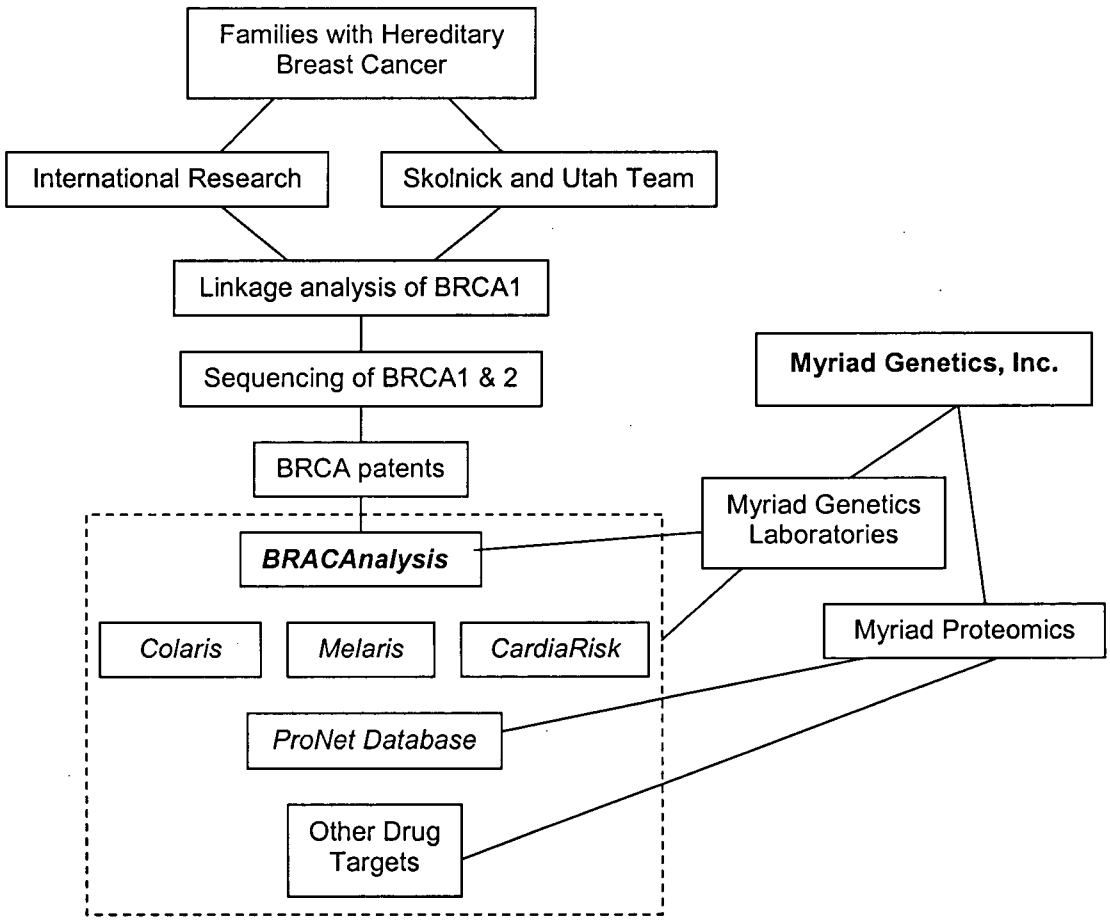
Myriad's efforts to enforce U.S. and international patents has much to do with the company's financial situation and obligation to its shareholders. Despite expanding the market for BRCA testing in North America and Europe, and implementing genetic tests for heart disease and colorectal cancer, Myriad still posted a net loss of $7 million for fiscal 2001 (Myriad Genetics 2001d). The company has entered into partnerships with a range of pharmaceutical companies to develop products based on patented genes, and is expanding into the area of proteomics,[23] through their subsidiary Myriad Proteomics. BRCA testing may have served to establish the company and build a market presence, but the test is only one part of their current portfolio of products and services, and it is these other projects that are likely to be central to the company's capacity to eventually show a profit. In Figure 2, *BRACAnalysis* is shown as resulting from interactions between many other networks, and is one of many products marketed by Myriad Genetics Laboratories and Myriad Proteomics,

[22] In the absence of functional tests or treatments, gene patents have often been the only property of value possessed by start-up biotech companies with which to obtain investment funds to continue their research and development programs (Gold 2000). However, this situation is changing with investors becoming less interested in investing in companies without first seeing evidence of a commercial product (Malinowski and Littlefield 1999).

[23] Proteomics is the systematic analysis of gene expression at the protein level within an organism. The isolation, separation, identification and functional characterization of proteins will provide a better understanding of disease processes, thereby facilitating the discovery and development of therapeutic proteins, drug targets and diagnostics.

subsidiaries of Myriad Genetics, Inc. The way BRCA testing is marketed is part of a larger picture than would otherwise be the case if BRCA testing were the company's only product.

Figure 2. Context of BRCA Testing within Myriad Genetics



Actors and Normative Values

Genetic technologies are not simply passive entities that are shaped by scientists, prescribed by clinicians and used by patients (Prout 1996). A genetic test will shape and be shaped by human behaviour, relations, and society. However, it is only a subset of these issues – the psycho-social effects of genetic testing – that tend to be of concern in the social

and ethical literature. For example, how do individuals and families deal with the complex risk information resulting from genetic testing (Codori 1997; Marteau and Lerman 2001)? How does this information affect their personal lives, friendships and family relations (Cox and McKellin 1999; Evans, Skrzynia, and Burke 2001)? What are the broader effects of genetic information in terms of discrimination and stigmatization (Lemmens and Bahamin 1998; Wertz 1999)?

Applying an ANT analysis and thinking of genetic tests as actors in a network, expands the scope of issues for consideration. As with other technologies (e.g., the telephone or elevator), there are normative values embedded in the scripts which define how genetic tests are marketed and implemented. There may, for example, be genetic essentialist or reductionist views present that promote the idea that genes are the most significant cause of disease (Lippman 1991; Nelkin 2001). Myriad's online resources for patients and physicians about risk information and the probability of developing breast cancer focus primarily on the role of genetics in disease, and much less on how breast cancer can be strongly influenced by other non-genetic factors such as an unhealthy diet, low activity level, stress, psycho-social issues, or pure chance (Baird 2001). In Myriad's marketing of *BRACAnalysis*, such as their advertisement featuring a woman saying "Doctor, I need to know" (Myriad Genetics 1997; Chandros and Prasad 2001), issues of patient or consumer autonomy and freedom of choice are highlighted. There is little attention in either the advertisements or the 'educational' material to the impact of genetic testing on families, community, culture or society (Burgess 2001). Built into the *BRACAnalysis* test is the view – which may also be part of the larger, and inseparable social context – that the resulting genetic information is necessarily valuable because it permits the consumer or patient to make informed choices about treatment, health

management, or life plans (Chadwick, Levitt, and Shickle 1997). This may also play up the 'need' for genetic information, and in a context of heightened public concern about breast cancer, there is the potential that patients and consumers may feel responsible for their own health care and at-fault or negligent for not pursuing genetic testing when it is 'necessary' (Lippman 1991; Nelkin and Lindee 1995).

While a genetic test as technological actor may have embedded in its scripts' notions of autonomy and individual responsibility, there may be countervailing influences – other actor-networks that become apparent on a broader analysis – that interact with the technology and diffuse some of this focus on consumer independence. Access to impartial genetic counselling may help patients to understand some of the limitations of testing, and after discussing a variety of individual and familial concerns with a counsellor, patients often decide that they do not need or want genetic testing (Lynch *et al.* 1997). Myriad also restricts access to BRCA testing to the extent that a patient's physician must order the test and provide the results and some level of counselling support. This restriction arose after criticisms by the medical community of Myriad's initial attempt to market BRCA testing as an 'over the counter' test-kit. Fears of liability should a patient be harmed by receiving the information without the benefit of counselling were likely also a factor.

The various actor-networks in the broader context have a direct effect on how the technology is implemented. While Myriad seeks to provide the best or 'gold standard' testing technology, ensuring the highest standards of test accuracy is undermined by Myriad's broad gene patents since these permit Myriad to control and potentially retard research and development that would otherwise improve testing methods (Institut Curie 2001). In terms of provision of counselling, Myriad has invested heavily in patient and physician 'education',

providing extensive online resources and supporting Continuing Medical Education programs for physicians so they can better counsel their patients (Aetna U.S. Health Care 1999). Even with this support, physicians will still lack sufficient medical education and understanding of genetics (James *et al.* 1998; Emery and Hayflick 2001), or training in how to address the complex social and family issues associated with genetic information necessary to provide effective counselling. Moreover, with the primary source of information about the test coming from the supplier, as is increasingly the case with knowledge about new pharmaceuticals (Mintzes *et al.* 2002), physicians may be unable to critique the accuracy or utility claims made about the testing methodology (Caulfield and Gold 2000a).

A technology will also shape the social context in which it is implemented. The commercialization of BRCA testing has significant consequences for the provision of genetic testing services in Canada. The broad nature of the BRCA patents (which allow Myriad control of all diagnostic and therapeutic uses of the two genes) and the need for Myriad to develop profitable services, has led the company and its Canadian licensee MDS to send 'cease and desist' letters to all the Canadian public laboratories providing testing. In British Columbia, the Ministry of Health Services, on advice from legal counsel, decided to comply with Myriad's request and thus the Hereditary Cancer Program (HCP) at the B.C. Cancer Agency has ceased provision of BRCA testing and refers all patients to Myriad or MDS. Commercial *BRACAnalysis* testing is substantially more expensive, and due to budgetary considerations the HCP decided it could not afford to provide BRCA testing to patients out of the HCP's limited operating budget (Kent 2001). Nevertheless, the HCP is continuing to provide counselling free of charge for patients at risk for hereditary breast cancer, regardless of whether they purchase genetic testing. This situation in B.C. has led to two categories of

patients, those who can and those who cannot afford the test. At the national level, patients are now treated differently depending on the province where they live.

Competing Scripts and Drifting Tests

Myriad's move to take over the provision of BRCA testing from public health care providers in Canada has been met with opposition on a range of fronts. Concerned by the mounting costs of patented genetic tests, the Ontario government and former Premier Mike Harris have taken a very strong stance against gene patents, arguing that they constitute a threat to the provision of affordable health care (Lindgren 2002; Eggertson 2002). British Columbia is the only province to comply with Myriad's patents (Kent 2001; Panabaker 2002). Other provinces – apart from Québec which performs some mutation testing locally but sends index testing to Myriad for full analysis – appear to be taking a 'wait and see' approach on patent enforcement and are continuing to offer testing (Lemire 2002); Ontario has even expanded its capacity for service provision. In Europe, there is an ongoing challenge of the European patents by the French Institut Curie (Institut Curie 2001), which if successful, could be financially devastating for Myriad simply due to the costs of fighting a multi-year and multi-million dollar legal battle. Success in Europe might even galvanize opposition in Canada and internationally and seriously threaten Myriad's continued solvency. The commercial elements built into the initial script of Myriad's *BRACAnalysis* test – that it is a patented product, priced at triple the cost at which most public laboratories could provide testing – are being rejected. Increasing numbers of scientists, clinicians and public health care institutions are challenging the view that the BRCA genes can and should be owned by

Myriad, or that genetic testing on these genes should only be conducted by Myriad or one of their licensees, and not by public health care institutions.

In the first part of the chapter (Positioning of ANT, page 56), the concept of technology drift was discussed and the passive diffusion model of technology development rejected. Technologies are not simply marketed and taken up by passive consumers, but are instead shaped by consumers in how they respond to technologies and translate them for their own purposes. From the perspective of many medical professionals, genetic tests are useful and appropriate only if they provide risk information that will help individuals and families make informed decisions about treatment, prophylactic measures, or life choices. While genetic testing remained restricted to the domain of medical professionals in public health care institutions, patients were limited in the extent to which they could translate testing to meet their own needs. Medical professionals were able to control who could or could not have access to testing, and what would be considered reasonable criteria for making such a determination (Carter 2001).

But genetic tests are beginning to drift from this more restricted usage to a situation where anyone with the financial resources and know-how can purchase a range of tests from a variety of sources, regardless of clinically determined risk status (Williams-Jones 1999). Individuals and families seek testing even when medical professionals do not deem them to be at sufficient risk, or where the risk information is considered to be of little clinical benefit; people may want to use risk information for very different reasons, such as anxiety reduction, initiation of family dialogue, or other 'non-clinical' uses (Burgess and Hayden 1996; Cox and McKellin 1999). The original reasons for the use of the technology have shifted.

One factor supporting this drift has been the commercialization of genetic services – companies have an interest in selling their services to as large a market as possible, and so are not likely to have particularly strict access criteria (Carter *et al.* 1997). The BRCA testing provided by Myriad, for example, has entry criteria which require only that a physician determine that their patient would benefit from testing (Birmingham 1997; Smith 1997). In contrast, public health care institutions such as the B.C. Hereditary Cancer Program, have guidelines requiring that a patient present with factors such as a strong family history with multiple cases of cancer, or early age of onset (e.g., pre-menopausal), or membership in a specific ethnic group (e.g., Ashkenazi Jewish) (Carter 2001). BRCA testing has drifted in two senses: the reasons for which testing is used have become more expansive and patient-centred, and provision of testing has moved outside the domain of medical genetics or cancer clinics and into the offices of general practitioners as a privately purchased service.

In being translated and seen as a 'consumer good', medical technologies may satisfy some human desires but also cause harms. They may have effects on the collective well being, such as on the sustainability of publicly supported health care, or may result in inequitable public access to services – those who can afford commercial testing may jump queues for diagnostic evaluation or monitoring. Translated technologies may also create a 'need' for other new technologies. New technologies may either replace existing ones or enter the market as novel products that at first have little practical use. Those technologies that survive may become part of consumers' daily lives, metamorphosing from toys to instruments, from being seen as luxuries to necessities; they may become integrated into existing networks and be stabilized, domesticated, and eventually taken for granted (Pantzar 1997).

Genetic testing has yet to reach the level of domestication of personal computers, for example, and the general population still does not routinely seek BRCA testing at a medical check-up, or shop for it online before planning a vacation. But genetic testing has clearly had an impact on the way medicine is practised. A host of predictive and diagnostic technologies (e.g., ultrasound, amniocentesis, or the Triple Screen for alpha-fetoprotein) are routinely used in prenatal testing for conditions such Phenylketonuria or Down syndrome. Some diseases can now be predicted or diagnosed based on DNA analysis; others may even become classified as 'genetic' diseases that are strongly associated with particular 'disease genes', where once they were simply 'familial' diseases.[24] Genetic testing has also increased the need for a range of other medical services and technologies: genetic counsellors to help interpret risk information, online web resources for when counsellors are not available, and access to ancillary non-genetic diagnostic and screening tests such as ultrasound or mammography. Genetic tests are evolving over time, changing the networks in which they are currently situated and affecting the actors with which they interact. Where genetic technologies will drift is an open question, but the fact that they will is a certainty.

The drift of genetic technologies, particularly if aligned with other movements in health care such as privatization, obviously have important implications for current health care policy. If the patient or consumer is to become empowered to make more health care decisions, then developing appropriate regulations to ensure accurate, understandable consumer information will be essential. Direct-to-consumer advertising, if allowed at all in Canada, would need to be very closely regulated. Companies have a strong interest in promoting the use of their products and services (Harper 1995; Agovino 2002; Mintzes *et al.*

[24] While these technologies may have become routine in the clinical setting, it does not mean that the broader social and ethical issues, such as whether one should be offering prenatal testing for Down syndrome, have been addressed (Levitt 2001).

2002), but unlike most consumer goods, people do not have the necessary experience or understanding to make free and informed choices about health care services and products that are often complex and potentially harmful. Regulations regarding the accuracy, safety, and usefulness of genetic testing will also be needed and they must be able to adapt to an ever changing social, scientific and political terrain (Secretary's Advisory Committee on Genetic Testing 2000; Caulfield *et al.* 2001; Baird in press).

Nevertheless, one should not underestimate the ability of consumers to evaluate, control, accept, reject or modify new technologies. Inherent in the concept of drift is the view that effectiveness and uptake of new technologies will depend to a large extent on whether the technology in question meets consumer 'needs', as defined by the consumer. These perceived needs are subject to manipulation by companies through marketing and other social pressures. Rejecting a technology may not always be possible, especially if it is so built into social life that we cannot simply decide not to use it even if it does not meet our personal 'needs'. Technologies will still be accepted, but they will also be adapted and translated by users for their own purposes; if unable to meet these ends, the technology may be rejected. The developer and the policy maker will be unable to predict with certainty the direction of drift, thus if they wish to influence the ultimate use of the technology, there must be ongoing feedback and interaction with the end-user or consumer. Critical evaluation of the broader social, political, and economic contexts in which the technology is developed and situated, as has been touched on in this brief discussion of Myriad's *BRACAnalysis* test, will be essential for effective policy and regulation of new genetic technologies.

Conclusion

Thinking about the development of genetic technologies in terms of actor-networks highlights the need to analyse the diverse elements involved. The bench scientist in the race to discover and patent the BRCA genes is inextricably linked through a host of complex networks to issues about the pursuit of academic and commercial science, power struggles amongst individual researchers, public perceptions of national research agendas, and international politics and patent law (Caulfield and Gold 2000b). As for the tools of genetic research, they too are inseparable from larger networks. Fujimura notes that it is "the collective activities and commitments of molecular biologists, enzymologists, venture capitalists, entrepreneurs, funding agencies, university administrations, governments...[that] created, produced, and supported a set of standardised transportable tools for manipulating eukaryotic DNA" (Fujimura 1996, 113). The development of BRCA testing is the result of interactions between actors as diverse as research scientists, universities, patients, the patent system, Myriad Genetics, health care professionals, and consumers. These actor-networks will not be uniform or stable, but will be continuously changing, coming into and out of existence, and the subject of numerous stresses and forces. To understand what is happening in the development of commercial genetic testing, it is essential to study in detail the various complex networks and sub-networks. This entails analysis of all the elements, from the scientist and the genetic test, to the corporate executive, government official, patient and consumer, as well as the interests, goals, and relations that link these actors together.

Such an empirical understanding provides a strong foundation for sustained social and ethical critique. Commercial genetic tests are not passive, value-neutral technologies that have no effect on consumers, the Canadian public health care system or society in general.

As has been shown in the case of Myriad Genetics, the development and marketing of a commercial genetic test for hereditary breast cancer raises serious concerns about continued and affordable access to BRCA testing in Canada, the place for commercial service providers in a public health care system, and the role of patents in facilitating or restricting health care research and technology development. Nor do genetic tests exist apart from the social world; they are developed and accessed for a variety of complex reasons. By applying the concepts of 'actor-network', 'translation' and 'drift' to the development and implementation of commercial genetic technologies, it is possible to better see the complex and multifaceted nature of the networks in which they are situated. One of the strengths of Actor-Network Theory is that it shows how certain effects are produced, including the connection to other diverse interests. The resulting rich detailed empirical information – which has only been briefly outlined in this chapter – is essential for inter-relational interests and enable a more nuanced, comprehensive and sophisticated ethical analysis of the development, commercialization and implementation of genetic technologies.

Linking Statement

Chapter 3 presented Actor-Network Theory (ANT) as a method for developing the empirical information and critical understanding of complex social and technical relations that is necessary to conduct comprehensive social, ethical and policy analysis of gene patenting and commercial genetic testing. Chapter 5 will re-introduce ANT briefly and apply it to the issue of technology assessment and health care decision making, in order to propose recommendations for how to regulate gene patenting and commercial genetic tests. The following chapter (Chapter 4) will introduce three approaches from moral philosophy (consequentialism, social contract theory, and public deliberation), and apply them to the problem of if and how to integrate commercial genetic services into the Canadian public health care system.

Chapter 4

Moral Philosophy and Just Decision-Making: Public and Private Access to Genetic Testing

Submitted to the *Kennedy Institute of Ethics Journal*

Abstract

Decisions about which services to fund through public health care insurance in Canada are made in an *ad hoc* fashion, and in a political context of limited financial resources allocated for health care, leading to an unjust distribution of health care services. This paper applies some tools drawn from moral philosophy to the case of commercial genetic susceptibility testing for hereditary breast cancer. Consequentialist approaches such as cost-effectiveness or cost-benefit analyses provide a method for performing broad and objective evaluations of genetic testing and comparison with other health care services. But these analyses must be supported by substantive considerations of social justice, such as equality of opportunity, and procedural justice approaches that integrate public participation and deliberation. When these approaches are brought together with Daniels and Sabin's 'accountability for reasonableness' method, it is possible to begin developing a more just decision making framework with which to make important progress in determining where genetic testing 'fits' with respect to other beneficial services, what services to fund as part of public health insurance, and which if any to leave to private purchase.

Introduction

The majority of Canadians who access genetic services do so through the public health care system, but for those with the means, private purchase has also become an option. The rapid expansion of the Internet and the creation of a 'global marketplace' have made it possible for Canadians to purchase genetic testing through international sources (Williams-Jones 1999). With the agreement between the U.S. biotechnology company Myriad Genetics and the Canadian diagnostic company MDS Laboratory Services, Canadians can now purchase genetic testing for conditions such as hereditary breast or colorectal cancer (Myriad Genetics 2000e, c). This development is not without controversy, and there is increasing public debate about whether the Canadian health care system should prohibit, permit or encourage provision of and access to private health care services (Evans 2000; National Post 2001; Mazankowski 2001; Romanow 2002).

A common objection to access to private health care services is that it is unfair. Health, it is argued, is fundamental to enjoying other important goods, such as the freedom to make life plans about one's career or education, or the choice to start a family. It is thus the responsibility of a just society to ensure that all citizens have access to needed health care. Further, it may also be argued that personal wealth should not permit some people to obtain better or preferential treatment. This objection expresses one of the fundamental tenets of public health insurance, namely that citizens should have equal access to needed health care regardless of ability to pay. This egalitarian ethic is enshrined in Canadian legislation, and according to the *Canada Health Act* (CHA), Canadians are entitled to health insurance that is publicly administered, comprehensive, universal, portable, and accessible (Canada Health Act, R.S. 1985, c. C-6). Health care services that are covered under the CHA may not also be

made available for private purchase because this would negatively effect 'universality' (§10) and 'accessibility' (§12). This legislation empowers the federal government to withhold health transfer payments to provinces that permit private services (§15), until those provinces comply with the CHA (Deber *et al.* 1998).[25] Provincial legislation in 6 of 10 provinces also prohibits private insurance of medically necessary hospital and physician services (Flood and Archibald 2001).

At first glance, federal and provincial legislation seem to form a basis for the public provision of all needed health care services and for a restriction on private purchase. But these requirements apply only to an agreed upon set of hospital and physician services (Flood 1999). Those services falling outside these areas (including those that have been de-listed) are legally open to commercial provision and private purchase. This is currently the case for dental care, some reproductive technologies, cosmetic surgery and most pharmaceuticals used outside hospitals[26] (Giacomini, Hurley, and Stoddart 2000). Despite the requirements for 'comprehensiveness' and 'universality' found in the CHA, the reality is that some beneficial services (non-hospital physician services or services de-listed for budgetary reasons) will continue not to be publicly insured and so will only be available to people with sufficient personal resources or private health insurance.[27]

[25] The power of the federal government to constrain privatization and two-tiered health care has been seriously compromised over the last decade, undermining the threat for non-compliance. For example, private MRI, day surgery, and laser eye clinics have developed and continue to operate in British Columbia, Ontario and Québec.

[26] Some financial support from provincial governments is provided to the indigent and the elderly to subsidise the costs of obtaining prescription drugs, e.g., PharmaCare in British Columbia.

[27] One might argue that by re-organizing and better managing the delivery of services, and for example, discarding those services with no proven benefit and eliminating the wasteful use of highly expensive pharmaceuticals that are no more effective than cheaper competitors, that it might be possible to publicly fund all services of proven benefit. However, if medical technological and pharmaceutical development continues unabated and these products prove effective (but also costly), it will not be feasible to fund them all as part of the public health care system. This issue requires substantial, ongoing evidence-based research.

Decision-making about health care resource allocation, that is, which services to cover under public health insurance, often occurs in a complex and interest-driven fashion that is influenced by a range of social, economic and political factors (Flood 1999). As Sherwin and others have argued (Sherwin 1996; Caulfield *et al.* 2001), the *ad hoc* nature of decision-making about the funding of health care services and the existing uneven distribution of benefits will mean that injustices exist. In the context of access to genetic testing, the situation is complicated by gene patents such as those for BRCA1 and BRCA2, owned by Myriad Genetics. Gene patents directly affect service provision by increasing the cost of testing (Merz *et al.* 2002), and may indirectly lead to greater demand for testing as a result of direct-to-consumer marketing of patented technologies, thereby further burdening publicly supported ancillary health care services such as genetic counselling. Patents may also restrict downstream research into better, cheaper or more accurate tests and therapeutics (Borger 1999; Knoppers, Hirtle, and Glass 1999; Heller and Eisenberg 1998). These are good reasons for constraining the application and scope of gene patents, restricting access to genetic services outside of the public health care insurance system, and for carefully evaluating which services are sufficiently beneficial to warrant coverage as part of public health care insurance.

In this paper, three philosophical approaches (consequentialism, social contract theory, and public deliberation) will be outlined and applied to task of just decision-making. The strengths and weakness of each approach will be highlighted by referring briefly to the Oregon Health Plan[28] for state-sponsored Medicaid, and then applied to the case of Myriad Genetics' commercial *BRACAnalysis* test for hereditary breast cancer, and its interaction with

[28] The Oregon Health Plan has been widely discussed in the bioethics literature, initially because of the innovation and ideal of applying a rational and objective approach to priority-setting and decision making about health care funding, and later because of the failure of this approach in achieving these ideals.

the Canadian health care system. It will be argued that in order to justly distribute the benefits of heath care, a more coherent decision-making framework for health care priority-setting is necessary. Such a framework, as applied to the complex issues associated with commercial genetic testing, would benefit by adopting aspects of the three philosophical approaches to be described. Particular reference will also be made to Daniels and Sabin's 'accountability for reasonableness' approach (Daniels and Sabin 1997, 1998; Daniels 2000), in order to clarify the need for a mechanism that incorporates both substantive and procedural justice.

Genetic Testing for Hereditary Breast and Ovarian Cancer

With the discovery and sequencing in the early 1990s of two large genes (BRCA1 and BRCA2) associated with hereditary breast and ovarian cancer, it has become possible to provide genetic tests to women and families in order to help them determine whether they are at increased risk of developing the disease, and thereby facilitate life planning, anxiety reduction, and treatment decisions. While there are still no cures, treatments such as prophylactic surgery (Lynch, Lynch, and Rubinstein 2001; Hartmann *et al.* 2001) and tamoxifen (King *et al.* 2001) can now significantly reduce the risk of developing these cancers. Given such advances, BRCA genetic susceptibility testing is becoming increasingly important for the clinical management of patients and families.

Genetic testing may also facilitate access to health care services. For example, a strong family history of cancer should, but often does not, trigger early access to cancer screening such as regular mammograms; this is especially true in the case of pre-menopausal women lacking a significant family history, and who because of their age are deemed not to

be at sufficient risk to qualify for regular mammograms. A positive result from BRCA testing, that is, a result that indicates a deleterious mutation, may provide the objective risk status and medical label of being 'at-risk' that is necessary for patients to have access to otherwise be restricted health care services. In a study of women who went through genetic counselling and testing, there was a generally positive attitude towards genetic testing, with increased access to health care services being mentioned as one of the important benefits (Holmes *et al.* 1999; Holmes 2000). A recent prospective study demonstrates that access to genetic testing and counselling can have a positive effect on risk-reduction behaviour and earlier diagnosis of tumours (Scheuer *et al.* 2002).

In most provinces in Canada, BRCA testing is provided to patients and families with a strong family history of breast or ovarian cancer (Panabaker 2002). But with the recent granting of four Canadian patents on the BRCA genes to the Utah-based biopharmaceutical company Myriad Genetics, the continued provision of public genetic testing services has been jeopardized. Myriad has licensed MDS Laboratory Services – one of Canada's largest medical diagnostics companies – to be the exclusive Canadian provider of Myriad's patented *BRACAnalysis* test (Myriad Genetics 2000e); they have also begun a campaign to convince Canadian health care institutions to comply with the patents and refer all tests to MDS or Myriad (Canadian Press 2001; Kent 2001).

To date only British Columbia, on advice from legal counsel, has complied with Myriad's demands and ceased testing; Québec performs some mutation testing locally but sends index testing to Myriad for full analysis. In August 2001, the B.C. Ministry of Health Services informed the Hereditary Cancer Program (HCP) at the B.C. Cancer Agency that, should they wish to continue providing BRCA testing, the HCP would have to purchase

testing from Myriad out of the HCP's existing operating budget. The cost to perform BRCA testing at the HCP is approximately $1200Cdn per test (Kent 2001). Purchasing testing from Myriad at three times the cost ($3850Cdn for full sequencing) would quickly exhaust the HCP's budget, undermining their ability and mandate to provide services to patients at-risk for a variety of hereditary cancer syndromes, and thus BRCA testing was discontinued by the HCP in July 2001. In complying with the patent, even when other provinces have rejected Myriad's claim and continue to provide in-house testing (Eggertson 2002), the B.C. Ministry of Health Services arguably took a stand in favour of protecting intellectual property rights. But given this position, to not then increase financial resources for the HCP to make up the difference in cost of Myriad's test, has meant the discontinuation of publicly provided BRCA testing in the province. In effect, the Ministry engaged in *de facto* priority-setting.

Justice in Access to Services and Priority-setting

Just access to health care might be thought to entail equal access to every needed medical service,[29] but taken literally and especially if 'need' is construed broadly, this approach is unworkable. The current political reality is characterized by limits on the financial resources available for health care, and the need to fund other important goods such as social services, education, or public works. Strictly speaking, government funding of services is not a zero-sum game. The total size of the budget can be expanded through economic development and increased taxation, with the result that individual sectors such as health care can increase their share without necessarily leading to a loss for other sectors. But

[29] The argument for equal distribution of services *independent of need* is obviously flawed. The simple fact that I want an appendectomy does not entail the right to one, particularly if I am healthy and do not have appendicitis; only those people who need a medical service should have it provided. Difficulties arise, however, when the definition of 'need', and who should have the power to decide (clinicians or patients/consumers), is in dispute.

with slowing (or negative) economic growth and social and political pressures on governments to reduce taxation and devote funds to deficit reduction, any significant increase in health care budgets will in practice result in decreased funds to other sectors.

To further complicate matters, the cost of health care in Western countries continues to increase, in part as a result of pressure from consumer groups, clinicians, and industry to introduce new and often expensive medical treatments, technologies and pharmaceuticals (Daniels 2001).[30] In Canada, total public health care expenditures increased from $9 billion in 1975 to $74 billion in 2001 (Canadian Institute for Health Information 2002b). As part of fiscal-restraint initiatives, some provincial governments are moving to cap or reduce funding to health care. For example, in British Columbia, the Liberal government has frozen the health care budget for 2002 at $10.3 billion or 40.7% of total budget expenditures (www.bcbudget.gov.bc.ca), increased Medicare premiums by 50%, and moved to reduce costs by, for example, closing regional hospitals and long-term care facilities. Thus in practice, whatever share of government monies are allocated to health care will be insufficient to support all possibly beneficial services. Decisions will be required to determine which services should or should not be funded, and whether and how private purchase of services should be permitted (Evans *et al.* 2000; Deber *et al.* 1998; Caulfield *et al.* 2001).

In the following section, cost-effectiveness will be examined as a consequentialist justification for determining whether: 1) to fund BRCA testing as part of public health care insurance (either through public laboratories or contracted out to commercial providers), and/or 2) to restrict private purchase of BRCA testing. This examination is different from a

[30] A study by the Canadian Institute for Health Information projects that spending on prescription drugs will increase by 10.6% from 2000 to 2001, for a total of $12.3 billion; between 1997 and 2001, prescription drug spending rose by 46.4% (Canadian Institute for Health Information 2002a).

full utilitarian analysis because the scope is restricted to health-related consequences, whereas a utilitarian approach would focus more broadly on the maximization of happiness; it also differs from a full cost-effectiveness analysis because other assumptions, such as the effectiveness of health care at improving population health, are not specifically evaluated.

Cost-Effectiveness and Consequentialism

Probably the best known example of priority-setting for health care spending is the Oregon plan for state-sponsored Medicaid (the Oregon Health Plan). In 1989, the Oregon government began evaluating all potential health care interventions to determine their benefits and cost-effectiveness ratios with the goal of ranking services for state funding. In conjunction with state-wide public consultations in 1994, a list ranking 696 conditions was produced. Of those conditions, the state government had sufficient funds to cover the first 565, excluding coverage for 131 (Ferrara 1994); in 1999, 574 of 743 conditions were covered (Oberlander, Marmor, and Jacobs 2001).[31]

Cost-effectiveness analyses such as were used in Oregon are designed to evaluate the consequences of a particular technology or service – they are to some extent consequentialist. By weighing services using a common scale or denominator, it is possible to then rank services to determine which constitute the most effective use of limited resources (Goldie 2001). Individual services or entire programs may be evaluated in this fashion, with the units of measure (i.e., the effects or consequences) being valued in health-related terms such as quality adjusted life years (QALY) for cost-effectiveness analyses, or QALY's that are then converted into dollar amounts for cost-benefit analyses (Shah 1994). Deciding on the

[31] Interestingly, genetic testing for hereditary breast and ovarian cancer, using Myriad's *BRACAnalysis* test, is covered for Medicaid patients in Oregon (Paige 2002).

perspective of the analysis is important – which costs and health benefits should be counted – and will depend on whether one takes a societal or individual perspective (Barker, Cooper, and Rose 1998; Rose 1985). For example, in evaluating a service such as heart transplantation, one might compare different techniques and determine the costs and outcomes for individual patients, such as 5 year survival rates. But if one were instead comparing heart transplantation with lifestyle changes as part of a larger preventative medicine initiative, the analysis would take a more societal perspective that included a broader range of costs and benefits, such as long-term outcome and survival, resource usage, etc., over a longer time horizon.

One of the objectives of applying this type of analysis in the Oregon plan, as well as in other instances of health care priority-setting, is to make systematic, objective and unbiased decisions about the funding of services. Influences from special interest groups and technology developers, or biases on the part of policy makers should be avoidable, thereby resulting in a more rational and fair allocation. Applying these measures, however, may not be straightforward. In the case of genetic tests, for example, it will be possible to determine with some accuracy the target population, mutation prevalence and penetrance for the condition, but the benefits may be more difficult to quantify (Goldie 2001).[32] Genetic testing services tend to provide risk information about conditions for which there is often no effective treatment or cure. The benefits of having such information are primarily social or psychological, making them difficult to measure precisely and attribute a specific QALY or

[32] The accuracy of genetic tests continues to evolve as empirical evidence is gathered. Thus for example, there is substantial ongoing debate about which method of BRCA testing is most effective (Institut Curie 2001; Tian *et al.* 2000). Similarly, there is growing concern that risk estimates for developing hereditary breast cancer may be over-inflated and in need of substantial revision (Hofmann and Schlag 2000).

dollar amount – genetic tests may then be undervalued and inappropriately ranked because their benefits and harms cannot be given numerical values.

Studies of families at-risk for genetic disease show that having access to genetic testing information can be extremely important for some people in terms of psychosocial benefits (Cox and McKellin 1999; Codori and Brandt 1994; Benjamin *et al.* 1994). Genetic testing information may be used to facilitate life planning, to initiate family discussions of issues such as social and psychological support, guilt, and responsibility for other family members, or to help people make changes in career plans (Burgess and Hayden 1996). "While the information does not alter the natural history of the illness for an individual, it does provide information that is highly relevant to the individual's future self-monitoring and personal life. This may have a very significant effect on health" (Burgess 1999, 185).

Genetic testing is requested far less frequently than geneticists predicted before testing became available, particularly when there is no effective treatment as in the case of Huntington disease; testing has less of an effect on populations and may be less valued by individuals (Wulfsberg 2000; Evans, Skrzynia, and Burke 2001). By contrast, as in the case for hereditary breast cancer where effective treatment options are available, genetic tests may be more positively valued (assuming that other concerns such as privacy and discrimination are addressed) and thus have important health benefits for particular populations. For patients with a strong family history of hereditary breast and ovarian cancer, an accurate test with high predictive value (Hofmann and Schlag 2000) can determine whether a patient has a mutation associated with increased risk of disease. Those patients without the deleterious mutation can avoid frequent, expensive and unpleasant monitoring, while those patients with the mutation can undergo regular monitoring and have access to prophylactic measures or

drug therapies that significantly reduce a patient's risk of developing the disease (Lynch, Lynch, and Rubinstein 2001; Hartmann *et al.* 2001; King *et al.* 2001). As Burgess argues,

> the availability and effectiveness of other monitoring measures modifies the assessment of whether the test affects health. The discovery that one does not have the gene related to familial risk can help avoid the inconvenience, risks and costs associated with intense monitoring. The existence of a surgical or medical intervention that reduces or eliminates risk renders the test an easy candidate for inclusion in the health care system (Burgess 1999, 185).

Genetic testing for hereditary breast cancer provides tangible clinical benefits – which are easier to quantify for a cost-effectiveness analysis – that might rank this services as important for health care coverage, especially if one also considers the long-term costs of morbidity and mortality from the disease (Heimdal, Maehle, and Moller 1999). An analysis of this test would also need to consider the full range of personal, clinical and economic costs for true positive and negative test results, as well as for false positive or negative, or for inconclusive test results. In other words, a variety of costs may arise that are based on the accuracy of the test. While BRCA testing may be cost-effective for provision to individuals meeting specific entry criteria (Carter 2001), this will not be the case for testing in the general population due to high rates of costly (both economically and in terms of individual and social harms) false positive and false negative results (Goldie 2001).

The benefit to an individual or family from receiving a service such as BRCA testing must also be situated in the context of providing a full range of health care services for an entire population. Thus another element of the cost-effectiveness equation will be consideration of the number of people who will benefit. This aspect is exemplified in Western philosophical tradition by various forms of utilitarianism. A utilitarian analysis would judge a particular health care service or program as morally right and worth funding if it produced the greatest intrinsic good, usually defined as happiness or pleasure, for the

greatest number of people. Thus it will also be necessary to determine whether health is an intrinsic good such as happiness and thus to be sought of its own merit, or an extrinsic good whose value needs assessment. This determination is likely to be a topic of debate, but for the purpose of this paper it will be assumed that health is an extrinsic good valued because of its affects on promoting intrinsic goods such as happiness.[33]

In applying a strictly consequentialist or utilitarian analysis to the issue of health care funding, the determining factor would be the extent to which health care leads to the greatest (intrinsic) good for the greatest number of people. Promoting non-health services (or a 'reduced' range of services) that also addressed more general lifestyle issues such as income disparity, employment and job stress, or diet could be far more effective than any health care services at ensuring health (Evans, Barer, and Marmor 1994; Kaplan *et al.* 1996; Mechanic 1999), and thus produce more happiness and less pain. Even if one restricts a consequentialist analysis to the particular situation of determining from a variety of health care services which are a priority and to be funded as part of public health care insurance, this approach would arguably not lead to a system that focused on 'high-tech' medicine. Technology- and resource-intensive services such as genetic testing, which tend to have very specific benefits for small numbers of people are not effective means of improving population health (Baird 2000; Vineis, Schulte, and McMichael 2001), and would not maximize the benefit of health (or happiness). A consequentialist analysis would argue for shifting resources from acute or chronic health care, to other areas such as public health initiatives that ensure widespread vaccinations, comprehensive pre-natal care, or reliable access to clean drinking water, which

[33] This view would concur with the value some social contract theorists, such as Norman Daniels, place on health and the need for fair access to health care (Daniels 1985, 2001). This issue will be discussed more fully below in the section on Social Contract Theory and Equality of Opportunity (p. 95).

together would have a significant impact on improving population health, increasing life spans, and thus arguably improving happiness.

In the case of BRCA testing, another consideration will be the larger or system-wide financial costs of providing the service. If a province or nation decided to defy the Myriad patent and provide in-house testing (using cheaper methods such as PTT or SSCP), the immediate cost of the service would be less than paying for the service from Myriad, e.g., $1,200Cdn for PTT (or $1,800 for full sequencing) compared to $3,850 (Kent 2001; Eggertson 2002). However, if Myriad sued the province or nation for patent infringement, then the costs in terms of legal fees and any damages awarded (as well as having to pay Myriad for testing), could be substantial. Further, if BRCA testing is only available for private purchase, as is now the case in B.C., then there are long-term costs and other implications to the public system that should be considered. In particular, when patients need only convince their physician that they should have the test since they are paying for it out of pocket (Birmingham 1997; Smith 1997), the public health care system loses its former ability to constrain utilization and ensure that tests are only available to those people for whom the tests will provide accurate and useful information (Carter 2001; Holtzman and Shapiro 1998).

Research in Europe as part of the Euroscreen 2 program has shown that the public is still largely unaware of the availability of commercial genetic testing (Chadwick *et al.* 2001). However, with more effective marketing and public awareness, and especially if direct-to-consumer advertising is permitted, companies such as Myriad may be successful in convincing the general public that a genetic test 'for breast cancer' is worth the expense (Chandros and Prasad 2001; Agovino 2002). Direct purchase would increase costs to the

health care system, as more people would require genetic counselling. In addition, those few people found to have positive test results (e.g., an identified deleterious mutation) may then become eligible for other health care services and monitoring, which will be paid for by public health care insurance. A consequentialist analysis that evaluated the immediate costs and benefits of BRCA testing would be incomplete if it did not also integrate these potential downstream consequences.

Within the scope of health care provision, most Western democracies fund both population-health measures and individually oriented, chronic and acute medical services. In practice, we do not often see strictly consequentialist approaches (i.e., utilitarian, cost-benefit, or cost-effectiveness) that fully determine health care resource allocation. Yet simply because this type of analysis is not used more widely does not mean that it is without value. In fact, an important criticism of many decision-making frameworks for allocating health care resources is that they do not sufficiently evaluate and weigh objectively the consequences of particular services and programs. For example, the most damaging criticism of the Oregon plan has been of the very objectivity held to be central to ensuring a fair process. In practice, it appears that decisions about which services were to be funded were more influenced by politics – that is the need to appease various professional, political, and consumer interests – than by rational cost-effectiveness analyses of competing health care services (Oberlander, Marmor, and Jacobs 2001). But problems with the application of the cost-effectiveness analysis in this case were not the result of inherent flaws so much as how the method was applied – the consequentialist analysis was undermined by pressure to appease special interests.

Nevertheless, there are some important weaknesses associated with the consequentialist nature of cost-effectiveness or cost-benefit analyses. In seeking to ascribe numerical or monetary values to all benefits and harms, they can miss non-reducible aspects of benefit and harm that are nevertheless extremely, or even more important than the monetary component. While one may be able to determine how many life-years or dollars were saved by a patient with a family history of breast cancer having access to testing, such a valuing is unlikely to include the significant social or psychological benefits or harms of access (or lack thereof) to testing, which are no less important. Moreover, even if such an analysis does incorporate non-financially or -numerically reducible costs, how then does it compare and weigh these with strictly numerical or financial costs and benefits (Modell and Kuliev 1993)? But of more concern is that in focusing on consequences such as benefits and harms, particularly if one also takes a utilitarian view and seeks to maximize pleasure or happiness (or health) for the greatest number of people, some people may have to suffer so that more people may benefit, e.g., focusing on population health measures to the exclusion of acute, emergency, or chronic medical care. In other words, a consequentialist approach such as cost-effectiveness may have an inadequate conception of justice and of how to fairly distribute harms and benefits.

Social Contract Theory and Equality of Opportunity

Another approach to objective and unbiased decision-making that also includes deliberation of what would constitute a fair or just allocation of resources is social contract theory. There is a long tradition in Western philosophy of developing thought experiments that consider what people would decide or choose in an ideal situation, in order to determine

what would be a right or just action and more generally what would constitute a just society.[34] Working out these issues in the abstract, developing substantive rules or principles, and then applying them to particular allocation decisions may circumvent some of the biases that influenced the cost-effectiveness analyses in the development of the Oregon plan.

For our purposes, a thought experiment can be run in which a group of rational decision-makers are charged with developing principles for a just health care system. These decision-makers, in an ideal bargaining situation, do not know their current or future positions in society (e.g., social class, fortune, assets, intelligence, health status and needs), and can thus be trusted to objectively determine a fair and unbiased set of principles. Of a range of principles that might be arrived at, one that has achieved some prominence in application to just health care and priority-setting is 'equality of opportunity' (Daniels 1985, 2001).

Equality of opportunity is a principle that can be rooted in a conception of justice that focuses on the creation of a 'fair or level playing field', and requires not only the elimination of discrimination but also efforts to ameliorate social factors that limit opportunity. Poverty and lack of education, as well as illness and disease, can have profound negative consequences for people's ability to freely pursue their life goals. One purpose of providing health care (or social assistance or public education) would be to help give people a fair chance at pursuing their individual life goals and objectives, and participate as full and active members of society (Daniels 1985; Sherwin 1996). For example, patients with a family history of hereditary breast cancer may live with the anxiety of being at-risk, as well as the objective risk of developing the disease. They may have to undergo regular high risk screening, care for affected family members, and deal with the personal trauma of early

[34] A notable example of this theory is developed by John Rawls in *A Theory of Justice* (Rawls 1971).

disease onset as well as the death of family members from the disease. When such considerations are added to the clinical and psychosocial benefits of BRCA testing, the test may be considered an important means of helping at-risk families have more normal lives and a fair range of opportunities. A just society should, through the provision of health care, "remove the barriers to opportunity that are due to disease" (Buchanan *et al.* 2000, 16) so that people who are disadvantaged have a better chance or opportunity to become normally functioning members of society.

Equality of opportunity provides a strong basis for an entitlement to health care, something that most Canadians support (Adams *et al.* 2001), but does not imply the unrealistic right to all possible health care services. Only those services that are effective at helping individuals maintain health (and a range of opportunities) should be publicly funded under this principle, while other services that do not meet this standard could then reasonably be denied funding. This principle would support restricting access to enhancement technologies, or treatments of unproven benefit (Buchanan *et al.* 2000). Concomitantly, services that are demonstrably effective at improving health and thus enhancing equality of opportunity would be strongly supported for inclusion under public health insurance. If BRCA testing were determined to be important for equality of opportunity in at-risk individuals, then this would be another argument in favour of provincial governments funding access to this service, either through public or commercial providers.

However, the focus on objectivity in social contract theory through the use of ideal cases and thought experiments may ignore the complex web of relations in which most people are enveloped and live their daily lives. We do not stand as isolated independent free agents, able to make fully rational and impartial choices. Instead, we are situated in networks

of relations that lead to corresponding duties and responsibilities towards family members, friends, co-workers, and communities (Brunger and Bassett 1998; Burgess and d'Agincourt-Canning 2002). For individuals who qualify for hereditary breast cancer testing at a provincial Cancer Agency because of an extensive family history of disease, or a family history characterized by early onset (Carter 2001), there are principles to be considered that may have little to do with equality of opportunity, depending on how this notion is conceptualised.

An individual seeking testing, and the health care system itself, may have responsibilities or obligations towards other family members who may also be at risk of developing breast cancer. Patients who receive testing are faced with choices about whether and how to discuss their results with other family members, and whether they should be advocates for promoting testing in the family; the nature of any responsibility will be complex in the family setting, but at a minimum will likely entail the need to think about the effects of individual decisions and test results on other family members. In the case of testing for specific mutations associated with increased prevalence in certain communities (e.g., the three Ashkenazi Jewish mutations), an individual choice may have significant effects on the larger community (Evans, Skrzynia, and Burke 2001; Koenig *et al.* 1998). At the level of the health care system, the issues for decision-makers are more clear; hereditary diseases by definition run in families, thus information about the risk status of one individual has implications for the risk status and health of relatives. While a person undergoing genetic testing may be the primary patient, other family members will often also become patients and require testing. In terms of just access to services, funded access for family members of an individual who has already received testing may then be warranted.

Other considerations may also underlie our sense of justice in this context, such as a desire to help those less fortunate (charity or a duty to rescue), the desire to redress historical wrongs, or the need to ensure a healthy labour force and relieve or prevent suffering (Evans 1992; Flood 1999). Decision-making about the importance of providing BRCA testing, while needing to include its effects on equality of opportunity, must also consider a broader set of issues. There is almost certainly more than one principle or goal of health care, and different stakeholders (e.g., decision makers, clinicians, patients, family members) will certainly vary in their evaluations of the purpose of public health care.

Public Participation and Deliberative Democracy

The Oregon approach to priority-setting has been commended for the application of efficiency criteria to the evaluation of health care services, but also for its attempt through public consultation to integrate community values related to health needs in a decision-making process. If the process could be sufficiently democratic and informed, it was hoped that a just allocation of services would result. A procedural notion of justice was implemented, instead of substantive principles of justice derived from consequentialist or equality of opportunity views. Yet the means by which public participation was integrated in the Oregon process has been challenged. Despite the purportedly democratic nature of the process (which included town hall meetings and public consultations), the majority of public participants were of middle or upper-middle socio-economic class, that is they were among those people least likely to use the Medicaid services they were ranking (Oberlander, Marmor, and Jacobs 2001). Limits on state funding for health services only have an effect on

low-income people who qualify for Medicaid, and these people were not sufficiently involved in determining those limits for the process to be truly democratic or participatory.

These problems with the Oregon approach should not be seen to undermine the value of public participation and deliberation. Innovative approaches to involving the public in policy development, such as public consensus conferences and science shops, have been employed in the U.K., the Netherlands, Austria and Germany, (Zaal and Leyedesdorff 1987; Vig 1992; Sclove 1995a, b). In Canada, an example is the Romanow Commission on the Future of Health Care in Canada, initiated by the federal government and engaged in widespread public consultations across the country. They aim to involve the public in a process that is objective, transparent, comprehensive, evidence-based, inclusive and respectful (www.healthcarecommission.ca).

By involving the public in policy development, the hope is that resulting policy will integrate a full range of public values and concerns and lead to widespread acceptance. Public participation and open dialogue about the benefits and costs of research is crucial if there is to be ongoing public trust in scientific research (Knoppers 2000); public trust can be quickly lost, as has been demonstrated in Europe with respect to genetically modified foods. In the case of health care reform or resource allocation decisions, policy developers may learn what citizens consider to be core services and are willing to pay for with their tax dollars. Public involvement is also a crucial aspect of deliberative democracy, as citizen participation in democratic society involves more than simply the election of government representatives. In some settings, local or national referenda are important mechanisms by which citizens directly engage particular issues and thereby effect change in government policy. As Emanuel argues, "...justice requires that those who have to live with the

consequences of the allocation be afforded the opportunity to affirm that the allocation reflects their values" (Emanuel 2000, 10).

There are nevertheless significant concerns with engaging the public in policy development. Large scale public deliberations such as commissions or referenda tend to be very expensive processes both in terms of time and resources; extended public consultations may even lead to more cumbersome and inefficient decision-making. Public consultations may only be effective to the extent that the results and views developed are actually implemented, such as through government policy or legislation. For example, while the report of the Canadian Royal Commission on New Reproductive Technologies was completed in 1993 (Royal Commission on New Reproductive Technologies 1993), it has taken almost ten years for legislation to be implemented.[35] In modern liberal democracies, there is clearly a place for elected regional and national government representatives to make decisions on behalf of the citizenry about law, policy, or regulations. But government representatives must still be seen to be responsive to public concerns, and transparent about how and why particular allocation decisions are made, if the public is to feel confident that their values are being taken seriously in decision making processes.

In the implementation of a specific public consultation or deliberation process, there may be problems with the public being accurately informed about an issue. Special interests with large financial resources, such as the pharmaceutical industry or influential health charities, can be extremely effective at presenting their views through marketing or advertising campaigns and can often outspend opposing or non-partisan sources. Moreover,

[35] In May 2002, the federal Health Minister presented to the House of Commons an *Act Respecting Assisted Human Reproduction* (Bill C-56). A previous version of this legislation, the *Human Reproductive and Genetic Technologies Act* (Bill C-47), was tabled in 1996 but dropped from the federal agenda in 1997 when an election was called.

these interests may also influence the type and accuracy of research conducted, thereby undermining the ability of patients and physicians to objectively evaluate products or services. As a result of these interests, pressures, and market forces, it is "the commodity, not the person, that dominates the social relations" (Graham 2001, 133); the important consideration is the selling of and access to the product or service, not whether it is something that a patient actually needs.

With reduced government funding of medical technology assessment and pressure to lift restrictions on direct-to-consumer advertising (Brill-Edwards 2000), companies such as Myriad may be very successful in presenting their message that genetic testing is an important service for people to access (Myriad Genetics 1997; Chandros and Prasad 2001; Agovino 2002). If this message is not balanced by independent information from medical professionals and experts in technology assessment, patients may be unduly influenced into purchasing services they do not need or want (Mintzes *et al.* 2002), and then faced with genetic information for which they are unprepared. Similarly, in the context of public deliberation for decision-making about health care funding, special interests may be extremely effective in presenting their perspective and swaying opinion such that their service or product receives strong support from participants, even when a more balanced review based on non-partisan information would favour not funding the service. The democratic nature of the decision-making process in this situation will have been completely undermined by the manipulation of the process and information in order to serve special interests.

There is clearly a place for expert involvement in public deliberations to ensure that technical information is presented in an accessible and non-partisan manner, thereby

permitting reasoned decision-making. But expert involvement is also needed for those areas that are beyond the capacity of most citizens (Lomas 1997). In determining access to health care services, technology assessment and evaluations of the accuracy, effectiveness, and usefulness of a particular health care service will tend to be relatively technocratic – it is largely scientists and physicians who determine which services or technologies are safe and useful, and for which populations. In general, society benefits from having scientific and medical professionals evaluate and decide whether a given technology is safe and effective, and regulatory structures that control access to medical services and technologies which could be hazardous if used inappropriately (e.g., prescription access to certain pharmaceuticals). It is simply unreasonable to expect the general public to have the technical expertise, experience, or time required to evaluate the safety and efficacy of all complex new health care technologies (Burgess 1999). There will be areas in which public deliberations are useful and even necessary, and others where it would be a hindrance and potentially harmful.

Daniels and Sabin suggest that decision-making processes can make significant progress in addressing issues of public distrust, legitimacy, and fairness by assuring what they call 'accountability for reasonableness'. Under this approach, four conditions should be met: 1) the rationales for coverage of new technologies must be transparent and publicly accessible; 2) the rationales must be reasonable, that is based on appeals to reasons or principles (e.g., substantive principles of justice) that are accepted as relevant; 3) there must be mechanisms to allow for ongoing review and revision of decisions as new information develops or the context changes; and 4) the decision-making process must be publicly regulated to ensure that the first three conditions are met (Daniels and Sabin 1998).

If the participants in the decision-making process are seen to share a willingness to openly discuss the reasons and justifications for a particular stance and for any decisions rendered, then even if a particular allocation or priority-setting decision does not please all stakeholders, it will still have been arrived at in a manner that is open, transparent and based on sound reasoning, and thus genuinely publicly accountable. Further, by including mechanisms that permit challenges and disputes of particular funding arrangements, and the opportunity to revise decisions in light of new evidence or research, such a framework would be dynamic and responsive to the changing social and political realities of health care and technology development.

This process could be applied constructively to a range of issues. For example, in determining the amount of resources to devote to research and services for hereditary vs. non-hereditary breast cancer, it is important to consider the positions of various stakeholder groups. While there may be strong support from some clinicians and patients for access to genetic testing services for woman at-risk for hereditary breast cancer, there may be criticism from other patients and advocates who feel that too much attention and resources are focused on the genetics of breast cancer to the exclusion of other social and environmental factors, particularly since genes of high penetrance account for only 5-10% of all cases of breast cancer (Lippman 1998; Press, Fishman, and Koenig 2000).

But focused deliberations will often be inextricably connected to larger scale issues, such as the impact of patents on health care research and service delivery, or the place for commercial service providers in a public health care system. As mentioned above, in British Columbia BRCA testing is no longer available as part of the public health care system. This test had never been a listed health care service (and so was not funded as part of provincial

health insurance), and was only available while the Hereditary Cancer Program could afford to pay for it through their program budget. An unwillingness on the part of the B.C. Ministry of Health Services to risk a legal challenge (and perhaps concern at higher levels about the negative impact on industry investment of challenging this patent), led the Ministry to comply with the Myriad patents. The resulting increase in the price of testing has made the test unaffordable for the HCP, so this service is no longer provided in B.C.

If BRCA testing is considered sufficiently important for patients and families in terms of clinical and psychosocial benefits, then this situation raises important questions. For example, is BRCA testing simply too expensive (at the HCP or purchased from Myriad) despite its benefits to warrant public funding, and thus acceptable to leave to private purchase? If BRCA testing is an important service to offer through the public health care system and worth the price charged by Myriad, then more resources should be dedicated to funding this service. Alternatively, one may need to query the appropriateness of having a patent system that permits the commercialization and control of 'disease genes', and the effect of this on the provision of health care through the public system.

The experiences of patients, families, and other stakeholders are crucial for understanding the benefits and harms of specific health care services, and determining their usefulness and importance – public deliberation will thus be important at the micro level in supporting more comprehensive technology assessment. At the meso or policy level, public deliberation will be essential for democratic decision-making processes such as that proposed by Daniels and Sabin. Not only will the public inform expert decision makers about what constitute shared values with respect to the goals for publicly supported health care, but the public might also be involved by electing democratic representatives to be involved in the

decision-making process. There are obviously a variety of ways in which public participation and deliberation might manifest, but there should be no doubt that such participation is required for a decision-making process to be fair and accountable.

Conclusion

Adult genetic testing will have to meet high standards to be included among funded health care services when compared to other beneficial services such as hospital care, wheelchairs, or pharmaceuticals (Caulfield *et al.* 2001). The case of BRCA testing in Canada is thus useful for illustrating the difficulty of integrating technical or practical considerations with more theoretical discussions. Determining whether access to BRCA testing delivers sufficiently beneficial consequences and enhances equality of opportunity to merit public funding can only be accomplished with active participation from those stakeholders most directly involved, that is, patients, families, clinicians, and support groups. Such stakeholder involvement would nevertheless need to be more than simply a matter of collecting or integrating public opinion, as was the case in Oregon. It would need to build on the scientific and technical evaluations (e.g., is the technology safe, useful, minimally harmful, supportive of normal functioning, or cost-effective relative to other options?), but also move beyond a strictly technocratic view and integrate a range of personal experiences of illness to better nuance and expand the basic medical or scientific definitions of benefit and utility (Wertz and Gregg 2000; Secretary's Advisory Committee on Genetic Testing 2000).

There will be cost implications for the system as a whole, e.g., counselling for patients who have privately purchased testing, and diagnostic testing and monitoring of those who test positive for a mutation, that must also be taken into account in comprehensive cost-effectiveness analyses. A further consideration is the implication of increasing numbers of

gene patents being granted nationally and internationally (Caulfield and Gold 2000b). The Myriad case is but one example of a rapidly growing number of tests for genetic susceptibility. If the current patent system permits the patenting of all genes, there will be serious negative effects on access to and provision of genetic services in the public health care system. Assuming that the Canadian patents on the BRCA1 and BRCA2 genes stand (there may yet be challenges to the patents from provincial governments), a host of other patents on susceptibility genes are likely to follow that make it more difficult to justify on cost-benefit or cost-effectiveness analyses the public provision of genetic testing services. Without sufficient public understanding of the implications of patents and commercial genetic testing on just access to health care services, public perception can be manipulated for individual or political gain.

There is no easy way to make decisions about what services to fund with a limited health care budget, or how to address the problems raised by gene patents and commercialization. But if the public were engaged as part of a reflective process that is supported by tools from moral philosophy, based on empirical evidence, and conducted in an open and transparent manner, there is the potential for real progress in addressing these issues. More systematic analysis is to be desired over the current *ad hoc* and manipulated decision making environment. Effective technology assessment will require not only in-depth, evidence-based analysis to determine if a new technology is safe, useful, and beneficial, but also need the financial and human resources to conduct such evaluations. Cost-effectiveness and cost-benefit analyses are required for systematic comparison of health care services within as well as across medical disciplines, but the consequentialist nature and limitations of these analyses mean that there must be support from substantive and

procedural justice approaches. There is thus an important place for clear reasoning about substantive principles of justice such as equality of opportunity, as well as procedural justice mechanisms that involve public participation and deliberation, as exemplified by the "accountability of reasonableness" approach. Theoretical tools such as consequentialist and cost-effective analyses, social contract theory and equality of opportunity, and public deliberation will be essential components for determining how to fairly distribute the benefits of health care, and whether to fund and implement services such as genetic testing for hereditary breast cancer.

Linking Statement

Chapter 4 focused the issue of how to fairly distribute the benefits of health care and make decisions about resource allocation and priority-setting; it was argued that through the application of tools from moral philosophy, a more just decision making framework or process could be developed. This chapter reflected only briefly on the implications of patents for the funding of and access to genetic testing services. The following chapter (Chapter 5) takes up this question in greater detail and lays out the various problems with gene patents, not only for the provision of health care services but also for ongoing research into new health care technologies. Chapter 5 concludes by making recommendations for how gene patents can be regulated to ensure that the benefits in terms of innovation and economic development are maintained while also permitting ongoing cost-effective and equitable provision of health care services through a public system.

Chapter 5

Regulating Gene Patents and Commercial Genetic Testing in the Canadian Health Care Context

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Abstract

The patenting and commercialization of genetic material has important implications (positive and negative) for the way scientific research is conducted, and how the technologies or services developed from this research are integrated (or not) as part of the provision of public health care. The objective of this chapter is to demonstrate that tools drawn from social science and moral philosophy (Actor-Network Theory, consequentialism, social contract theories, and public deliberation) can enable more comprehensive technology assessment and priority-setting, specifically for the case of genetic testing for hereditary breast cancer. With such an analysis, practical recommendations will then be made for regulating gene patents and commercial genetic testing. Specifically, it will be argued that changes are needed in the scope of patents and the way they are administered, licensing mechanisms should be introduced to facilitate ongoing research and application of new technologies in the public health care system, and the substantial buying power of provincial health care insurance plans should be leveraged as a means of shaping the ethical behaviour of commercial developers and providers.

Introduction

Research in the fields of biotechnology and genomics hold the promise of improved diagnosis and treatment of diseases, the development of pharmaceuticals tailored to individual genetic make-up, and genetically modified foods that deliver vitamins and vaccines (Roses 2000). But there is also growing concern about the commercial nature of much of this research (e.g., the role of industry financing and its effect on academic freedom), the influence of market forces on the products of research (e.g., commercialization of technologies), and the effects of commercialization on the provision of public health care services (Cohen 1997; Parizeau 2001). The recent World Health Organization report *Genomics and World Health*, while highlighting the great potential for genetics and genomics research to provide significant public health benefits for the developing world, also cautions against the proliferation of patents and the commercialization of genomics research because of the fear that existing inequalities in access to health care will be further exacerbated (WHO Advisory Committee on Health Research 2002). In Canada, some of these concerns have begun to crystallize around the issue of gene patents and commercial genetic testing. In particular, they are exemplified by the situation regarding access to breast cancer susceptibility testing (BRCA testing) in light of Myriad Genetics' patents on the BRCA genes (Willcocks 2001; Hurst 2001).

With the granting to Myriad Genetics of four Canadian patents on the BRCA1 and BRCA2 genes associated with hereditary breast cancer, and the subsequent exclusive licensing of BRCA testing to MDS Laboratory Services of Toronto, Canadians able to afford it can now purchase testing with the agreement of their physician, who can then order the service from MDS. Presented as a boon for patient choice and autonomy, the

commercialization of this service also has serious policy implications. Compliance with the patents by provincial health care institutions significantly increases the costs of testing ($3850Cdn for the test from Myriad or MDS compared with $1200Cdn for testing at public laboratories). The patents have made testing too expensive for continued coverage by some provincial health insurance plans, so the tests are only available to patients who can afford to purchase testing privately. This raises important ethical and policy issues, such as equity in access to health care services, inefficiencies arising from a mix of private and public service provision, and the potential for rapidly increasing health care costs associated with patents and the development of commercial health care services.

But these issues must also be set within the context of priority-setting for public health care. Decisions about the funding of health care services have historically been made in an *ad hoc* manner subject to influence from special interests, that does not consider the full range of costs and benefits of services, the way in which services should best integrate into the health care system, or the broader effects of commercialization and privatization. In this chapter, the current context of decision making for health care allocation and priority-setting will be described, followed by a discussion of the problems for research and the provision of public health care services raised by the patenting and commercialization of genetic material. Four theoretical approaches will then be briefly sketched and applied to the issue of gene patents and commercial genetic testing in order to develop recommendations for how to address the social, ethical and policy implications for public health care insurance and genetics research, while maximizing the commercial and research benefits of patents in facilitating innovation and development of new health care technologies.

Priority-setting and Funding of Health Care Services

Ideally, decisions about whether a particular service or technology should be provided to the public (as an insured or 'listed' service, as an uninsured service that is only available for private purchase, or as a controlled or restricted service), would follow a comprehensive technology assessment based on scientific and epidemiological analyses of accuracy, utility, benefits and harms. Services or technologies that are found to be safe and useful may then arguably be considered 'medically necessary', justifying coverage as part of publicly insured health care. For those services not considered medically necessary, a determination would then need to be made about whether these services should be available for private purchase or restricted.

The *Canada Health Act* (CHA) refers to the provision of 'medically necessary' services but the term is used in a broad and largely circular fashion. Any treatment or intervention judged by a physician to be necessary is included, and thus should be covered as an insured service. But such an evaluation does not result in the automatic inclusion of a service as part of provincial health insurance plans. While a particular physician or group may feel that a new treatment is necessary, they have to convince their provincial Ministry of Health that the service warrants coverage (Evans 1992). There are no commonly agreed upon criteria for determining which services should receive full or partial funding through public health insurance, and which should be left to private purchase or secondary health insurance. Funding decisions have and continue to be made in an *ad hoc* manner, influenced by marketing and incentives to a range of actors, as well as interest group pressure for inclusion of particular technologies or services (Baird in press). There may be little consideration of how patients actually use or benefit from a service, or how a service fits into the broader

context of public health care provision. Some services of questionable utility will be funded because of various commercial, professional and public pressures, while other services that are demonstrably useful and beneficial may be under-funded or not funded at all because, for example, they lack sufficiently influential supporters. This approach to funding health care services leads to inefficiencies in health care delivery, but more importantly, it also produces a health care system that unevenly and unjustly distributes the benefits of health care.

One way of determining a more fair allocation and funding of health care services would be to rigorously apply the concept of 'medically necessary'. However, this concept has not been operationalized in either federal or provincial legislation nor contextualized to provide a workable decision-making guide (Rachlis 1995; Caulfield 1996). 'Medically necessary' may be narrowly tied to unrealistic evidence standards and unspecified outcome measures, reducing to simply 'effective medicine' which is too narrow a concept to be useful, or 'valuable to health' which is too broad. Nevertheless, the concept of 'medically necessary' points towards a need for a fair and coherent method of determining which services should be publicly funded; as Caulfield notes, 'medically necessary' can still be useful "as a broad concept that symbolises our society's values, beliefs and goals for the health care system" (Caulfield 1996, 85).

Recent efforts to develop more coherent, effective, and just decision-making frameworks for determining funding of health care services have occurred at both the provincial and national levels. In Alberta, the Mazankowski Report *A Framework for Reform* has recommended the creation of an expert panel empowered to develop criteria to evaluate and review health care services and make decisions about which to fund through provincial health insurance (Mazankowski 2001). At the national level, the Romanow Commission on

the Future of Health Care in Canada (www.healthcarecommission.ca), which is holding public consultations across the country, has been tasked with making recommendations on how to sustain the public health care system. In its interim report, the Commission suggests that the concept 'medically necessary' must be re-evaluated and reformed to take into consideration the evolving nature of health care; the provision of health care has shifted beyond hospital and physician services to include pharmaceuticals and outpatient services, among other things. But reform will have to also consider the broader costs and benefits of services, and the values Canadians want their health care system to reflect (Romanow 2002).

These reports highlight the necessity for evaluation procedures that are based on substantive empirical evidence about the services under evaluation, as well as the need for public debate and incorporation of Canadians' values in decision making processes. But it will also be critical to have a detailed understanding of how a particular service under consideration is developed, the context in which it exists, and the broader social, ethical and policy implications that arise from its implementation (Hoedemaekers 2001). For example, is the technology or service proprietary and the subject of intellectual property claims? If so, can the technology be provided directly through the public health care system (e.g., as is the case for pharmaceuticals provided in hospitals and laboratory tests, some of which are contracted out), or is it only available through particular licensees? What are the broader consequences for patients and the health care system of public or commercial provision of this service?

In the case of genetic susceptibility testing for hereditary breast cancer (BRCA testing), until July 2001 testing and counselling were provided in British Columbia as a public service by the Hereditary Cancer Program (HCP) at the B.C. Cancer Agency. But with

the awarding of the Canadian patents for the BRCA1 and BRCA2 genes in 2000 and 2001 to Myriad Genetics (Myriad Genetics 2001b), public laboratories providing in-house BRCA testing were held to contravene Myriad's patent rights. Along with their Canadian licensee MDS Laboratory Services (Myriad Genetics 2000e), Myriad began a campaign to convince all Canadian public laboratories to cease providing in-house testing and instead purchase Myriad's *BRACAnalysis* test. The B.C. Ministry of Health Services, on advice from legal counsel and probably due to concerns about the potential costs of a patent infringement suit, informed the B.C. Cancer Agency that should the HCP wish to continue providing BRCA testing, they would have to make arrangements to purchase testing from Myriad out of the existing operating budget. BRCA testing had not been covered by provincial health insurance (the B.C. Medical Services Plan), but had instead been funded from the HCP's operating budget, provided by the B.C. Cancer Agency.[36] The increased cost of purchasing testing from MDS or Myriad would quickly exhaust the HCP's budget and undermine its ability to provide services for families at risk for other hereditary cancers. As a result, BRCA testing in B.C. is now only available to those individuals with the financial means to purchase testing, although the HCP will facilitate this process and continue to provide associated genetic counselling services (Coldman 2001).

The BRCA patents, and the way in which they have been enforced by Myriad and MDS, have had a direct impact on the provision of BRCA testing in British Columbia, as well as in the rest of Canada and internationally. This is a harbinger of a phenomenon that may become widespread as hundreds of other genetic tests for disease susceptibility are proposed for use. Such contextual information is of critical importance in assessing the

[36] Initial funds to purchase a DNA sequencer and evaluate approaches to the provision of genetic testing and counselling for hereditary breast cancer were provided by the B.C. chapter of the Canadian Breast Cancer Foundation.

financial costs of the service, if and how it should be provided (e.g., through public health care institutions, contracted out to commercial providers, or left to private purchase), and the wider consequences for the health care system of funding or not funding this service. Without such a broad consideration, it will be impossible to effectively determine which services are a priority, which are affordable, or where existing structures need to be reformed. The following discussion explores in more detail one of these issues, namely the patenting of disease susceptibility genes (specifically BRCA1 and BRCA2) and the effects of commercialization on provision and access to genetic services in British Columbia.

The Problem with Gene Patents[37]

In 1980, the landmark U.S. Supreme Court case of *Diamond v. Chakrabarty* (447 U.S. 303, 1980) made possible the patenting of biological materials. International trade and patent agreements such as the *General Agreement on Trade and Tariffs* (GATT) and the *Trade-Related Aspects of Intellectual Property Rights* (TRIPS) extended the influence of this case (Knoppers 1999), leading to changes in patent laws worldwide and the granting of more than one thousand human gene patents by 1995 (Caulfield and Gold 2000b), and more than 25,000 DNA-based patents by 2000 (Cook-Deegan and McCormack 2001). During the same period, U.S. government policy such as the 'Bayh-Dole Act' (*Patent Rights in Inventions Made with Federal Assistance*, 1980), made it possible for and encouraged publicly funded researchers to commercialize their work in the form of patents, licenses and spin-off

[37] There has been substantial and often vociferous debate in both public forums (Willcocks 2001; Nature 1996) and academic circles (McGee 1998; Caplan 1998; Merz and Cho 1998), about the ethics of gene patenting. While the ethical permissibility of human gene patents is an important issue, for the purposes of this thesis it will be accepted that genes are patentable, as is currently the case in most countries. The focus of the discussion will instead be on the social, ethical, and policy implications of the patenting and commercialization of genes and genetic tests on research and the provision of health care services.

companies (Cook-Deegan 1999; Malinowski and Littlefield 1999). The U.S. National Institutes of Health (NIH) and most major American research universities created technology transfer and industry liaison offices to patent and license discoveries. According to one study, by 1995, 40% of gene patents were filed by public institutions or charities (Thomas 1999). Canadian and European universities have made similar arrangements to their U.S. counterparts.

Basic and applied biomedical and genetics research in North America and Europe is increasingly occurring in close interaction with the private sector. Clinician- and bench-researchers may be supported by financial and technical resources from companies, be on boards of directors of companies (Natowicz and Ard 1997), and be encouraged to patent products that come from such collaborations. However, while it has been argued that patenting and commercialization of the products of biomedical research may support new and speculative work, patents may also hamper research as a result of increased secrecy and multiple overlapping patent claims that make some research too costly to pursue (Heller and Eisenberg 1998; Knoppers, Hirtle, and Glass 1999).

Secrecy

A patent grants an inventor a monopoly for 20 years[38] for a new invention and the ability to exclude other people from developing or marketing their own version. In exchange, the patent applicant agrees to provide a detailed description of the invention which becomes publicly accessible when the patent is granted. Upon expiration of patent protection, other individuals or companies then have sufficient information to develop and market the

[38] As a member of the World Trade Organization and signatory to TRIPS, Canada changed its patent rules in 1989 and extended patent protection from 17 years (prior to 1989) to 20 years; the U.S. made similar changes to its patent law in 1995.

invention. However, while this agreement would seem to preclude secrecy about new inventions or innovations, the existence of the possibility to patent may increase secrecy at least during the developmental stages of research. Pressure may be brought to bear on researchers from commercial partners or university administrations to be more secretive in order to protect against other researchers pre-empting or filing competing patent applications. A significant negative effect of this behaviour is the delay or unnecessary repetition of research. Given the length of time between the filing and granting of patents (usually on the order of three to five years) and the rapid pace of knowledge development in genetics and genomics, the details of the invention may only become available years after the initial discovery. By this point, the information may have been replicated by other researchers and published in the academic literature, undermining any value the patent may have had when it was filed (Cook-Deegan and McCormack 2001).

In the early 1990s, the search for the genes associated with hereditary breast cancer was an international collaborative endeavour, with researchers sharing their discoveries at academic conferences and through journal publications. By the mid-1990s, and following the sequencing and patenting of BRCA1 in 1994, this collaborative atmosphere had transformed into a competition between two research groups (Davies and White 1995). Mark Skolnick's U.S. team at the University of Utah and Myriad Genetics raced against a U.K. team led by Michael Stratton at the Institute for Cancer Research, to be the first to sequence and patent the BRCA2 gene. This race culminated in simultaneous news conferences in 1995 announcing the full sequencing of the gene and the filing of competing U.S. and U.K. patents; there is still disagreement about the legitimacy of the respective patents (Meek 2000).

Patents are one of the most often cited reasons (along with internal academic restrictions, issues of crediting and authorship, etc.) for restrictions on or delays in scientific publication (Blumenthal 1997). Requirements such as non-disclosure agreements may be initiated by or placed on scientists that delay or inhibit academic debate and journal publications. Researchers may have financial interests in the products of research, such as owning shares in biotech companies that commercialize their research, or be in a conflict of interest in publishing research results that are supported by commercial sources. All of these interests have the potential to seriously retard timely publication of results and threaten the objectivity and credibility of the scientific process (Krimsky *et al.* 1999). Even without the influence of patents, the commercial nature of biotechnology research can lead to competition and secrecy. The use of trade secrecy laws to protect products or inventions may make researchers and companies more secretive and less likely to share information about their products (Eisenberg 1987; Baird 1998). While patents may mitigate to some extent moves towards secrecy by requiring descriptions of the patented product, along with other commercial incentives, patents may contribute to an increasing culture of secrecy that negatively affects health sciences research (Blumenthal 1997; Campbell *et al.* 2002).

A Patent Anticommons

The completion in 2001 of the first full draft of the human genome (Science 2001), with an estimated 30,000 to 80,000 genes (Harrison *et al.* 2002), has laid the groundwork for future investigation into the genetic determinants of health and potential treatments and cures. In a context where genes can be patented – once they are described and associated with a particular function and have a demonstrated application – the map of the human

genome presents a cornucopia of potential targets for gene patents. As these genes become patented, enormous economic and social power is placed in the hands of biotechnology and pharmaceutical companies. It is argued by some proponents of gene patenting that this commercialization process can be ethical and lead to the rapid development of new treatments and cures for disease (Doll 1998). But there is also the real possibility that patents may block downstream research and inhibit the development of new technologies and health care services (Borger 1999).

Apart from the concerns about increased secrecy, gene patents may also constrain research by making the process too expensive – widespread patenting of genes and gene fragments may lead to what Heller and Eisenberg have called the 'tragedy of the anticommons' (Heller and Eisenberg 1998). The 'tragedy of the anticommons' is the opposite situation to Hardin's well known 'tragedy of the commons', in which a shared resource becomes overused (Hardin 1968). For example, if farmers have unrestricted access to a 'commons' such as a pasture for grazing cattle, individual self-interest will lead farmers to maximize their use of the resource at the expense of the collective interest – the pasture's capacity will be quickly exhausted through overgrazing, ultimately harming all farmers.

Conversely, Heller and Eisenberg suggest that a tragedy of the anticommons will occur when multiple, overlapping property rights allow individual owners to exclude others from a scarce resource, leading to a situation in which an important resource is actually underused (Heller and Eisenberg 1998). In order to conduct both basic and product oriented research, genetics and genomics researchers use a range of tools such as the polymerase chain reaction (PCR), genes and proteins, and gene fragments such as single nucleotide polymorphisms (SNPs) or expressed sequence tags (ESTs) (The Lancet 2001). However,

when these tools are patented, then upstream patents can become tollbooths that increase costs and slow downstream research. For example, Hoffmann-La Roche's patent on PCR, which is a fundamental tool in modern recombinant DNA technology and research, continues to be a hotly contested issue (Dickson 1994; Dalton 2001).

Multiple patents on basic elements such as genes or research tools mean that researchers may have to negotiate multiple license agreements in order to use research tools, as well as invest significant time and financial resources on legal support to search patent registries for potential conflicts. Upstream patent holders may disproportionately value their patents, particularly if they are a primary source of income. Patent holders may demand high license fees, or 'reach through' licenses and a percentage of any profit from downstream products (Heller and Eisenberg 1998; Murray 1999). Small biotechnology companies and academic institutions may simply not have the financial or technical resources to afford such expenses, making certain avenues of speculative or basic research – particularly when they do not appear to lead to a marketable product – unaffordable and not warranting further investigation (Baird 1998).

Because patents confer monopolies, they necessarily increase transaction costs and restrict use, but this has been considered an acceptable cost for society to pay in exchange for continued innovation. But if a tragedy of the anticommons occurs and gene fragments, complete genes, and other basic biomedical research tools are locked up in expensive and overlapping patent agreements, the transaction costs may be such that only large biotechnology and pharmaceutical companies are able to afford ongoing research. These multinationals then have the power to control the direction of research and the application of genetic technologies, and thus strongly influence the development and provision of new

health care technologies and services (Baird 1998). Nevertheless, even some of the large biotechnology companies are concerned by the possibility of a tragedy of the anticommons and have argued against the patenting of gene fragments (Marshall 1999). A similar case can also be made for the effects of patents on whole genes, both in terms of restricting research and application of new technologies.[39]

Development and Provision of Health Care Services

The way a product or service is provided to patients depends on various factors, including the cost of research and development, marketing and overhead expenses, and the potential market size. Many companies will use and enforce patent rights to protect their novel intellectual property, and may enter into license agreements to expand the market for their products (Caulfield 1998). Yet due to prohibitively expensive license fees from gene patents, and the threat of patent infringement law suits, some genetics laboratories are not developing certain tests or investigating new gene mutations (Caulfield and Gold 2000b). In a study of U.S. laboratories, 30% acknowledged that they had stopped research on or provision of testing for hereditary hemochromatosis due to the restrictive license requirements imposed by the patent holder (Merz *et al.* 2002).

Similarly, the broad U.S., Canadian and European BRCA patents give Myriad the power to constrain research and development of products that use the BRCA1 and BRCA2 genes. Basic research into the function of the genes or resulting proteins, for example, would be permissible without infringing Myriad's patent rights, although there is still contention about what constitutes basic research exclusions (Baird 1998); Myriad has signed agreements

[39] Developers of DNA databases, patent offices and a working group of the World Intellectual Property Organization are considering how DNA sequences from patents can be deposited directly into public databases (Cook-Deegan and McCormack 2001).

with the U.S. NIH and National Cancer Institute to provide sequencing at cost ($1,200US) for research purposes (Reynolds 2000). However, research that provides a commercial or clinical service, defined by Myriad as any research in which a fee is charged for testing or in which results are provided to patients, would be prohibited. Important research, such as the identification of population specific mutations or incidence in the general population would violate Myriad's patents and be prohibited (Blanton 2002).

Research to evaluate the accuracy of existing testing methodologies, such as Myriad's full DNA sequencing approach, or to explore alternate methods such as the Institut Curie's DNA colour bar coding approach for detecting large deletions and re-arrangements (Gad *et al.* 2001), could not be carried out without contravening Myriad's patents. As there are a variety of different methods available and in use internationally to test for BRCA mutations, such as protein truncation testing, full DNA sequencing (Myriad's method), single stranded conformational polymorphism (SSCP), or DNA colour bar coding, the possibility for ongoing technology assessment (e.g., test sensitivity, specificity, positive predictive value, etc.) is jeopardised (Institut Curie 2001). The BRCA patents give Myriad the ability to constrain research into the appropriate uses of BRCA testing and comparison of which methodology is most effective, and given the company's efforts to establish a global monopoly on BRCA testing, they have a strong motivation to deter research that may lead to competing technologies. Myriad's full DNA sequencing approach becomes the *de facto* 'gold standard' without the possibility of independent verification.

Company Mandates

Myriad has signed an agreement making MDS Laboratory Services the exclusive Canadian provider of BRCA testing. But in order to understand the way in which these two companies seek to provide BRCA testing in Canada, it is necessary to understand the larger context of the companies' missions or mandates.

MDS Laboratory Services, a subsidiary of MDS Inc., is one of the largest diagnostics and laboratory service companies in Canada. It has regional laboratories in Ontario, Québec, British Columbia, Alberta and Saskatchewan, and a national testing facility that allows them to provide services coast to coast (www.mdslabscanada.com). They currently provide a host of routine and specialty diagnostic and testing services for patients, physicians and hospitals, and thus an expansion into the provision of genetic testing for hereditary breast cancer (Myriad Genetics 2000e) may appear to be a logical extension of their mandate. MDS may be interested in seeing BRCA testing de-listed from provincial health insurance plans so that they can legally offer it for private purchase independent of the health care system, without contravening the *Canada Health Act* (Flood and Archibald 2001). However, given their existing cooperation with public health care providers and institutions in the provision of laboratory testing services, it is more likely that MDS seeks to work within the public health care system but as the sole contractor or provider of technical genetic testing services. This approach has significant advantages for the company because it maximizes the size of their market capture but leaves public health care institutions to cover the costs of medical infrastructure, gatekeeping and genetic counselling (Caulfield *et al.* 2001). MDS has taken the confrontational approach of asserting its exclusive license to perform BRCA testing, and

sent 'cease and desist' letters to the various provincial laboratories. This may be the result of being 'shut out' by public laboratories that were unwilling to give up their control of BRCA testing. Nevertheless, if MDS is successful in convincing laboratories to cease testing, then MDS will be in a strong position to then work with the public health care agencies to reach an arrangement to be sole provider.

Myriad's position is somewhat different from that of MDS because Myriad no longer sees itself as being primarily a genetics diagnostics company. While they continue to develop and patent other disease genes and diagnostic tests, which are provided through their subsidiary Myriad Genetics Laboratories, Myriad has re-envisioned itself as a biopharmaceutical and genomics company "specializing in the use of proteomic and genomic technologies to create break-through medical, diagnostic and therapeutic products" (www.myriad.com). The company has signed license agreements and launched collaborative endeavours with large biotechnology and pharmaceutical companies such as Eli Lilly, Novartis, Monsanto, Roche, Shering AG and Schering-Plough (Myriad Genetics 2000a), with the intent to provide the drug targets that are essential for continued development of the pharmaceutical industry (Feuerstein 2001).

With the rapidly growing ability of DNA chip manufacturers (e.g., Affymetrix) to develop products that can scan for thousands of probes, companies such as Myriad who have gene patents associated with hereditary diseases may be positioning themselves to gain a foothold in what they hope will be a developing market for population screening and drug development (Baird 2000). Population screening is currently limited to services such as prenatal or newborn testing (e.g., for Down syndrome or Phenylketonuria), and carrier status testing for thalassemia in Cyprus, Greece and Italy (Chadwick *et al.* 1998). Although not

likely in the immediate future, DNA diagnostic chips that provide genetic risk information about hundreds of diseases or conditions could become over-the-counter products that are widely available to the general public.[40] A patent on one of those genes – licensed at a few dollars per diagnostic chip – could be extremely lucrative if a market of millions or even billions of consumers could be generated; this would be a significant improvement for Myriad over their current market of approximately 10,000 women per year (Blanton 2002).

The cost of BRCA testing will continue to be high unless there is a large market (e.g., DNA chips), competition from other providers, or a change in technology. But as a result of their broad gene patents there will not be any direct competition with Myriad to drive down the price of BRCA testing, thus they can effectively market or license this service to national health care providers at whatever price Myriad believes they can obtain. With the relatively small numbers of BRCA tests that are likely to be generated in the publicly supported health care systems, where stringent access criteria have to be met (Carter 2001), there will be little incentive for Myriad to reduce prices. Thus despite an apparent desire to integrate with existing public or private health insurance programs, the provision of genetic testing services that are cost-effective for public health insurance plans may not be a long-term priority for Myriad – they may do better for their shareholders by strongly marketing testing for public and private purchase outside the health care system, as a 'consumer good'.

Marketing and Consumer Information

The need to off-set initial large research and development expenses may drive early or premature implementation of BRCA testing in the national and international arenas

[40] The advent of this type of testing would raise a host of challenging social, ethical, and policy issues (The Council on Ethical and Judicial Affairs American Medical Association 1998), that are outside the scope of this thesis.

(Andrews 1997; Healy 1997). One means of building demand for services will be by marketing and advertising to physicians, patients and the general public. From the industry perspective, effective advertising that emphasises the benefits of a product and its superiority over competing products is essential. Companies attempt to provide information that is more favourable to the uptake of their service, since even a neutral approach will negatively effect sales and reduce shareholder value. Genetic service companies are thus following the lead of the pharmaceutical and nutriceutical industries and beginning to market their products to clinicians and to the general public through mass media and the Internet (Pines 1999; Williams-Jones 1999).

Since direct-to-consumer marketing is controlled in Canada, the marketing of health care products and services such as pharmaceuticals and diagnostic tests is aimed primarily at health care professionals (Brill-Edwards 2000). Health care professionals are the gatekeepers for what services will be prescribed and covered under provincial health insurance. Given this role, a major effort is made on advertising directly to clinicians, with the pharmaceutical industry spending $4.04 billion US on this activity in 2000 (Mintzes 2000; Mintzes *et al.* 2002). Commercial genetic service companies are not wholly driven by profit motivations, nor do they seek simply to exploit the public – they have to be conscious of their long term reputations. But one of a corporation's main responsibilities is to make a profit and increase shareholder value, and the extremely competitive nature of the genetics technology market will mean that building a client base and market is essential (Malinowski and Blatt 1997). There are thus incentives for producers to create 'need' when there is insufficient consumer demand (Caulfield and Gold 2000a), as well as make exuberant claims about products in order to influence investors (Melzer and Zimmerman 2002). An example of this is Myriad

and MDS's extensive efforts to market the utility of their *BRACAnalysis* test to physicians (Aetna U.S. Health Care 1999) and the general public in the U.S. (Chandros and Prasad 2001) – in the Fall of 2002, Myriad will be launching an extensive public marketing campaign for BRCA testing in the U.S. (Agovino 2002).

Educated consumers are likely to have little difficulty in self-diagnosing common health conditions such as a cold and purchasing the appropriate over-the-counter remedies. The situation is very different for more serious medical conditions, in which case clinical expertise is required to make a correct diagnosis and prescribe the appropriate treatment. Given the complexity involved in the development and use of genetic technologies, consumers are unlikely to have the necessary experience or knowledge to independently evaluate which services it would be appropriate to pursue. If a company providing genetic testing has a monopoly position in the market (provided by their patents), and is also the only source of information, then consumers will be hard pressed to make informed choices. In the context of publicly provided genetic testing, evidence-based genetic counselling for patients and families has become the standard of care (Burgess, Laberge, and Knoppers 1998; Emery and Hayflick 2001). The issues for individuals and families in terms of understanding the basic genetics, the impact of genetic information on the individual and their family members, as well as social issues such as discrimination are deemed sufficiently complex to require expert support and counselling. An important public interest issue for the private purchase of

genetic services will be whether appropriate education and counselling are provided (Burgess 1999).[41]

If individuals are to be informed participants in their health care, they need expert and unbiased health care advice and support. Recent literature shows that people would like access to unbiased information about biotechnology (Einseidel 1998). Without such access, people are vulnerable to marketing that can manipulate them into purchasing services they do not need, and which may in fact be harmful. Even if patients decide to rely on their physicians to help make decisions about the appropriateness of genetic testing, it is unlikely that most physicians will be equipped to address this issue (Kinmonth *et al.* 1998). Physicians may lack sufficient knowledge, not only in terms of education about genetic technologies and how to provide counselling, but also with respect to the validity of claims made by industry about the accuracy and benefits of testing (James *et al.* 1998). Physicians may thus be open to the influence of commercial marketing strategies and unable to effectively criticize the information they receive, as is arguably the case at the moment with respect to prescription drugs (Mintzes 2000; Graham 2001).

Pressure may be brought to bear on physicians to prescribe or administer genetic testing even when they do not think it appropriate. Access to health care services is increasingly being driven by patient demand, with greater emphasis placed on patient choice and autonomy by both patients and medical professionals (Caulfield and Feasby 1998). Studies by Wertz have found that in the United States in particular, but in Canada as well, patients with the financial ability increasingly feel they should have the right to choose the

[41] This does not mean that the public is uneducated or unable to grasp the complex social and ethical implications of these new technologies. One has only to note the recent negative public reaction to human cloning, stem cell research, or the genetic modification of agricultural products and livestock to see that many people are becoming genuinely concerned about the pace of biotechnology development, the lack of public involvement or consultation, and the close relationship between government and industry.

services they want and to pay for them out-of-pocket if the services are not covered by public health insurance (Wertz 1995, 1999). Genetics professionals are trained to put a high value on patient autonomy, and because of this, a large proportion of geneticists in the studies were willing to refer patients out of province or out of country for procedures not covered at their institutions or in their jurisdictions. When combined with fear of physician liability for not providing a service (Caulfield and Gold 2000a), the powerful influences of marketing to create patient demand while also controlling access to information may mean that physicians are in fact weak gatekeepers for access to genetics-based health care services. How then are the above mentioned risks associated with gene patents and the provision of commercial genetic services to be addressed?

Regulating Patents and Commercial Testing

In considering whether and how to fund provision of BRCA testing through a public health care system such as Canada's, it is necessary to understand the scientific aspects of the test, such as its sensitivity, specificity, benefits or harms for a particular population. The above mentioned problems with decision making, in combination with concerns about gene patents with respect to research, access to unbiased consumer information, and the equitable provision of services, mean that a more comprehensive approach to technology assessment and decision making is also required. It is essential to analyse the larger social and political context in which the test was developed and marketed, and how it shapes and is shaped by

patients, consumers, researchers, clinicians, government policy, and the commercial biotechnology industry, to name but a few of the relevant actors.[42]

Theoretical Tools

One method that can aid in developing a more coherent technology assessment and decision making framework is Actor-Network Theory (ANT). This theory developed out of the field of science and technology studies with the aim of exploring the taken for granted nature of science and technology, as well as the complex social and technical networks that lead to scientific and technological developments (Latour 1993; Callon 1986). According to ANT, society is made up of 'actor-networks' of human and non-human actors, and for the purpose of critical analysis these actors (humans, machines, technology, institutions, corporations) can be treated as symmetrical – they are 'actors' to the extent that they have the ability to act and be acted upon (Law 2001).

In this view, BRCA testing can be understood as an actor-network made up of various different testing methodologies (e.g., protein truncation testing, full DNA sequencing), physicians, genetic counsellors, geneticists, laboratory technicians, patients and families. This technology developed out of and continues to be shaped by its history and context – a wide network of patients, research subjects, scientists, universities, gene patents, biotech companies, public health care professionals, and consumers (Fujimura 1996). An ANT

[42] A recent draft report by the Ontario Ministry of Health and Long Term Care for the Premiers conference on Healthcare Reform (January 2002), attempts to address some of these issues. This report proposes a set of recommendations to address gene patents and the commercialization of adult genetic testing. Specifically, the development of a cross-jurisdictional framework is emphasized, that would consider the social, legal, ethical and financial implications raised by breakthroughs in genetics and genomics. They propose to establish a variety of mechanisms to co-ordinate public engagement (largely through promoting education) in determining the role of genetics in health care; increase professional education; enhance genetic technology assessment; enhance control and oversight of service delivery and quality control; expand human resources for review; reform the patent system; and develop guidelines to protect patient privacy and address issues of discrimination and disability (Ontario Ministry of Health and Long Term Care 2002).

analysis demonstrates that commercial genetic tests such as Myriad's *BRACAnalysis* test are not passive, value-neutral technologies that exist apart from the social world; they are developed and accessed for a variety of complex reasons. The positive and negative consequences of commercial BRCA testing are produced as a result of complex interactions between diverse actors and interests, so any solutions to the problems raised by this technology are also likely to be complex and multifaceted. But while ANT can contribute important information about the development and function of technologies or organizations, and is an important addition to more comprehensive technology assessment, it is not a theory that specifically addresses the issue of health care priority-setting. For this latter purpose, further tools drawn from moral philosophy are needed.

Consequentialist analyses are a common aspect of priority-setting initiatives for health care funding, often taking the form of cost-benefit or cost-effectiveness analyses. The goal of these analyses is to objectively weigh and compare various health care services or programs so that they can be ranked and unbiased decisions made about which services to fund. A prominent example of this approach to priority-setting is the Oregon Health Plan.[43] A cost-effectiveness analysis of genetic testing services such as BRCA testing would evaluate the full range of costs and benefits, both to the patients and families accessing the service as well as for the health care system in general (Modell and Kuliev 1993; Goldie 2001). The direct benefits of BRCA testing for individuals are often psycho-social, such as anxiety reduction and facilitation of family discussions. But there are also clinical benefits such as being able to make decisions about risk-reduction behaviour, prophylactic surgery or the use

[43] The Oregon approach to priority-setting has been heavily criticized for the way it applied cost-effectiveness analyses (Deber *et al.* 1998), the fact that the objectivity of the process was undermined by various professional, political, and patient interests, and that it only applied to a proportion of the population who were not well represented in the process (Oberlander, Marmor, and Jacobs 2001).

of pharmaceuticals such as tamoxifen. Broader consideration would evaluate, for example, whether BRCA testing is still cost-effective for public health insurance plans when the price increases to $3850Cdn as a result of Myriad's BRCA patents, and consider the long term effects on the health care system of private purchase of testing. If provincial laboratories defy Myriad's patents, there may be serious negative consequences in terms of law suits and the potential for greater economic harms if intellectual property is seen by industry as no longer protected. A consequentialist-type analysis that considers these diverse issues is thus an important part of any technology assessment or priority-setting framework.

However, for consequentialist (and particularly utilitarian) analyses, a fair distribution of harms and benefits in access to health care services will focus on maximizing happiness or pleasure and minimizing unhappiness or pain for the greatest number of people – individual needs and benefits will be less important. Social contract theories, such as that developed by Norman Daniels (Daniels 1985, 2001), can make an important contribution to more fair and coherent priority-setting, by implementing principles that also consider the needs of the individual. A thought experiment is proposed in which a group of objective and unbiased decision-makers are charged with developing a just health care system. The decisions made in this ideal setting can then inform practical consideration of what substantive rules or principles should underpin such a system. For example, the principle of 'equality of opportunity' highlights the importance of having access to health care in order to ensure a person has a full range of opportunities. People at risk for hereditary breast cancer may live with anxiety, have to undergo regular screening, care for affected family members, etc., factors that impede their ability to pursue other life goals. Incorporating this principle of justice means that the effects of a health care service such as BRCA testing on individuals

become more nuanced, to include not only clinical benefits, but also the opportunity to pursue individual life goals such as family planning, or career or educational opportunities. In so doing, issues of justice and the need to equitably distribute the costs and benefits of health care services are integrated.

Effective technology assessment and health care priority-setting also require active public involvement. At the level of evaluating a particular service such as BRCA testing, there is clearly a place for expert analysis to determine objectively test safety, accuracy, harms and benefits, and the population for which it is most appropriate. But, as Actor-Network Theory helps clarify, technologies have a tendency (or inevitability) to drift beyond the purposes of the developers. It will thus be essential to also include stakeholder perspectives (e.g., patients, families, support groups) that integrate the range of personal experiences of illness, the varied benefits and harms of the test, and the uses to which the test will be put by patients and consumers.

Public deliberation will also be crucial if there is to be public acceptance of heath-care funding decisions, and more generally a belief that the health care system is fair and accountable in the distribution of services. Procedural justice mechanisms such as Daniels and Sabin's 'accountability for reasonableness' (Daniels and Sabin 1997, 1998) could be implemented if we wish to make decisions about health care funding of services in a manner that is reasonable, accountable, transparent, fair and democratic. By engaging stakeholders in an open and transparent process that is based on empirical evidence and supported by tools from moral philosophy, and which genuinely strives to integrate public considerations, it would become possible to make progress in evaluating and determining which services

should be funded through the public health care system, which should be left to private purchase, and which restricted.

The remaining sections of this chapter will focus on applying the insights gained from ANT and moral philosophy to technology assessment and evaluation of genetic testing for hereditary breast cancer, in order to address some of the problems raised earlier and make recommendations for how this technology, and the commercial factors such as gene patents that shape its development and implementation, are to be better regulated.

Product Safety and Oversight

There are a variety of ways to ensure that medical products and services are used only by those individuals who need them and for whom they will be safe and useful. Formal regulations, such national and international codes, laws, or guidelines can prescribe how services should be developed, tested and marketed. For example, before a medical product is approved for sale in Canada, it must pass through years of extensive testing and examination (e.g., regulated the *Food and Drugs Act*) and overseen by the Therapeutics Products Directorate (TPD) and the Biologics and Genetic Therapies Directorate (BGTD) (Brill-Edwards 2000). There are multiple layers of professional supervision (e.g., nurse, physician, pharmacist), governed by standards of practice that are in place to protect the consumer or patient from harm. There may also be market incentives (e.g., fear of liability from unsafe products, maintenance of public credibility) and cultural values (e.g., trust in advice from medical professionals and distrust of commercial advertising) that constrain how a product or service will be marketed. There is a thick layer of consumer protection (a complex set of

actor-networks) in place to ensure efficacy and safety of products or services before they become available for a professional to prescribe, or for a consumer to purchase.

However, as discussed above, these protections are being undermined by patents and commercial influences which may pressure premature adoption of new technologies without sufficiently detailed study or post-marketing evaluations (Brill-Edwards 2000). Important lessons can be drawn from the failures in the regulation of pharmaceutical development and commercialization; as ANT demonstrates, it is often in the failure of networks that the implicit norms and values are revealed (Law and Callon 1992). The last few decades have seen a rapid decline in the level of government oversight of pharmaceutical research, development, marketing and sales. Pharmaceutical manufacturers are conducting more of their own clinical trials, setting standards for evaluation, and producing new drugs that in many cases offer minimal improvement over existing products (Barer *et al.* 2000). With governments increasingly focused on economic development and commercialization within the health care setting, quality assurance and cost-effectiveness evaluations of new medical technologies have suffered (Baird in press). There has been pressure from various parts of government, the private sector, and special interest groups to streamline the pharmaceutical review process, resulting in increased work loads on already understaffed regulatory bodies at Health Canada (the TPD and BGTD), and ultimately a weakening of oversight and ability to conduct in-depth, independent critical review (Brill-Edwards 2000). The result is that objective, evidence-based evaluation and priority-setting about which drugs to include in provincial formularies is undermined.

By seeking to facilitate economic development through the health care system, government is failing in its mandate to ensure public safety. If there is to be effective

oversight and evaluation of new technologies, as well as comprehensive decision making about which services warrant funding as part of public health insurance, then there must be well staffed and resourced arms length, independent review mechanisms that have the power to constrain companies (even at the risk of slowing economic development), in order to protect public safety and the broader public interest. The nascent stage at which commercial genetic services providers are in the development and marketing of genetic testing provides an important opportunity to develop effective regulations in this area.

Appropriate review and oversight mechanisms must be established to control how new genetic technologies are developed and marketed to the public (Baird 2001; Caulfield 2000; Hoedemaekers 2000). Gatekeeping and support structures for genetic testing have to be focused on selecting for and helping those people at increased risk who will likely benefit from testing. Such determinations must include active stakeholder participation, both because of the complexity of the networks and the way in which genetic technologies will be used, as well as to make decisions about access to services in a manner that is reasonable and publicly accountable. Comprehensive, objective, evidence-based technology assessment will be essential to ensure accuracy, laboratory quality, etc., for all tests (Caulfield *et al.* 2001). It will be in the public interest to restrict some tests, e.g., BRCA testing, to those people who meet evidence-based criteria with respect to accuracy and predictive value (Carter 2001), because these tests will be misleading and inaccurate if used more generally for population screening (Vineis, Schulte, and McMichael 2001). Others tests will be of such low predictive value, for example APOE testing for Alzheimer's disease (Quaid 1998), that the costs far outweigh any benefits, making them appropriate to restrict or prohibit.

Patents

Given the role of patents in the development and implementation of genetic technologies, effective regulation must also address the various problems raised by the way in which patents are currently administered. A commonly discussed approach to constraining the application of patents on genes and other biological materials is compulsory licensing. The patent holder would be permitted to exploit their patent but not allowed to simply hold a patent and block other research and development. Licensing is a means of ensuring that inventions are used and made available at reasonable cost to prevent a tragedy of the anticommons (Baird 1998). In the case of patented genetic tests such as Myriad's *BRACAnalysis*, licensing could be an effective means of forcing the patent holder to meet internal and external guidelines for the provision of testing, such as requiring access through selected gatekeepers in the public health care system or mandatory provision of public or commercial genetic counselling services (Burgess 1999; Williams-Jones 1999). In particular, licensing would be an important mechanism for facilitating ongoing evaluation and technology assessment by encouraging researchers in both academic and commercial settings to compare technologies (e.g., BRCA testing) to determine which should be considered the 'gold standard', and how existing methods could be improved. The benefits of patents in supporting innovation could be achieved while also maintaining public accessibility to the best possible services.

Unfortunately, mandatory licensing as a solution runs into difficulty because current permissive U.S. and international patent and trade agreements make restrictive licenses difficult to implement (Caulfield and Gold 2000b). Thus another way may be for national patent offices to take a leadership role (Knoppers, Hirtle, and Glass 1999), and for example,

add conditions to patents such as the public morality/interest clause present in E.U. patent law (Baird 1998). Patents are limited monopolies granted to individuals and corporations on behalf of national governments, and if the use of patented materials has serious negative consequences (e.g., for research or provision of public health care), violates a sense of public morality, or simply does not meet larger social goals, then governments could use their patent offices to constrain how patents are awarded. It might be possible to reduce the power of patent holders to exclude others from use of patents by including strong protection for research or forced licensing to public health care institutions to support equitable access and ongoing research (Caulfield and Gold 2000b). The potential for placing liability on patent holders for negligent or unethical use of genetic material may also be a useful mechanism for shaping how a patent holder, for example, controls access to a genetic test and how it is administered (Caulfield and Gold 2000a).

However, because patent law is supposed to be morally neutral, it is simply not set-up to include social, ethical or policy considerations. Patent offices in Canada and the U.S. have no explicit authority to reject a patent because it may be against public morality or the public interest, and even in Europe where this power is available, it has not been used to block or limit the patenting of human genes (Caulfield and Gold 2000b). Social and ethical considerations are rarely brought to the table in the patent evaluation process, and strong public opposition to patents as being unethical or immoral has had no effect in most cases on how patents have been awarded. Moreover, there is a widely held belief amongst government administrations that patents are crucial for continued innovation and economic growth, and public institutions are joining the race to patent research. So while some government agencies and international organizations (e.g., the U.S. NIH and Secretary's Advisory

Committee, the World Health Organization), may call for caution in the application of patents, economic forces inevitably dominate development and application of patent law (Caulfield and Gold 2000b). Most industrialized countries view biotech as an increasingly important segment of the economy and thus are not inclined to restrict patents if this might reduce industry investment in research and innovation. For social and ethical considerations to gain a voice, governments would have to be pressured to also consider other values besides economic development, and then reform the patent system and give patent offices both the financial resources and the necessary social, ethical and policy expertise to effectively review patent applications.

Successful opposition to gene patents has occurred primarily as a result of public action groups such as Greenpeace challenging patents for not meeting the legal patent requirements (Ramirez 2000). However, this situation may be changing. Myriad's move to enforce their patents has been met with strong professional (and increasingly governmental) opposition across Canada – and in Ontario in particular (Canadian Press 2001; Eggertson 2002) – with several provinces rejecting Myriad's patent claim and continuing to provide BRCA testing through their regional laboratories. The Canadian Cancer Society and the National Cancer Institute of Canada have called on the federal government to ensure that the BRCA patents do not interfere with Canadian women accessing BRCA testing, and for provincial governments to launch court challenges of the patents (Canadian Cancer Society and National Cancer Institute of Canada 2002). The legal costs of challenging individual health insurers or public institutions may be affordable for a small biotech company such as Myriad (which in 2001 earned $45 million US but still posted a net loss of $7 million). But Myriad is unlikely to have the financial resources required to fight protracted legal battles

with provinces or nations. Such practical considerations may be a determining factor in how the gene patents on BRCA1 and BRCA2, which are arguably too broad, will be limited or overturned in national and international court challenges (Benowitz 2002; Dorozynski 2001; Wadman 2001).

There have also been some intriguing uses of the patent system by community groups to protect free and equitable access to the benefits of genetic research. The patenting of the gene associated with Canavan disease in some sense sparked this development. A community of people, patients and relatives developed around a particular rare disease (Canavan), and enlisted aid from a researcher to find the associated gene. However, the community lost control of the gene and free access to the resulting genetic test, when the gene was patented by the researcher. Other communities and groups are learning from this and other cases, and are now requiring researchers to negotiate agreement or acceptability of research at the outset (Burgess and Brunger 2000), demand that the community or group be named on any subsequent patents, or require the free licensing of resulting genetic tests to health care institutions to ensure ongoing control of and access to the tests (Kolata 2000). In the case of the BRCA genes, the patenting in the U.K. of BRCA2 was a defensive move on the part of the Cancer Research Campaign to ensure that Myriad would not gain control of the gene, and that the U.K. National Health Service would be able to provide cost-effective genetic testing to the public (Meek 2000). Finally, some groups, such as the Wellcome SNP Consortium have prevented patenting, or at least minimized the secrecy effects of patents on research, by making information about genetic research widely available through public databases (Williamson 2000). These different approaches demonstrate how a mechanism such as patent

law can be re-envisioned, or 'translated' in the language of Actor-Network Theory (Callon 1986), and used in new ways to shape how a technology is developed and used.

An important benefit of patent law is that it puts control of a technology in the hands of an identifiable person or corporation, who can then be held morally responsible and legally liable. There is an economic incentive to maximize profit, so it is unwise for patent owners to be seen to act unethically and attract negative press, which would undermine consumer confidence and thus shareholder value. For example, negative public opinion of genetically modified (GM) foods in Europe has resulted in a supermarket moratorium, with Monsanto, which owns patented GM products, being seen as the chief culprit. Monsanto, in large part because of its strong enforcement of patents on farmers and nondisclosure of information about its GM products, has had great difficulty countering this widespread negative press (Stipp 2000). Even though public opinion may be ignored in the awarding of gene patents, it can on occasion be used as an effective tool when focused on a particular application of a gene patent. If patients, families, advocacy groups and health care professionals in British Columbia were able to mount a protracted media campaign about the loss of access to BRCA testing, government inaction on this issue, and the actions of MDS and Myriad with respect to pricing and interaction with the health care system, the negative public opinion might encourage the various actors to begin discussions about how to provide equitable and affordable access to this service.

The power of public participation, when it can be effectively mobilized (although this may be very hard to accomplish), could be an aid in shaping the application of patents. This points toward the need for integrating such views in the actual patent evaluation process. For example, it could be possible to expand on the model of government advisory committees

such as the U.K.'s Human Genetics Commission or the Canadian Biotechnology Advisory Committee, and establish patent advisory committees with members of the public as well as experts in social, ethical and policy analysis, to directly inform and support consideration of social and ethical concerns in the patent review process. This would have the significant advantage of expanding the scope of patent evaluation, and go a long way towards enhancing public accountability. Yet as discussed above, such innovations would require a major shift in the way governments use patent offices and require they view the goals of the patent system in a broader framework.

The Public Health Care System's Buying Power

Perhaps the most hopeful option for controlling how patents are applied is to harness the very market forces that lead to the problems mentioned earlier. In Canada, the largest purchasers of health care products and services are the provincial health insurance plans. Patients and physicians decide which drugs or services to use, but it is the provinces (in collaboration with the various professional colleges) that determine which services are covered by insurance and this significantly shapes prescribing habits (Flood 1999). It is more difficult for companies to sell tests or medications if these products are not on insurance plans – and given the purchasing power of insurance plans, there are real incentives for companies to have their products listed. The pharmaceutical industry spends billions of dollars per year advertising to doctors to convince them to prescribe particular drugs, and hopefully also advocate for access to these drugs as part of health insurance plans. As Gold argues, this situation provides a unique way to incorporate ethical considerations with respect to the use of biological materials (Gold 2000).

Provincial insurers could require, as condition of listing in the health insurance plan, that the vendor and product conform to requirements that encourage evaluation and meeting of ethical standards. For example, what are the effects of a genetic test on the health care system as a whole, not just on individual patients? A service might only be listed if the patent holder or licensee demonstrated to regulatory or oversight agencies (e.g., Health Canada), that the ethical concerns associated with the technology are appropriately addressed. This might mean limiting the scope of marketing of tests, requiring access to (or even subsidizing of) genetic counselling services (Burgess 1999), and working closely with medical professionals to control access. In other words, this may be a mechanism by which governments can directly shape how patented services are implemented (Gold 2000). Cost-benefit or cost-effectiveness evaluations might mean that some services would have to be provided at or below a specific price to be worth covering; and social justice considerations would determine how and to whom services would be provided. In the case of BRCA testing, this might mean that testing would be deemed cost-effective at $2000, for example, and thus reasonably purchased through MDS or Myriad. But if the companies were not agreeable, then they would lose access to the market of patients in the public health care system. It may be possible for Health Canada regulatory bodies such as the Therapeutics Products Directorate and the Biologics and Genetic Therapies Directorate to restrict a company from providing a product for private purchase by expanding on their current powers with regards to oversight and regulation of pharmaceuticals. If a drug or medical technology is deemed to lack sufficient evidence of efficacy, or new safety concerns arise, these bodies could halt or restrict sales of that product; similarly, social and ethical considerations could be added as criteria to this review process.

The advantage of using the public health insurance system, instead of or in addition to patent law, is that the former permits wider consideration of ethical issues. It also deals with products that may be patented outside Canada, which cannot be addressed by local patent law. Using the buying power of public health insurance plans would allow provinces to constrain usage in the event of ethical breaches in research, development or application occurring in Canada or elsewhere (Gold 2000). Market incentives and restraints will have a powerful influence on the behaviour of companies who have a duty to improve shareholder value. Governments can offer the tempting carrot of facilitated access to a large market of patients, while also showing the stick of strong patent constraints such as forced licensing or restricted access, in order to influence how commercial providers of health care services operate and interact with the public health care system.

There are nonetheless problems with this approach. The need for harmonization and agreement across the country in order to ensure a common front in relations with commercial providers is undermined by provincial jurisdiction for health care. The federal government could assist by showing leadership and working to bring about harmonization between the provinces, perhaps by use of its spending powers or through enacting enabling legislation. However, a significant challenge is that this approach would require a major change in government attitudes towards patenting. The federal government is strongly lobbied by the powerful biopharma industries, and seeks to encourage job creation and economic growth. They do not have to pay for pharmaceutical products as it is the provinces that do so through provincial health insurance plans. Thus patent policy is made by an actor who does not have an immediate stake in the consequences. The prevalent liberal economic model and drive to facilitate commercialization and economic development through health care is an

impediment to this new approach, but there are signs that government agencies such as Health Canada may be increasingly receptive. In particular, provincial government initiatives to reduce or at least control health care spending are being undermined by patents, particularly with respect to pharmaceuticals, that are driving up health care costs. Thus it may well be in the interest of the provinces to pressure the federal government to restrict or constrain pharmaceutical and gene patents to address these concerns. As Gold argues persuasively, "by using the power of *de facto* control on the sale and distribution of medications, tests, and services with the province, provincial health insurance plans can go a long way to ensure that ethical concerns have been addressed with respect to research and development, and marketing and distribution of the products of biomedical research" (Gold 2000, 434).

Conclusion

Commercial diagnostics companies are increasingly becoming a presence in the provision of genetic testing services. With the information coming from the Human Genome Project, more genes that are associated with an increased risk for disease conditions will be found, patented and promoted by companies offering genetic testing for profit. Some genetic tests may not be publicly funded because even though they are reasonably priced, there are insufficient funds available to cover them; other tests may be priced too high based on cost-effectiveness analyses to warrant funding; while some tests will not be funded because they are of little or no benefit or are harmful. For those tests that are covered by public health care insurance, some will be under-funded and result in long waiting lists, generating a private market for quicker service. The question faced by clinicians, administrators, and policy

decision makers is how to obtain the benefits from patenting and commercialization in the development and provision of genetic testing services, while minimizing the harms to research, consumer safety, and public health care.

In Canada, health care services delivered to patients have generally not been treated as consumer goods or commodities subject to the usual influences of the market. The complexity of the service or technology is such that it is considered beyond the means of most consumers to evaluate and make informed decisions (Deber *et al.* 1998; Caulfield *et al.* 2001; Donaldson and Gerard 1993). Moreover, health care services differ from other consumer goods because they often lack competition with other similar products, as would be the case for vehicles, educational choice for children, or credit cards. The market forces in these latter cases drive the development of choice and diverse information sources. This is not the case with health care, where there is often only one provider of the services, as may become the case in Canada for Myriad's patented *BRACAnalysis* test. The public is vulnerable when purveyors of health care services or products have a significant financial interest in aggressively marketing these products (Barer *et al.* 2000). While the possibility of private purchase for some genetic tests is a reality, this does not invalidate the need for regulation and standards for appropriate provision. On the contrary, one of the roles of governments is to protect the vulnerability of citizens accessing health care services. There is clearly a need for government regulation and oversight of new health care technologies, which should include a system for evaluation and technology assessment of genetic tests. Consumers will need some level of counselling, social support, and unbiased information which would be best delivered through the public health care system. Genetic tests of

unproven scientific and clinical utility should be restricted from provision either through public health care institutions or by commercial genetic testing companies.

There are good reasons to support public funding of a test if it actually identifies a genetic factor that increases risk substantially, allows preventive or early diagnostic strategies, is not harmful or only minimally harmful, and is the least expensive option for a proven health benefit (Caulfield *et al.* 2001). When the test or service in question is also protected by patent rights, provincial governments working on behalf of their citizens may be in a strong bargaining position to negotiate with companies such as Myriad or MDS to obtain the service for a reasonable cost, where individual consumers could not. Provincial government positions would be further strengthened by judicious changes in patent law at the national level, such as forced licensing in exchange for continued patent protection and access to the Canadian market, or inclusion of public interest criteria in their assessments of whether a patent should be issued. Decisions about if and when particular services should be contracted out to the private sector must consider the larger social, ethical, economic and policy implications.

Public engagement in the patent review process (e.g., through participation in ethical advisory committees), and as part of larger decision making processes about health care priority-setting (e.g., to inform technology assessment as well as participate in decision making) is essential if the public is to trust that these processes are fair and accountable. A reflective process that is supported by tools from moral philosophy, based on empirical evidence and understanding of the complex actor-networks involved, and conducted in an open and transparent manner will enable real progress in determining which services to fund

through the public health care system, which to restrict, and which to leave to private purchase while ensuring these services are safely and equitably provided.

Chapter 6

Conclusion

General Conclusions

The case of Myriad Genetics and its commercial *BRACAnalysis* genetic test for hereditary breast and ovarian cancer highlights important social, ethical, and policy issues related to technology assessment, priority-setting for health insurance, and private purchase of health care services. In the preceding discussion, no firm determination was made about whether BRCA testing should be funded as part of public health insurance and/or provided through the public health care system. Such a determination requires detailed empirical investigation into the short and long-term benefits and harms of BRCA testing for individuals and families, the more general costs of providing this service as compared to other health care services, and the overall priorities of public health care. Instead, this thesis demonstrates that tools drawn from the social sciences, moral philosophy, and health law and policy should be integrated to support sophisticated analysis of the relevant social, ethical and policy issues, and contribute to a more coherent and just approach to technology assessment and priority-setting. Moreover, substantive recommendations are made to address some of the problems raised by gene patents and commercial genetic testing with respect to research and access to services. The following specific conclusions can be drawn from this thesis:

1) Actor-Network Theory (ANT) provides an important method for developing the empirical basis necessary for comprehensive social, ethical, and policy analysis of the commercialization of genetic technologies. ANT supports better assessment of the complexity of new genetic technologies, illuminating how they are developed (and should be

regulated), and how they are likely to change. Treating humans and non-humans (e.g., technology, groups, corporations) as actors enmeshed in a host of actor-networks makes explicit the extent to which technologies shape and will be shaped by a diverse range of other actors, as well as the ongoing nature of the process. Technologies are active – they have instructions 'scripts' that embed normative values about how the technology should operate and be used – that have an effect on the people, agencies, groups, or health care systems with which the technologies interact. Thus it is necessary to have a broad understanding of the context or networks which underpin a technology for effective technology assessment, for determination of which services should be included as part of public health insurance, and for deciding how best to ensure the safe and effective application of the technology. In particular, the concept of 'drift' – that the scripts of a technology will be changed, so that the technology is used in new and unexpected ways – is important for assessing the benefits, risks, and relative costs of new technologies, as well as the consequences of patient-paid access. ANT can also aid decision-making about the most effective means of constraining the development and application of gene patents and the regulation of technology. By clarifying the development and use of technology through associated complex networks in commercial genetic testing, ANT illuminates those pressure points (e.g., the drive for profit, positive public opinion, provincial health insurance purchasing power) that may be most amenable for shaping corporate behaviour and provision of services.

2) Consequentialist (e.g., cost-effectiveness) analyses and the procedural and substantive tools of justice theory are valid and important contributions to the development of more comprehensive and just decision-making frameworks for health care priority-setting. For example, an application of consequentialist methods highlights the need for objective

consequence-oriented evaluations of health care products and services in order to compare services across a spectrum. Social contract theory builds on these more empirical evaluations by raising for consideration issues of justice, such as equality of opportunity, so that the decision-making framework is not only objective and maximizing of benefits but also incorporates substantive principles of justice in its distribution of harms and benefits. These substantive considerations of justice must also be set within a procedural framework, for example Daniels and Sabin's 'accountability for reasonableness' approach (Daniels and Sabin 1997), to ensure that decisions are made in a manner that is reasonable and publicly accessible.

Public participation through stakeholder involvement will be needed to inform and better nuance technology assessment and consequentialist analyses for determining the benefits and harms of particular health care services. More importantly, however, public involvement will be critical as an aspect of democratic deliberation. In their capacity as citizens and tax payers, people are more likely to trust and accept that a particular allocation of health care services is fair and worth paying for if they can see that the process is transparent, publicly accountable and reflective of their views. But for a policy, e.g., one developed by an expert consensus panel, to be both substantively and procedurally just, it must not only be transparent and reasonable but also incorporate appeals mechanisms whereby citizens (both lay and expert) directly participate in the ongoing review and revision of decisions as new information develops or the context changes; the policy must also be publicly regulated to ensure the procedure is consistently transparent, accountable and reflective of the full range of citizen values.

3) Regulation and oversight of genetic technologies is essential in order to constrain

market forces – such as the *pressure* to patent and quickly (and prematurely) market new technologies in order to secure venture capital investment – that often negatively affect the safe and effective provision of health care. Marketing and advertising by companies, especially if direct-to-consumer marketing is permitted, raise serious concerns for the free and informed choice of patients and consumers' use of health care services. Sustained provision of information – unbiased by vested interests in promoting products – from health care professionals and government agencies is needed if informed choice is to occur. But there must also be a renewal of oversight for quality control and technology assessment, to ensure that only those technologies that are safe and effective are made available to patients. While recognizing that market forces may lead to the development of new beneficial services, it is essential to realize that health care services are very different from other consumer goods. This difference means that they require special consideration, regulation and oversight.

The broad regulatory apparatus dealing with patents, including patent policies and patent office practices, must be reformed to include the consideration of the range of social, ethical and policy implications of the patents under evaluation. This will require a change in the role and function of patent offices, and a shift in the view of governments to see patents not only as a mechanism for ensuring innovation and economic development, but also as a means of improving the ethical development and application of new technologies. Finally, federal and provincial governments must be willing to face the powerful commercial interests and use the authority of patents and the purchasing power of health insurance plans to shape the conduct of commercial research and development. However, this will necessitate a balancing of competing agendas within and between the federal and provincial governments,

e.g., economic growth and innovation (federal responsibility) vs. provision of health care insurance (provincial responsibility). Only with such practical collaboration will governments be able to ensure the benefits of commercial development while protecting the public interest in having safe, affordable and equitable access to health care services.

Limitations

The limitations of this project are in part the result of pursuing an interdisciplinary approach to social, ethical and policy analysis. The extent to which any particular tool or theory could be fully explained and applied (or for that matter, critiqued and compared with other theories) is necessarily limited. There may also be real tensions between the various disciplinary approaches used – with some more inclined toward theoretical description while others are focused on practical recommendations and solutions – that threaten the coherence or unity of the larger analysis.

A detailed analysis and application of a theory, e.g., Actor-Network Theory, would be the subject of an entire thesis project; a comprehensive comparison of multiple disciplinary approaches that sought to be fully integrative and applied is best conceived of as work for an interdisciplinary team. This thesis establishes the feasibility and value of taking an interdisciplinary approach in order to address complex problems that may not be amenable to a single disciplinary approach. As is explained in Chapter 1, the task was to demonstrate how such a framework could be constructed by providing examples of specific tools that would be useful in supporting a more comprehensive, just, and effective decision making framework. The specific limitations of this approach are nonetheless worth exploring in some detail.

1) The general conclusions made above (p. 151) raise the question of why more precise recommendations were not made, particularly with respect to the case study of Myriad Genetics' patented *BRACAnalysis* susceptibility test for hereditary breast cancer. The following conclusions seem to follow from the analysis in this dissertation:

a) BRCA testing is an effective and useful health care service that should be made readily available to patients who need this service, and should be covered as part of provincial health care insurance plans.

b) Myriad's BRCA patents are too broad and have a significant negative impact on the equitable and affordable provision of and access to an important health care service, therefore the Canadian patents should be overturned or at least severely constrained.

However, these conclusions cannot be justified solely from the analyses presented in this dissertation. For example, the ANT analysis demonstrated in Chapter 3 and applied in Chapter 5 is only a brief sketch of how one would conduct a technology assessment and review of the actor-networks involved in the development and commercialization of BRCA testing. A detailed analysis, e.g., of the operation of Myriad as a biopharmaceutical company or the politics involved in decisions about economic development and health care resource allocation, would be required in order to support specific conclusions or recommendations. Similarly, a determination of where BRCA testing 'fits' in terms of being a health care service worth funding under provincial health insurance plans will require further consideration from a variety of other fields. Comprehensive, evidence-based scientific and clinical evaluations of the benefit and utility of BRCA testing for specific patient populations will be a critical starting point. With such a background, detailed economic analyses of the

costs, benefits, and cost-effectiveness of testing can then be integrated in order to compare in-house BRCA testing with the commercial *BRACAnalysis* test, situated in the larger context of Western liberal democracies that support the patenting of genes and other biological materials to encourage innovation and economic development. Thorough-going social analyses, such as ethnographies that explore the way patients and families use and interpret genetic information, would also be an important component of the broader discussion as these will provide the detailed empirical information not likely to be acquired through other more theoretical evaluations. Public consultation will be necessary to explore the value of particular health care services within the larger discussion about the appropriate goals for health care.

2) While a few critiques of ANT were raised in Chapter 3, the interdisciplinary scope of this dissertation meant that it was not possible to conduct a detailed critical analysis or comparison of this theory with other science and technology studies approaches that might similarly enrich an ethical analysis. Although I have briefly described and applied ANT to the case of commercial genetic testing, ANT is not the only or even necessarily the pre-eminent approach for evaluating genetic technologies and supporting ethical analysis. Other methods drawn from anthropology and sociology contribute important perspectives that support a rich understanding of the social structures, organization, or culture of Myriad Genetics and academic and commercial science, that may be lacking from or less well addressed by an ANT analysis. Engaging with substantive critiques of ANT, situated within a broader examination of a range of methods in science and technology studies, will be crucial to continued effective use of this theory in supporting ethical enquiry. The objective of applying ANT to the case of commercial BRCA testing was to demonstrate that social

science analyses in general are essential to conducting comprehensive, evidence-based ethical analyses of emerging biotechnologies.

3) ANT appears to be a remarkably neutral approach, which is a particular advantage in the context of this dissertation because it avoids the over-politicization and villanization of Myriad Genetics and the patent system, which is so prevalent in many discussions. Nevertheless, this apparent amoral stance is not unique to ANT and is in fact problematic as no analysis is totally "value-free" – assessing the activities of industry and health care as if they are merely the translation of interests without any consideration of how legitimate those interests are *is* a moral stance and assumption. Moreover, while ANT can contribute to a better understanding of how technologies are developed and marketed, this theory is notably lacking in its ability to understand the forces acting within individual *human* actors (i.e., it lacks a psychology), and at the macro level, there is some controversy about whether ANT is capable of accounting for 'epiphenomenona' such as culture or society that are greater than the sum of the actor-network interactions.

Recommendations for Future Research

1) The integration of tools drawn from moral philosophy and social sciences described in this thesis are needed to enhance technology assessment and develop a fully coherent and just decision-making framework. It is also important to explore tools from the fields of economics, sociology, health law and policy analysis, for example, and consider how they too can be integrated.

2) While commercial genetic technologies serve as a useful case study, they form only a small part of health care. Exploration and evaluation of other health care services and

technologies would expand our understanding of how technologies are developed and should best be regulated, and what would constitute a just health care system.

3) There are serious problems with the way the current patent system deals with biological materials, and significant work is still needed in the area of possible reforms, a few of which have been suggested in Chapter 5. Greater attention should be paid to ensuring that patents do not negatively affect the provision of affordable health care services, while maintaining their benefits in promoting innovation and commerce. If current policy and practice related to patents are assessed to be too broad and not in the public interest, at least as it applies to genes and other biological materials, it may be necessary that these patents be revoked or constrained, and the patent system reformed. Creative mechanisms such as mandatory licensing should be evaluated and tested as a means of ensuring continued and affordable access to new health care technologies. But more importantly, the view that the only goal of patents is to promote innovation, and that economic development will suffer drastically without them, must be rejected.

4) A broader examination of a range of social science methods, e.g., in the field of science and technology studies, is necessary to determine which theoretical approaches can best support comprehensive, evidence-based ethical analyses (and how they are to be integrated), so that progress can continue in determining the role of genetics technologies in health care, and how they are to be provided in a just and equitable manner that maximizes the benefits while minimizing the harms of these new genetic technologies.

Contributions to Knowledge

1) To my knowledge, the case study of Myriad Genetics (Chapter 2) is the first of its kind to be submitted for publication, that a) provides a detailed history of the BRCA1 and BRCA2 patents and the resulting commercial *BRACAnalysis* test, and b) lays the groundwork for a better understanding and analysis of the complex social and ethical concerns associated with the continued and affordable conduct of biomedical research and provision of publicly funded health care services in Canada and Europe.

2) This study represents the first attempt to integrate Actor-Network Theory as part of a method to support sophisticated, empirically-based, social and ethical analysis of the development and implementation of a new health care technology, specifically commercial BRCA testing (Chapters 3).

3) The combination of philosophical tools from consequentialism, social contract theory, and public deliberation (Chapter 4) for the purpose of social and ethical analysis of new genetic technologies in the context of health care priority-setting, is a new and important contribution towards more just decision making and policy development.

4) Finally, this study is unique in its integration of tools from moral philosophy, the social sciences, and health law and policy for the purpose of making practical recommendations to improve policy development, and assess/oversee new genetic technologies and gene patents (Chapter 5).

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