



# Genetic Testing: Help, Hope or Hype

*Proceedings of the 15<sup>th</sup> Annual Health Policy Conference  
of the Centre for Health Services and Policy Research  
November 8, 2002*

Edited by:  
Patricia Baird  
Bryn Williams-Jones

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## About CHSPR

The Centre for Health Services and Policy Research (CHSPR) is an independent research centre based at the University of British Columbia. CHSPR's mission is to stimulate scientific enquiry into issues of health in population groups, and ways in which health services can best be organized, funded and delivered. Our researchers carry out a diverse program of applied health services and population health research under this agenda.

CHSPR aims to contribute to the improvement of population health by ensuring our research is relevant to contemporary health policy concerns and by working closely with decision makers to actively translate research findings into policy options. Our researchers are active participants in many policy-making forums and provide advice and assistance to both governmental and non-governmental organizations in BC, Canada and abroad.

CHSPR receives core funding from the BC Ministry of Health to support research with a direct role in informing policy decision-making and evaluating health reform, and to enable the ongoing development of the BC Linked Health Database. Our researchers are also funded by competitive external grants from provincial, national, and international funding agencies.

Much of CHSPR's research is made possible through the BC Linked Health Database, a valuable resource of data relating to the encounters of BC residents with various health care and other systems in the province. These data are used in an anonymized form for applied health services and population health research deemed to be in the public interest.

CHSPR has developed strict policies and procedures to protect the confidentiality and security of these data holdings and fully complies with all legislative acts governing the protection and use of sensitive information. CHSPR has over 30 years of experience in handling data from the BC Ministry of Health and other professional bodies, and acts as the access point for researchers wishing to use these data for research in the public interest.

For more information about CHSPR, please visit [www.chspr.ubc.ca](http://www.chspr.ubc.ca).

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## Foreword

Patricia Baird and Bryn Williams-Jones

As genetic technologies make the detection of genotypes associated with both gene-based diseases and predispositions to common diseases increasingly possible, we are increasingly seeing the promotion of widespread genetic testing and screening in both the public and private sectors. Advocates hope that these technologies will be the first step in a transformative process, in which medical diagnosis and treatment will become less a matter of trial and error, and more “scientific” and “accurate”. They hope that genetic testing for a range of inherited conditions and predispositions will allow drug prescriptions and treatments to be personalized to individual patients. But these hopes remain, for the near future at least, elusive. Important questions have yet to be answered about the utility and accuracy of existing technologies, and about the hype and rhetoric employed by various parties (medical professionals, the media, government agencies, the biotechnology and pharmaceutical industries) to build public acceptance of new genetic tests. Additional aspects to be evaluated are the commercialization and direct-to-consumer marketing of genetic tests, which have serious implications for influencing medical research and affecting access to health care services.

An exemplar of these issues and concerns—discussed in many of the conference presentations—is Myriad Genetics’ patented *BRCA*Analysis test for hereditary breast and ovarian cancer. This case raises many questions that are generalizable to other genetic tests and technologies. How is it that a US biopharmaceutical company came to own patent rights on two genes (BRCA1 and BRCA2) that were discovered through a ten-year international, largely publicly-funded research endeavour? Why is this company able to constrain the way health care programs provide access to genetic testing services? Have government policies that support the patenting and commercialization of the genes and biological materials taken into account the consequences of these policies for public health? Does the patent system, as it relates to genetics, need examination and revision to protect the public interest?

While the majority of Canadians who access genetic services do so through the public health care insurance system, there is also a developing international market for private purchase of genetic tests. The *BRCA* analysis test is one example of this trend. Some have argued that a parallel commercial or private health care industry is a necessary (and just) mechanism for ensuring that individuals (as autonomous consumers) can access health care services in a timely and efficient manner. They argue that such a private sector might even relieve stress on an already overburdened public system by “skimming off” those individuals willing to pay for quicker or preferential access to services. But as highlighted by the Myriad case, the elements that underpin the development of this market—the patenting of genes and resulting genetic tests—have negative consequences for effective gatekeeping by health professionals, and for the continued provision of appropriate genetic services through the Canadian health care system.

Most existing genetic tests—like many other health care services and unlike most consumer products—are double-edged technologies. They can be both beneficial and potentially quite harmful. A test may reveal that an individual has an increased risk of having a particular disease, but because many other factors are also involved (multiple genetic or environmental components, as well as sheer chance), most people so identified will never develop the associated illness. Even though prevention and pre-treatment mechanisms may be effective in reducing the risk of disease, they may involve long-term medication or major lifestyle alterations. Monitoring may be required for decades before symptoms, if any, appear. The persons may come to view themselves as “pre-ill”. Moreover, while a particular test may be accurate and cost-effective for a specific subset of the population (e.g. those with a strong family history of cancer), it will be inaccurate, with high rates of false positives, and prohibitively expensive when used for the general population.

The rapidly increasing numbers of genetic tests—generated in part by the identification of genes through the Human Genome Project, along with their patenting and commercialization by biotechnology and pharmaceutical companies—means there are



key ethical, legal, and policy questions to be examined and their policy implications assessed by academics, policy-makers and practitioners. For example:

- When are genetic tests indicated (and which type)? Who should pay for them? Whom should they be offered to?
- Who should have access to the results? What are the equity implications for access to services?
- What are the effects on the sustainability of the health care system? What are the effects on social justice of private markets for testing?

These and other related questions were explored during the Centre for Health Services and Policy Research 2002 conference, “Genetic Testing: Help, Hope or Hype?”

## Genetics and predictive medicine: selling pills, ignoring causes?

Helen Wallace

When former US president Bill Clinton and British Prime Minister Tony Blair announced the completion of the draft sequence of the human genome in the year 2000, Clinton speculated that man's lifetime could now be extended by 25 years. The completion of the genome project led to claims of an imminent genetic revolution in health care, and a new strategy for tackling disease—shifting from cure to prevention. The European Commission stated it would use the genome sequence as a basis to look at genetic technology policy. A former chief scientific officer of a pharmaceutical company declared genetic testing should be used for common diseases like heart disease, cancer and osteoporosis, enabling a shift to predictive and preventative measures.

This conference addresses the issue of the hyping of genetic testing, and I would argue that promoting these tests as a predictive and preventative measure against disease is a marketing strategy that sells medications and ignores underlying causes.

It is not yet known whether genetic tests will allow us to effectively predict an individual's risk of developing conditions such as heart disease or osteoporosis. Even if a disease can be predicted, it is unclear if this will help to prevent disease. Also, the possibility of insurers, employers, or other people in a position of power misusing genetic predictions of ill health must be considered. We cannot ignore the broader implications of these tests for society, and must acknowledge that they could be used to discriminate against people with particular genetic makeups.

From the day the draft of the human genome was announced, the media has propagated the idea of a patient going to their physician with their DNA sequence, expecting an answer to "Doctor, what is going to be wrong with me?" The press indicated the genetic

code would predict our future illnesses and identify who will be at risk of major diseases. Britain's health minister sang a similar tune in January 2002 during a major government address about the future of genetics: "The genetics revolution is already underway and is changing the world in which we live—holding out the potential for new drugs and therapies, new means of preventing ill health and new ways of treating illness. In time we should be able to assess the risk an individual has of developing disease—not just for single gene disorders like cystic fibrosis but for our country's biggest killers—cancer and coronary heart disease—as well as those like diabetes which limit people's lives."<sup>1</sup>

However, the accuracy of this prediction about the value of genetic tests has been called into question. First and foremost, as shown by migration studies, environmental exposures can be a much more important factor than genetic makeup when assessing the risk of disease. For instance, smoking and a cholesterol-rich diet significantly increase the risk of developing heart disease. Although genetic factors play a role, it is accepted that environmental factors are dominant in most cases of the disease.

Also, the role genes play in disease is complex. For instance, the BRCA1 and BRCA2 genes implicated in the development of breast cancer represent varying risks in different populations. Studies have found in high-risk families, a woman with the BRCA1 gene has an 80 per cent risk of developing breast cancer in her lifetime. However, a woman in the broader population with the BRCA1 gene has only a 40 per cent chance of developing the disease in her lifetime. The discrepancy between these risks is not yet understood, but is likely based on a combination of the interactions between genes, interactions between genes and the environment, and interactions between multiple environmental factors.

With regard to osteoporosis and heart disease, many patients who have a genetic predisposition will not develop the illness, and many more afflicted with these diseases will *not* have the associated genes. So focusing resources on prevention via genetic testing will ignore many who become ill, and target some people who won't ever become ill.

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<sup>1</sup> UK Department of Health. Britain must be at the leading edge of genetics - Milburn. New national network of genetics centres announced [press release]. London: UK Department of Health; 2002 Jan 16. Ref. No. 2002-0025.

An additional concern about the predictive value of genetic tests is the sometimes-erroneous connection drawn between genes and the risk of complex diseases. Initial studies linking certain genes to an increased risk of a disease are often disproved by later research. Patents are often filed on genetic tests with the predictive values obtained from the first study only. This is worrisome, since there is a high commercial incentive for marketing such tests, and their predictive value might be exaggerated.

Physician and epidemiologist Sir Jeffrey Rose has examined prevention strategies in populations, and his work is worth revisiting. Rose argues prevention strategies focused on high-risk individuals are limited and less effective than strategies targeted at the general population. For example, banning tobacco advertisements will prevent more cases of lung cancer than picking the heaviest smokers out of the population and focusing prevention strategies on them.

The psychological effect of genetic testing on patients is also uncertain. Ideally, patients who have been identified to have an increased risk of disease would change their lifestyle to reduce relevant environmental risk factors, but limited studies investigating this potential effect are not promising. Data indicate that while some patients find genetic tests induce lifestyle modifications, others become worried and fatalistic. Some people may feel powerless to alter their lifestyle, or to cease working in an environment that inevitably exposes them to risk factors underlying a given disease.

Finally, targeting medicine at the “healthy ill” is unlikely to be safe, effective or affordable. It has been suggested that people with a genetic predisposition for a disease may be given medication to prevent the onset of that disease. While preventative medication can play a role in some instances, it is possible that hundreds of people will be encouraged to take medication to prevent only a few cases of illness. If the preventative medication approach becomes the norm, the issue of side effects from those drugs becomes paramount. Also worrisome is the stigma attached to a person testing positive for increased risk factors—they could be erroneously labelled in society as “ill.”

The financial costs would be a substantial burden if most people with risk factors take preventative medication for the remainder of their lives.

Targeting consumers with genetic testing is a strategy that ignores the causes of major common diseases. Common chronic diseases in the developed world include asthma, obesity, and late-onset diabetes. These ailments are on the rise, but not because of an increase in genetic causes. While changes in diet are clearly linked to obesity, and the causes of asthma are complex, many environmental factors underlie their increase in frequency. Factors like poverty and toxins in the environment also play a huge role in common diseases, but are not specific to any one illness. But it is convenient for companies contributing to environmental hazards to blame disease on genetics, rather than their products or pollution. The fast food industry, for example, would benefit from the notion that genetic makeup, rather than a fat-rich diet, causes obesity.

While genetic tests target a specific disease, lifestyle changes can protect against several diseases simultaneously. For example, approximately 50 different diseases are associated with smoking, so preventive efforts focused only on people susceptible to lung cancer will ignore the contribution of smoking to the development of other illnesses. An aging population may contribute to the rise of disease, but it is possible to change factors like the marketing of tobacco and unhealthy Western diets.

The United Nations has stated that poverty is the world's biggest killer and health inequalities cannot be ignored when discussing the role of genetic testing. Even in developed countries, poverty is a significant risk factor for disease. In the United Kingdom, people in the lowest social class are twice as likely to die from a heart attack compared to those in the upper class. The poor are more likely to smoke, and often live in more polluted areas or nearer to factories.

Including developing nations in the picture brings the pertinence of genetic testing into further question. The World Health Organization predicts that by 2020, 70 per cent of cancer patients will live in countries with less than five per cent of the combined global

cancer resources.<sup>2</sup> Given the current price of genetic tests, they would hardly be a feasible method of cancer prevention for impoverished countries.

The allocation of research funding is very relevant to tackling disease. Much controversy has surrounded the fact that 90 per cent of research funds are spent on ten per cent of the global disease burden. Diseases common in the Western world, like cancer and heart disease, are much more likely to receive funds and attention. With the advent of genetic testing, we are risking the shift of resources not just to rich sick people, but also to rich healthy people. One force behind this shift is that marketing medication to rich healthy people is more lucrative than marketing to poor ill people. Companies in wealthy countries often patent genes in several countries, including developing nations. Since patents give a company an exclusive right to produce genetic tests involving those genes, monopoly pricing means the tests can be costly, and therefore relatively inaccessible in developing nations. The companies that patent genes in wealthy and developing nations influence health care in a way that ignores the lack of resources in poorer countries.

Widespread genetic testing would introduce the potential for genetic discrimination. In the United States we have already seen a few cases of insurance companies refusing to cover individuals with an adverse genetic test result. In other cases, employers have discriminated against applicants because of their test results. These scenarios paint a disturbing picture of the future, where genetic makeup could affect access to jobs or other benefits. The possibility that genetic information could one day be used for such purposes must be kept in mind.

Currently, one of the key threats genetic test results pose to society is the potential for exclusion from the workplace. To reduce their liability, employers may keep the genetically susceptible out of workplaces that pose a threat to them, such as industries using hazardous chemicals or radiation. However, if the predictive values of such genetic tests are poor, employers may needlessly exclude as many as 30 per cent of people from the workforce. It remains to be seen whether workplaces will change practices to ensure

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<sup>2</sup> Stewart BW, Kleihues P, editors. World Cancer Report. Lyon: World Health Organization, International Agency for Research on Cancer (IARC) Press, 2003.

their employees are protected from exposure to dangerous substances, or whether they will take the approach of excluding the genetically susceptible from the workplace altogether. More worrisome still is the question of whether workers with a “risky” genetic background will be excluded from compensation if they become ill. Employers may argue the worker knew the risks, because he or she had the genetic test, and accepted the job knowing the work environment would elevate his or her chances of becoming ill.

Aside from discrimination, a huge amount of fear and social stigma may also be generated by identifying people at elevated risk for disease, especially for widely feared diseases like cancer or mental illness. What authorities will do with such genetic information obtained from individuals is another contentious matter. Civil liberty issues arise with the idea of databases containing the genetic makeup of individuals being kept within health services or commercial testing agencies. Legislation is not currently in place in most of the world to address whether this violates an individual’s civil rights. In the UK for example, the police, with the court’s approval, can seek access to a genetic database collected for research purposes, if they assert it is in the public interest. Government has not yet drawn the line between what information seizures are considered to be for public good, and what constitutes an invasion of privacy. More recently, the government has expressed interest in using genetic data to identify and trace individuals in times of crisis.

The possibility exists that projects the public does not agree with will be conducted under the general and innocuous-sounding banner of “medical research.” A notable example of this phenomenon is gene patenting, which may continue without the consent or knowledge of the general public, due to their lack of information and lack of understanding of the consequences. Gene patents have the potential to significantly escalate the future costs of health care. In addition, personal genetic material gathered by testing companies may be later used for studies on criminality or behaviour, which individuals may not have given their consent for, and which they would have found inappropriate.

Another potential use of personal genetic information is in the direct marketing of diet pills, vitamins and medication. One US company already sells genetic tests along with advice on health supplements. A UK company that markets genetic tests originally planned to retain genetic data on their customers and mail them information on products connected to their test result. The issue of how personal genetic data could be used commercially for marketing needs to be addressed.

When considering who benefits most from genetic testing, the biotechnology and pharmaceutical companies—rather than those tested—are near the top of the list. Any company with a patented genetic test has a clear financial incentive to expand the market for that test as widely as possible. It's advantageous for pharmaceutical companies to market their tests to a bigger group of individuals, by creating the impression that many healthy people fall into a high-risk category.

Two major alliances have formed to develop genetic tests for complex common illnesses, such as schizophrenia or heart disease. The first is between Roche, the largest diagnostics company in the world, and deCode genetics. The two have an exclusive deal that uses deCode's data from the population of Iceland to identify genes potentially linked to complex diseases. The other alliance is between Abbott Laboratories, the world's second biggest diagnostics company, and Genset, a French company that is leading the patenting of genomes. Their deal relates to the development and marketing of diagnostic and prognostic testing for common complex diseases. GlaxoSmithKline is also active in developing genetic tests, and has talked openly about their strategy to sell predictive tests to people. The US company Millenium Pharmaceuticals has argued that selling patented genetic tests is a good source of interim revenue for the often lengthy time between the identification of genes involved in disease, and development of tailored drugs. It is disturbing that the regulations governing genetic tests are much less strict than the regulations for the development and marketing of medications.

The US company Myriad Genetics is already generating a profit from their monopoly on the BRCA1 and BRCA2 tests for breast cancer. The company is now marketing the test



to the general population, and their magazine and television advertisements depict women talking about a single relative who had breast cancer. Based on that single occurrence in their family history, the advertisement advises them to get tested and ascertain their genetic risk of developing the disease. This campaign is a clear attempt to expand the market for this test outside of individuals who have a strong family history indicating a high risk of developing cancer. But the predictive value of this test outside high-risk scenarios is far more limited and uncertain. Myriad also advertises a cardio risk test on their website, which claims to test for the presence of a gene linked to hypertension. Myriad obtained their patent on an early study indicating the gene may be linked to hypertension, but subsequent studies have not reinforced the association. The marketing of costly tests based only on early study results is a cause for concern.

UK biotechnology company Sciona has been selling genetic tests with promises of tailoring dietary advice to an individual's genetic makeup. The tests, which were being sold at the High Street Body Shop in London, claimed to determine how much broccoli you should eat and which vitamin supplements you should take. GeneWatch UK has been running a campaign with a British consumer association to have those tests pulled off the market. No direct marketing had been done with the test results Sciona obtained, but they had expressed interest in such a strategy. Sciona has recently bought up a smaller company with patents to hundreds of genes, and they are now developing other genetic tests.

A final company of similar concern is the US-based Great Smokies Diagnostic Laboratory. They produce tests—called Genovations—to assess an individual's genetic risk for developing osteoporosis and heart attacks. These are marketed through alternative health practitioners, who will then advise patients to take particular supplements depending which genes are identified.

Tobacco companies have also invested heavily in research on genetic susceptibility to lung cancer, because any established links might downplay the causative role of cigarettes. This tactic also serves to confuse the public about the causes of lung cancer,

and it would serve the tobacco companies well if smoking cessation messages were targeted only at those with a high risk of developing lung cancer.

Fast food companies are not yet promoting research on the genetic causes of obesity, but there are some food companies developing genetically modified foods tailored to your genetic makeup. Similarly, the nuclear industry has funded work examining genetic susceptibility to radiation damage in the workplace. Such sponsored research raises fears that companies are keen to blame genes for related diseases rather than having their business subjected to external controls.

While it is still unclear what the British government's reaction to regulating genetic tests will be, GeneWatch and a UK consumer association have lobbied cosmetic companies, supermarkets, and pharmacies to approach these products with caution. In turn, retailers have expressed concern about selling products with little scientific proof of their efficacy or predictive value.

Genetic testing has the potential to be useful, but only when used in appropriate circumstances. There is a push, in the interest of turning a profit, to expand genetic testing to the general population. To counteract this trend, regulations and controls must be put in place. Society needs to refute claims that genes will determine everything about an individual's future, from susceptibility to disease to the sort of person they will be. It must be made clear to the public that while genes do play a role in disease, they are not often the dominant factor in health outcomes. We need to advocate for population-based preventive strategies and policies, which are more broadly effective than a genetic approach to prevention. A good start would be the reallocation of resources currently directed at genetic studies back into population-based strategies.

A body that regulates and assesses the usefulness of each genetic test is also needed. This point is currently a contentious one in the UK. Some people take the position that citizens should have a right to spend money on rubbish if they wish to. This neglects the harm that may result, and the costs to the health care system from people who may ask for

monitoring tests because they believe they are at higher risk. In addition to a regulator, the administration of these tests should be done under medical supervision. Assessing the risks of disease is more accurately done with knowledge of family history, and the advice of a genetic counsellor. Buying a test in the Body Shop will not result in an informed evaluation of medical risks. Finally, legislation is needed to control the collection, storage, and use of genetic information, and to protect against genetic discrimination, particularly by employers and insurance companies.

## Genetics in medicine – distilling the hope from the hype

Peter H. Byers

Today we are in the Iron Age of the genetics revolution. We know where we've been, but it's difficult to see where we're going with the technology and knowledge we've acquired. Compared to poverty and pollution, genetics play a small role in many of the common diseases we are faced with today. But should we manage to rid ourselves of those factors, the role of genetics will become increasingly important in tackling disease.

One landmark in genetics and medicine was the O.J. Simpson trial, because it introduced the importance of forensics to the general public. Another milestone was the identification of single-gene predisposition in individuals to breast cancer in some families, which gave us the idea that some people, and not just those in such dominant families, may carry a genetic marker indicating a risk of disease. Of equal impact were the discoveries of genes that similarly predispose individuals to colon cancer or dementia. Finally, the Human Genome Project is highly influential in genetics and medicine because it has given us a draft of the entire human DNA sequence.

The O.J. Simpson trial dominated the media for months, not just in the United States and Canada, but also in non-English-speaking countries where American football is seen. Not only did the trial hold the attention of the public, it also introduced the language of genetics into public discourse. The public was bombarded with evidence about allele frequency, and the press in turn was forced to disseminate the background knowledge for understanding the significance of this information. The thought of cab drivers talking about alleles, gene frequencies, and genetic predispositions previous to this trial was unimaginable, but the media coverage of the case considerably increased the general public's understanding of genetics. Genetics was frequently explained in newspapers and in broadcast media coverage of the trial, which for the first time gave the general public an understanding of population genetics.

In the case of breast cancer, it was found that perhaps ten per cent of women with breast cancer had a dominantly inherited predisposition to developing the disease. This mobilized a network of both lay people and professionals to seek out the genes responsible for this pattern of inheritance. Thanks to the cooperation of communities and researchers, large networks of funding and involvement were created. This research led to the identification of three genes implicated in the disease: BRCA1, BRCA2, and p10. The identification of these genes generated high hopes for the role of predictive testing in preventing breast cancer. However, it must be emphasized that predictive genetic tests are difficult to correlate with actual disease manifestation.

Like BRCA1, BRCA2, and p10, the discovery of genes linked to colon cancer was also pivotal. Genes were identified for familial adenomatous polyposis and hereditary nonpolyposis, and their discovery led to the development of predictive testing and genetic counselling of affected families. However, even if such testing identifies individuals with genotypes of interest, it is not yet known whether individuals outside the context of affected families would have a similarly high risk. It's also not clear if those who test positive for an increased risk can reasonably change their behaviour to ward off the disease.

The Human Genome Project is unquestionably the most significant biological experiment of our scientific history. It's extraordinary that four nucleotides strung together in sequences can determine how we look, aspects of who we are, and our course of development. The genome makes us human, and being human comes with both weaknesses and talents. The genome project has also been responsible for enormous technical advances that can now be applied to medicine, advances that have both immediate and future applications.

However, with the completion of the sequence came the public's expectation of an immediate understanding of what that sequence means. The promise of an instant application for the gathered information is one of the biggest faults of the Human Genome Project. In a society with short attention spans tuned into three-second television

gaps, there are immediate expectations for these scientific findings, findings whose applications in reality will take centuries rather than minutes to play out. We must consider the big picture, and proceed knowing this data will be useful 20, 30 and 50 years into the future.

These landmark events, especially the Human Genome Project, have changed the social, medical, political, legal, and ethical landscapes in which medicine operates. Unlike past ventures such as the Manhattan Project, the genome project is one of few scientific programs with a built-in arm to examine the ethical, legal, and social implications of the findings. Some are concerned that only five per cent of the project's resources are set aside to look at these considerations, but the very fact that the implications are being considered is an advance over past bio-science projects.

So where do we stand in the timeline of our genetic revolution? It's now half a century since we discovered the structure of DNA, and 18 years since the invention of the polymerase chain reaction, which allows us to quickly synthesize large amounts of DNA. Fourteen years after the decision to sequence the human genome, we are now awaiting the announcement of the "finished" version, which is set for April 25, 2003, exactly 50 years after the discovery of the structure of DNA. However, we are still a few years away from the verified genome sequence. Piecing it together is a complex procedure, and each new draft posted on the University of California at Santa Cruz database has significant changes and rearrangements from the last one. We are at least a decade away from a reasonable count of all the proteins our body makes, and possibly a century or more away from a comprehensive understanding of the genome.

Researchers estimate we have approximately 35,000 genes—sufficient to encode over 100,000 different proteins, given varying translation. We have found the functions of over 500 genes, have educated guesses about the functions of 12,000 more, and are clueless about what the remainder of the genes in the genome code for. We've identified less than five per cent of the total number of known genes in which mutations result in identifiable phenotypes that we call diseases. Most of these genes appear with a

frequency of less than one in 50 in the general population. Some genes appear more frequently in particular populations, like the gene for sickle cell anaemia, which is present in one out of eight people in certain regions of Africa. However, protein-coding genes only make up three per cent of the genome, and our understanding of the function of the remaining 97 per cent of the genome is meagre. It is clear the non-coding portion has a purpose, as we have found regulatory elements there we were not anticipating.

The way we use the genetic information we have gathered varies greatly between different settings. In paediatric medicine, genetic disorders account for 50 per cent of hospital admissions, and these patients usually receive acute care as inpatients. In general medicine, 50 per cent of hospital admissions are caused by genetic diseases, but in the form of chronic adult-onset conditions. While children are generally admitted to hospital for metabolic disorders, chromosome rearrangements and dysmorphic syndromes, adults are afflicted with cancer, cardiac and vascular disease, and dementia.

We're seeing two major changes in clinical medicine as a result of our increasing understanding of genetics. First, many individuals now survive genetic paediatric conditions, and metabolic disorders are consequently becoming more common in the general population. Secondly, pre-natal diagnosis and risk assessment is an exponentially growing industry. In the past four years, our clinics in Seattle have gone from annually counselling two families about genetic risks for cancer, to 500. Many more people are seeking information about their genetic predisposition to disease than previously.

We have long had a few effective models of genetic intervention, such as newborn screening for phenylketonuria and hyperthyroidism. These tests are cheap and simple to perform, independent of specific mutations, and treatments exist for both diseases. Phenylketonuria can be controlled through diet, and hyperthyroidism through replacement. However, interventions for other genetic disorders are less certain to be successful.

One of the diseases I deal with is Marfan syndrome, which is a dominantly inherited genetic disorder where patients are at risk for an aortic dissection. The currently accepted mode of intervention is to delay the progression of aortic tearing with the use of beta-adrenergic blockers, which decrease heart rate and blood pressure, and are also used in the treatment of angina and hypertension. The prescribed treatment of Marfan syndrome is independent of the genetic mutation, and has been adopted because there is tremendous pressure from families and physicians to treat these patients. However, the efficacy of the treatment is questionable, and all Marfan patients must take the medications to achieve benefits that may only accrue in a few. But the medications are relatively inexpensive, and adverse effects from them are uncommon. The genetic test may help with the identification and clarification of the complications of this disease, and provide a confirmed sample group for testing possible cures.

In adults, models of genetic intervention now include oophorectomies in women with BRCA1 and BRCA2 mutations. As Rebbeck and colleagues discussed in the *New England Journal of Medicine* in 2002,<sup>3</sup> either mutation indicates a woman has a higher risk of developing ovarian cancer compared to the background population. The study followed 551 women with either gene, 259 of whom had oophorectomies, and 292 who did not. Of the 259 who had their ovaries removed, only eight developed cancer within eight years. However, many more women in the group that had retained their ovaries developed cancer. This strategy is beneficial to the individual, but costly from society's point of view. Each individual test is expensive, and so would not be a cost-effective method of prevention if applied throughout the population, rather than just to those with a family history of breast and ovarian cancer.

Another disease with a successful but high-cost intervention is Gaucher disease, where enzyme replacement therapy results in an improvement of symptoms. Similarly, an expensive treatment for severe combined immunodeficiency is retroviral gene replacement. However, treatments like this are currently shrouded in controversy, given the potential for the development of leukemia-like symptoms after receiving the retroviral

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<sup>3</sup> Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, van't Veer L, Garber JE, et al. Prophylactic Oophorectomy in Carriers of BRCA1 or BRCA2 Mutations. *N Engl J Med* 2002;346(21):1616-1622.



therapy. This reminds us that these experimental treatments are not without costs and potential harms.

As for the immediate future of genetics, there will likely be the development of technologies that allow the cheap and rapid sequencing of individual genomes, thanks to the success of the Human Genome Project. There is a strategy underway to develop chip-based DNA sequencing, where the entire genome can be arrayed on a small area of a slide. A genome could be stored, and the protein-encoding parts of interest in the genome could be re-sequenced with ease.

In the next five to ten years, there is likely to be the rapid identification of low-frequency, high-penetrance genetic diseases, and we will slowly begin to understand the function of the 20,000 genes we currently know little about. Starting with a big wave in the next few years, the number of genes in which mutations have been identified will likely increase from 1500 to around 35,000. We will owe this explosion to the advancement of technology, which has now made it possible to screen for genetic mutations in individuals or families within weeks or months, rather than years.

There is a great thrust to identify genes involved in hypertension, vascular disease, schizophrenia, other mental disorders, and diabetes, and this will be reflected through the funding available for hunting down these genes. However, I'm not convinced of the success of such hunts. Many current models for disease may be inaccurate, and the presumed genetic causes may be oversimplified or wrong. While many agree that disease is often the result of multiple gene loci, all work to date has identified only single-gene disorders. It may be that diseases result from a significant set of hidden genes that are difficult to find, because they don't occur with high frequency in the population. For example, diabetes might be caused by mutations in gene A in some people, gene B in another group of individuals, and gene C in yet others. In addition, some disorders may be caused by an interaction between two or more genes. In that case, it may take two, three, four, or five variants to account for one specific phenotype. These models will have an enormous impact on future strategies for treating disease, because treatment of

disorders caused by one genetic mutation takes once course of action while multiple-gene diseases may require another.

Even once a gene has been identified, our success in progressing from gene identification to understanding the mechanism of disease has been poor. Furthermore, our track record of translating genetic information into a course of treatment has been appalling. Forty years have passed since the identification of the cause of sickle cell anaemia, yet few, if any treatments for it depend on a patient's genetic mutation.

In the long term, we should anticipate many surprises in our growing genetic knowledge. Past revelations have included the discovery of introns 20 years ago, which told us our genetic coding sequences are not contiguous. Planning genetic interventions and strategies without knowing more about the genome puts us at the mercy of luck. The need to keep genetic investigation and its applications in the public theatre is vital – the public's input is critical when examining the ethical implications of genetic technologies. For example, the decision by the United States government to patent genes without broad public consultation was one of the worst decisions ever made. It was done because universities needed funding to support research and develop the technology, and to obtain those funds they had to partner with private industry. Efforts to combat a similar move in Canada and the European Union are commendable.

But patent issues will probably disappear off the radar screen in the next 20 years—as the patents expire. This point is not optimistic, because the next 20 years will be full of heated debate and possibly perverse consequences of patenting (such as secrecy in science or lack of access to monopoly-priced diagnostics or treatments). Given the topic has entered the public domain, it will be more difficult, but not impossible, to continue patenting genes. The debate over gene patents will raise issues of privacy, and bring into question our societal role in handling genetic data. The idea of genetic testing as a predictive tool may become far more accepted than it currently is. The creation of universal health care in the United States seems inevitable, and that may catalyze greater public acceptance of genetic tests.

Also, the choices of which disorders we intervene in are likely to change over time. In the future, employers may screen potential workers for susceptibility to occupational exposures for their protection. However, this situation is complicated by the fact that screening workers can be discriminatory against those with certain a genetic makeup.

On a global scale, genetics and genetic interventions are low on the list of priorities, except in industrialized nations. Yet if more prevalent causes of disease like poverty, epidemics, pollution, and accidents are reduced, the role of genetics in disease will become increasingly important. We cannot predict what diseases will vex us most in the future, for 100 years ago we had no inkling of the future significance of cancer or dementia in society. One hundred years ago infectious disease, accidents, and environmental hazards were our most pressing problems. It would have been foolish in the past to disseminate antibiotics to the masses at a time when there were open sewers. Similarly, we don't yet have enough of a command of genetics to be able to apply it to the population at large. Like the emergence of cancer, dementia, and heart disease, the importance of genetics will rise, and we will eventually bring to the table a better understanding of how our individual and collective genomes influence these diseases.

## Patent pressures: balancing innovation policy with other social agendas

Tim Caulfield

The topic I'm going to discuss has already emerged to some degree in the discussions today: commercialization, and its impact on health care policy in Canada, and around the world. To a large degree, I'm going to focus on issues related to patents, but we have to remember that patents are just part of a broader commercialization agenda. First, I'll discuss some of the broad social concerns that have been associated with human gene patents. Then I will touch on the reality of gene patenting in Canada and around the world, and what have been characterized as new concerns, many of which are related to health policy issues. These concerns really aren't new, but have been articulated from the beginning of the Human Genome Project and are now starting to have a practical impact. I'm referring to such things as the Myriad Genetics controversy. Unfortunately, you have to have practical concerns to actually push a policy response forward. These practical concerns are going to necessitate some type of harmonization of policy in Canada and around the world, and I have a few recommendations related to this.

Even before the beginning of the Human Genome Project, concerns were expressed about the patenting of human genetic material. I will not critique any of these concerns here (although I do have views on each one of them), but I will briefly discuss them to set the broader context. There is a very extensive literature on the implications of patenting, not only from people in the legal community, but also from many other groups in society. One of the many concerns raised is that the idea of a human gene patent is an infringement on the concept of human dignity. This is clearly a very broad concept, but it is pervasive in all the literature. Essentially, the concern is that owning a patent on something so important to who we are as human beings undermines individual identity and human dignity.

Another issue has been bio-piracy. This idea, which has been raised by people like Jeremy Rifkin and other technology critics, is that gene patents facilitate the ability of First World nations to go to developing nations and basically pirate their biological resources. To this we can add another somewhat obvious broad social concern—the idea that patenting leads to an inappropriate classification of life. Many other general concerns have been articulated and they have been played out both in the academic literature and to some degree in the popular press.

In addition to these concerns, a more practical complaint about gene patents is that they skew the direction of university research. The criticism is that because patents are so inherently associated with the commercialization process, they lead universities away from basic research and towards research that is capable of being patented and commercialized. In fact, there is some evidence that this is happening—most of the research I'm aware of has happened in the US, by people like David Blumenthal and Mildred Cho.

There is also the worry that patenting promotes secrecy—an issue in science because it is built on knowledge freely shared, not kept secret. One of the major reasons for societies to allow patenting is that in the longer term it facilitates the dissemination of information associated with the novel invention, so the community as a whole can benefit. Patents therefore necessitate or require disclosure of information. However, in the shorter term it has been documented that patenting does promote secrecy. Researchers have to be very careful about disclosing information before a patent has been filed. There is some evidence that this has affected dissemination of new information, in particular in the field of genetics. Lastly, there is Andy Collins' idea that the human genome is actually a finite resource, and researchers may not want to do work in the area because of concerns that they are infringing on patents. Again there is some evidence to suggest this may be happening.

Practical concerns like these three motivate many policy makers, and prompt such views as that expressed by Prime Minister Blair and President Clinton at the announcement of

the completion of the human genome sequence that “the genome belongs to all.” Yet the next day, Clinton said that they were not implying that it was wrong to be able to patent, just that spiritually it’s wrong. While not rejecting patenting outright, these concerns did lead to some practical effects in the US. The patent office was asked to apply the patent criteria more carefully and more stringently in the process of reviewing gene patents, particularly with regard to what is known as the utility requirement.

So we’ve had broad concerns articulated about patents for a long time, with a minor degree of formal policy response. At an international level, statements on these issues exist—for example, UNESCO’s position is that the human genome in its natural state shall not give rise to financial gain. Technically speaking from a patent law perspective, you cannot patent anything in its natural state, so this statement was more rhetoric than reality. Nevertheless, the response from the international community was similar in attitude. Many professional organizations have also spoken out against the idea of gene patents—the American College of Medical Genetics, for example, has made a formal statement declaring that “genes and their mutations are naturally occurring substances that should not be patented.”<sup>4</sup> In addition, many non-governmental organizations, such as the Council for Responsible Genetics, have come out against the idea of gene patenting. All these concerns have been articulated, and in legal circles have led to a vigorous controversy with very strong policy statements on both sides of the debate. While there were minor policy responses, in reality, there has never been any question that since the late 1980s it has been possible to patent human genetic material. In my view, this will not change.

The permissibility of gene patenting started with the United States Supreme Court decision in the case of *Diamond v. Chakrabarti*, over the patenting of an oil-eating bacterium. Some people have argued that this case is the beginning of the modern era of biotechnology, and also the symbolic beginning of the idea of “owning life” for the purposes of commercialization. If something can be characterized as new, not obvious, and useful, it can be patented. In the US, if these criteria are met a patent is issued. In the

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<sup>4</sup> American College of Medical Genetics. Position Statement on Gene Patents and Accessibility of Gene Testing. *Genet Med* 1999;1:237.

world of patent law—largely as a consequence of precedents set by patents relating to synthetic and naturally occurring chemicals, and the *Diamond v Chakrabarti* case—if you can find a naturally occurring substance or entity and you can purify it through human innovation, then you can patent the result. This is the sort of jurisprudence in the world’s patent laws that allowed the original gene patents to happen, and something that was started in the US. A recent issue of *Science* had an article outlining measures of the US patent office that are leading to a broadening of traditional patent criteria, and I think that’s an accurate assessment of what their role has been.

The reality of gene patents is that by 2001—as shown in work by Robert Cook-Deegan—in the US alone there were over 25,000 DNA patents.<sup>5</sup> There are currently about 35,000. Nevertheless, since this was published in *Science* in early 2001, the rate of patenting has declined somewhat, a result of the more stringent patent review around utility requirements. A gene patent has to have some clear utility, a requirement meant to prevent the patenting of such things as expressed sequence tags and single nucleotide polymorphisms. But it appears that patent lawyers have found ways to get around these requirements, as the numbers of patents are on the rise again.

The other important aspect to be considered, particularly from a Canadian perspective, is where inventors file for patents. Inventors usually want a patent in the European Union, Japan, and especially in the US because that’s where all the major capital is. It is also where the biotechnology industry is thriving—approximately 70% of biotech activity is in the US. As a consequence, US gene patent policy has a tremendous impact on what happens in other countries. The Canadian government has to consider this context in setting commercialization policy, innovation policy, and how they are going to respond to the issues that have been raised about patents.

Why haven’t those concerns had a real policy impact? First of all, there are some well-articulated justifications for patents. From the time of Thomas Jefferson, governments created patents to stimulate innovation and compel the disclosure of useful information.

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<sup>5</sup> Cook-Deegan RM, McCormack SJ. Patents, Secrecy, and DNA. *Science* 2001;293(5528):217.

The purpose of patents was for the greater good of society, to stimulate innovation. However, in the new world of modern biology, a growing number of people like Rebecca Eisenberg have argued that there is little evidence in the context of biotechnology that patents do stimulate innovation, or contribute to the greater good. It is difficult to document this, as the best way to assess consequences would be to remove patents from an area. However, the perception of patents as beneficial is embedded in the thinking of commercial institutions and governments and, increasingly, in the thinking of research institutions.

The idea that patents compel the disclosure of useful information is important. A colleague and I have argued that if we remove patents there is a strong possibility that there would actually be more secrecy. If patents were removed, researchers would rely instead on trade secrets, and companies would have to be more aggressive in order to carve out a sector of the market share. Patents stimulate investment by giving a sense of security to investors and companies. This is particularly important in the area of biotechnology where investment is needed early on in the process of research and innovation, and the actual commercializable product is possibly ten years away. Investors and companies want to know that they are likely to see a return on their investment, and need monopoly control so that others will not copy their product.

Another central reason why these issues have not led to policy change is that patent law is simply not structured to handle social concerns. As outlined, in the US and Canada patent application is very much based on an amoral legal framework. The system is designed (and frequently analyzed) through the lens of patent criteria. All other social or ethical concerns are left for the market or other regulatory regimes to deal with. The position is that we should not worry about social conflict regarding the granting of patents. When you consider how this view ties into a liberal tradition and a liberal democracy, you see why this argument has had a lot of weight. The objective is to say to an inventor, "Here's your invention, and as a state we are going to allow democracy to determine the good or bad invention, whether it is socially worthwhile or morally reprehensible. That's up to the market." I do not agree with this view, but it is an argument that still carries a lot of



weight and force. In contrast to North America, other jurisdictions, like Europe, *do* have a morality code (*ordre publique*), which is a provision to allow policy concerns into the assessment of patents. However, perhaps not surprisingly, this mechanism has not really been used, and certainly has not been used aggressively in the context of gene patents. It has had a greater impact in the context of stem cell technology and cloning technology, but we have yet to see how that will evolve.

The reason none of those broad concerns have had a real impact is because of the major interests at play in what has been called the biotech century. The hyperbole around the biotech century lauds the idea that patents—not just in the context of biotechnology, but patents in general—will generate what has been called the “new economy”. The idea of this new economy—and I think this is probably true in the western world—sees patents or intellectual property emerging as a dominant form of property. We are moving beyond land ownership, the ownership of cattle, the ownership of industrial concepts, to a world where the ownership of ideas, or control over ideas and inventions, is promoted as the dominant form of property. To put it in Anne McCormack’s words, no other sector of the economy depends as much on strong patent protection as the biotech industry. Scholars such as Juan Enriquez of Harvard and Joseph Strauss from Germany have gone so far as to use intellectual property to measure the economic worth of countries. They compare how regions patent in order to weigh and to measure the economic potential of an area. These views are impinging on the academic sector as well and universities in Canada do the same thing. For example, the University of Alberta is always trying to catch up with the University of British Columbia and see how they are patenting, and work towards making their commercialization of research more successful.

As a result of this new economic thought, governments and universities are embracing intellectual property. The nature of research is changing, with growing ties between academia and industry. Some argue that those ties were always there and academia has always had some type of external pressure on it, be it Cold War paranoia, or the explicit war agenda of the Manhattan Project. Nevertheless, it is fair to say that no other major scientific initiative has been so closely tied to commercial interests as the Human

Genome Project. In fact, we have this strange phenomenon where publicly funded research councils such as the Canadian Institutes of Health Research (CIHR), Genome Canada, and the National Centres of Excellence, actually have in their mandate—to quote from the CIHR—“to encourage innovation, facilitate the commercialization of health research and promote economic development.” That is the explicit mandate of our publicly funded basic research institution. It exemplifies the change in attitudes, as it is something that would have been shocking in the 1960’s—a publicly funded research body to support research in the public interest having commercialization as a core agenda. Obviously in this new context patents are going to be encouraged, and are being encouraged by all levels of government. Looking at statements by the Minister of Industry, we see the embracing of the idea that science is going to be a driver of the Canadian economy. Biotechnology is being promoted and supported by governments in Canada as an important sector of the economy. In the US, university licensing agreements bring in billions of dollars.

In spite of all this, I think emerging controversies, which I’ve touched on in this talk, are challenging this accepted view. The impact of gene patents on health policies, particularly with regard to the Myriad case, is a very good example. We have Myriad trying to enforce their BRCA gene patents, with the provinces fighting Myriad’s case because of the unaffordable costs for the publicly-supported health care system, and resulting limitation in access. We have politicians such as Premier Harris explicitly speaking out against gene patenting. There has been a similar response in Europe. We have in Canada a paradoxical policy tension. Governments and universities are explicitly promoting gene patenting, which then increases the costs of the health care systems those same governments have to pay for. Ironically, Myriad is doing exactly what many governments are encouraging their researchers to do—that is, commercialize. This policy arena will inevitably get a lot more complicated if and when pharmacogenetics comes online, and if and when genetic multiplex testing becomes available.

The final topic I want to mention is the idea that owning of a gene somehow leads to the complete ownership of a disease. Complete ownership does create the possibility of a

captured market, and the likelihood of promotion of a market-driven concept of disease and disability. It could lead to a narrowing of the definition of normalcy as health care markets are inappropriately expanded. There actually is some evidence that this is occurring, and there are examples of damaging impacts on access to services. It is not inherently evil for governments to promote commercialization. Nevertheless, we have got to recognize the policy paradox. We have to understand that we live in a market economy, for better or worse, but we need more research on the actual benefits and risks of patents. Despite the strong perception of the benefits of patents, a lot of the purported gains are simply not there. We urgently need to find out what in practice are good and bad about patents. We need to introduce mediating policy options such as the use of mandatory licensing—this is absolutely necessary. Governments need to retain some control over assets and pricing. In fact, I am leaning toward the idea of considering extending the patent time period if governments were allowed to have control over access and policy. In addition, I think we do need a public policy provision in our Patent Act. I also think we need independent evaluation and regulation of genetic tests and gene products. Lastly—and I think this is tremendously important—we need strong, publicly funded health research that does *not* require a commercialization element. There are many health questions to be asked that do not require a saleable product as the answer. Without this balance in portfolios of research, we are going to lose the credibility of the entire science enterprise and that would be one of the greatest losses of all.

## Where there's a web, there's a way: commercial genetic testing and the Internet

Bryn Williams-Jones

In this conference, we've heard a lot about the interface between science and public opinion, and whether or not science may be racing ahead of the social, ethical and policy debate. Part of the aim of this talk is to think about what would constitute a closer interaction between these two, particularly given the public perception that scientific research in university labs and in the commercial sector seems to be independent of social or ethical forethought.

With the rapid development of the Internet over the last ten years, buzzwords such as 'e-commerce' and 'e-health' are gaining prominence, with the promise that the online world will revolutionize the way work is done. Increasingly, Canadians, Europeans, and Americans are shopping online at Amazon.com and other web retailers for books, the latest CDs, or international holidays. But people are also looking for health care information—information about particular diseases, drug reactions and the best drug for their condition. Using the Internet as a resource to help take control of their health care, patients are going to their physicians with stacks of computer printouts and particular information about their conditions. Alongside information gathering, some people are also beginning to purchase health care products and services online. Nevertheless, health information remains the primary focus of health-related searches on the Internet, in part because of fears by consumers about their information privacy (i.e. credit card information) and the safety of medications purchased online. Health information web sites have proliferated, some providing a range of material on health in general, including information about genetics.

The one area in which e-health companies seem to be marketing products effectively is in online medical pharmacies that provide low-cost prescription drugs with, and sometimes

without, a prescription. The Internet allows people to access a range of services that may not have been available to them within their own health care system, but it also makes it very difficult to regulate corporate behaviour or enforce any sort of quality control, especially when the company may be outside local jurisdiction. The focus of this paper will be on companies such as Sciona, which use the Internet to market genetics services. In particular, I'm interested in exploring how genetic testing companies use the Internet as a vehicle, a mechanism to market their services.

In Canada and Europe, genetic testing has for the most part been available to people through the public health care system. A result of this is restrictive entry criteria that limit access to testing—for example, BRCA testing is not offered to the whole population because it would be both inaccurate and cost-prohibitive. Instead, testing is offered to those people who meet pre-defined criteria (supported by clinical and epidemiological evidence) that determine them to be most likely to benefit from the service and obtain useful clinical information. But with a developing international market for commercial services, facilitated by growing access to the Internet—Internet cafés abound, and growing numbers of people have computers in their homes—individuals can find genetic services online and can then decide whether they want to purchase them.

The basic technologies underpinning DNA testing are becoming simpler and cheaper genetic testing services are increasingly becoming available. But it is still unclear what the efficacy and utility of some of these tests are, and whether or not they really will be useful to the general consumer public or only to very specific populations. This uncertainty raises important concerns about how these genetic tests are marketed by companies. Obviously companies will want as large a market as possible—a very small market will be unlikely to bring in enough revenue to recompense the significant capital investment in the research, the patent process, and the product development.

I did a study<sup>6</sup> to assess how easy it would be for members of the general public to gain information about and access to genetic testing. I conducted a simple web search in 1999

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<sup>6</sup> Williams-Jones B. Re-framing the discussion: commercial genetic testing in Canada. *Health Law J* 1999;7:49-67.

(which I replicated in 2001), looking for a few key words (‘commercial genetic testing’), and found very little change in the number of websites for companies offering genetic services. The focus of the majority of online companies selling genetic services commercially—and there were literally hundreds of these—was on testing for paternity, forensics, and immigration. Increasingly, we are also seeing companies offering pharmacogenetics testing, where patients are screened for a range of drug targets to see whether or not they would have a positive or negative reaction to these medications. The numbers keep changing as companies develop, change the way they market, or go out of business. Companies may also change the way they do their marketing based on political pressure. For example, a review of Sciona’s website shows the company has backtracked, so that they no longer seem to be offering direct-to-consumer (DTC) testing for genetics and dietary information. This is a reversal in policy based in part on a review by the Human Genetics Commission in the UK that questioned the accuracy of their marketing claims and testing methods.

In contrast, the number of companies selling commercial genetic testing for adult onset or hereditary conditions was very small—about a dozen companies—and only a handful of these were selling DTC testing. By and large, most of them only made testing available to consumers if the services were purchased through a medical practitioner. Patients as consumers were required to visit their GP and request the test, having the GP sign off and purchase the test for the patient. Interestingly, a review of these company websites found only a small percentage had privacy policy statements. These varied from the minimum level of “we will keep your information private” to having detailed privacy statements about how the company would protect the consumer’s information and who would have access. Only a few companies provided counselling regarding the test results, however. Myriad Genetics is an example—they do not provide counselling directly, but they hope that patients will receive counselling through their physicians (who are required to order the test). Myriad goes a step further and makes substantial information available online—targeted towards both the physician and the patient—about the basics of genetics, and risks of breast cancer or colorectal cancer, etc.

Strictly speaking, Myriad is not an Internet or an e-health company, but they are using the Internet as a vehicle to make information available and as part of a larger public marketing campaign for their *BRCA*Analysis test for hereditary breast cancer. This test was initially marketed in early 1996, but only really took off in the last few years. Myriad essentially controls the US market for BRCA testing but has been much less effective at doing so in Canada, Europe, or the UK. Part of this failure relates to insufficient consideration of the differences in health care systems in Canada, Europe, and the US, and to how the test was marketed (direct to consumers and in opposition to public health care providers).

There were also problems with the way the BRCA patents were implemented. Patents provide monopoly protection, which fundamentally goes against the notion of free-market economies. However, part of the purpose of granting such monopolies is to stimulate innovation and economic development. But we have to think about whether or not patents are actually doing this work successfully in the case of genes. A very significant public investment supported the research to discover and sequence the BRCA genes, but then a private company appears to get to own the results. There is a potential for patents to hinder research, by blocking upstream access to basic genes or research tools, thus preventing or hindering downstream research. There has been substantial debate around the patenting of the polymerase chain reaction, because the owners of the patent have been charging unreasonable license fees. Similarly in the case of BRCA, there is growing concern about Myriad's behaviour with regard to licensing of the tests, and its control of testing methods more generally. For example, Myriad has attempted to stop French laboratories from using a more complex testing method, and demanded that they send all BRCA testing to Myriad for analysis. However, recent developments with a company in Malta are shifting the patent dispute. This company is arguing that they can legitimately offer competing tests without violating any of Myriad's patents, because Malta is not a signatory to the EU patent system. So this company is planning to set up a competing market, and offer their services widely. Other issues to bear in mind are the fact that Myriad is a company that in 2001 made \$45 million but was still \$7 million in the red. Negative public reaction to Myriad's strong-arm tactics, alongside an expensive

response to legal challenges from France and other European countries, could potentially bankrupt the company.

So what is the place of direct-to-consumer testing? In most cases, as I've said, testing is marketed through a physician, so it is not strictly speaking direct-to-consumer. Nevertheless, in a fee-for-service health care system such as Canada's, patients can shop around to find a physician who will sign the request for the test they want, because ultimately it is the patient paying for the test. Some level of counselling is usually involved as a means of avoiding liability, both on the part of physicians and the company. If a physician is providing information and Myriad backs that up with online resources for both patient and physician, then if the patient is harmed psychologically or emotionally, the liability is distanced from the company because they have done their best to prevent undue harm.

In Canada and in the UK, legislation controls DTC marketing of drugs and medical services as part of broad consumer protection. Not so in the US, where drug ads proliferate in the media. Being right next door and part of shared media enterprises, many Canadians have access to US media and advertising. In the case of the marketing of BRCA testing, this raises issues for Canadians and for the health care system around how to deal with requests for counselling and access to testing. In the face of advertising pushing the importance of obtaining genetic information to avoid the risk of developing breast cancer, how do Canadian health professionals respond to patient demands for testing (and counselling) when this service is not offered locally? Do they simply send their patients on to Myriad? Genetic testing may be drifting outside of the medical clinics and into the consumer setting. People may choose privately paid genetic testing for a range of reasons that may not be clinically defined. So it is also important to be thinking about the appropriate role for clinicians. Should they be telling people they will not sign for them to have the test because it is not going to be useful? If patients have C\$3800 to spend, can access the testing privately, and wish to for their own reasons, what position should physicians take? These types of issues have to be weighed and thought out.



There is a great deal of animosity in the academic community that does social and ethical analysis of genetics and health care about any sort of interaction with the commercial sector—such interaction is seen as harmful. However, if we think about the way health care has developed, there has likely always been involvement with the commercial sector. For example, pharmaceutical companies have worked with scientists and researchers to develop new products. Clearly, however, there will be very real concerns about conflict of interest, manipulation, or exploitation. The challenge is how to engage with industry in an effective manner that does not result in submission to economic or industry agendas. Given the rapidly changing nature of marketing in light of developments such as the Internet, this will require very serious consideration.

Returning to Myriad's BRCA media campaign, the company is positioning itself as providing a public awareness service in support of Cancer Awareness Month. The overt rationale is the need to inform consumers about the company's products, so that consumers can make "informed choices". This is reasonable to an extent, but this is a situation in which there is only one company and no competitors. So a consumer's choice is basically whether or not to buy the test (if they can afford to). There is no option to choose from a range of competing products, as would be the case in a shopping centre or a grocery store, which therefore undermines the economic ideal of market forces pushing toward better product information. Since the information is provided by the company that stands to benefit from increased test purchases, the information may not be objective and balanced. One of the real concerns, then, is going to be determining how to obtain balanced information so consumers really can make informed choices. There is an urgent and clear need for ongoing basic health research that is not directly involved with the commercial sector. Ongoing objective research into disease aetiology, epidemiology, and test accuracy is essential, but so too is the translation of this scientific information into the public forum to make it as widely accessible to citizens as commercial information is. Greater efforts must be supported by publicly-funded organizations for scientists and clinicians to work with the media and public action groups to disseminate an alternative set of information so that it is not the commercial sector alone (or their lay "front" organizations) providing information about the products and services they wish to sell.

Another issue, specifically around the Internet and direct consumer access, is consumer privacy. One of the drivers for DTC access is privacy and control—by purchasing a test from a company, consumers can learn their risk or health status, but avoid the health care sector or the insurance industry finding out. Yet this benefit of controlling personal information also comes with some risks. Internet-based access raises a set of particular issues related to security and hacking. A 17-year-old hacker would not likely be interested in breaking into a genetic testing company's website and database—it lacks the glamour of breaking into the Department of Defence. But if one considers the role of competitive market forces, a company might consider it worthwhile to hire that 17-year-old hacker to crack its competitor's database, to gain some competitive advantage. We already have this type of industrial espionage in other sectors.

Also of concern is the kind of privacy protection put in place by the genetic testing company itself. The company will obviously be storing consumer's DNA that has been sent in for analysis, but how are these samples stored? Who has access to the samples? Are they being sold to third parties for medical research or other purposes? Do consumers have any say? What happens if the company goes bankrupt? Consumer information becomes part of the company assets, and can be sold off to the next competitor—and consumers have no control of these factors. As my brief web search showed, the policy statements of many of these genetic testing companies are minimal in most cases.

Some sectors of the e-health industry are moving towards implementing better protection, largely in the form of internal self-regulation and voluntary codes of ethics. As it is, consumers still have substantial distrust of e-companies, in large part because of concerns about posting credit card information on the Internet. To be fair, given the standard encryption built into modern web browsers, consumers are much more likely to lose their credit card numbers through everyday use at the gas station or the restaurant than they are on the Internet. But there have been some very noticeable and well-publicized events where large databases of people's credit card information were illegally obtained, and thus it is reasonable to be concerned about similar security breaks in the case of health information. Besides privacy, there are also issues related to quality control and oversight

of testing procedures, that extend even to companies within our country, particularly given cutbacks in the special provincial agencies involved in the regulation of health care technologies. If one then integrates the complexity of small out-of-state biotech companies springing up—some of which may be fly-by-night or fraudulent operations—it becomes a morass for any sort of oversight and regulation.

Some of the necessary regulatory mechanisms for this arena will clearly need to be external or government-sponsored. But market forces can also be powerful behaviour-shaping mechanisms, with companies vying for a squeaky-clean image to build customer trust. Groups such as the First Genetic Trust, which banks donations of DNA for research, provides an extensive policy statement about privacy protection and allows donors to remove their samples at any time, as part of a process of continuous informed consent. The challenge for companies using the Internet to market their services is how to make sure that they look completely legitimate—this is an important market force.

There are also elements within the medical professions, the scientific community, and government that can shape the way commercial entities act. For example, in the case of patents, governments are ultimately responsible for handing out these limited monopolies. If they wished they would be able to use this authority to prescribe particular ethical standards, by threatening to revoke patents in the face of practices that are against the public interest. It may be worth considering, for example, enforcing standards in requirements for the provision of genetic counselling to accompany genetic testing. The utility of counselling may be a topic for debate, but given that it is the standard of care in the medical community for many genetic tests (such as for hereditary breast cancer), it could be argued as a necessary and important condition of commercial provision of testing.

How would one ensure that companies such as Myriad do not simply displace responsibility for counselling to general practitioners, who may not have more than ten minutes to talk with patients and are not trained to provide the sort of counselling and support offered in medical genetics clinics? If the concern is that the public health care

system cannot afford more time for physicians to provide adequate counselling, or employ sufficient genetic counsellors to pick up the load, then it is necessary to consider what type of regulation would be needed to convince companies that they have to provide this. One forceful approach would be for health care regulators to require appropriate standards of counselling for patients (whether counselling is done privately or through the public system), with the threat of removal of a company's license to operate if they do not comply. The flipside would be offering the carrot of greater access to an otherwise inaccessible and large patient community within the public health care system, if companies cooperate. To some extent this is the case with the pharmaceutical industry wanting to have their products listed on provincial drug formularies, because that is where the primary market is in Canada and other countries with universal health care systems.

Consideration of using the public health care system as a moderating force on industry behaviour also raises the issue of justice. One of the concerns about commercial genetic testing and direct-to-consumer access is that some people can afford access to testing while others cannot. The nature of the Canadian health care system is that medically necessary services are provided to all—this means a basic set of services are provided as part of public health insurance, but many other useful services are not. For example, some genetic tests are covered by provincial health insurance plans while others are not. There clearly needs to be more work in basic health services assessment and technology assessment to more rationally evaluate which services are appropriate for public coverage.

However, we still need to be thinking about how commercial forces operate, and how they can influence and change the way a health care system works. There are, for example, many concerns about our relationship with the United States and our membership in the North American Free Trade Agreement. The movement of large commercial health companies from the US into Canada raises the fear of them “hijacking” our health care system. This potential issue has not, as far as I know, really been tested yet, so what we're seeing is a grey area. In British Columbia, for example,

there is the real potential of genetic testing services becoming no longer affordable to the public system because the BRCA patents and licenses have proven too expensive. Myriad is selling the patented test for C\$3800 in contrast to the much cheaper cost of testing in provincial laboratories. The BC government (unlike all the other provincial governments) has however decided to comply with the “cease and desist” letter it received from Myriad and terminate public provision of testing. Might Myriad be the beginning of a chain of other US companies with gene (and other) patents, moving in, and the costs then affecting what health care services are provided in Canada? Such a situation raises the real possibility of even genetic testing services of proven benefit no longer being affordable as part of public health care insurance plans.

To return to e-commerce health service providers, I believe the Internet is going to become a major part of industry and public infrastructure, and integrate into the way we do so many different things. Our challenge then is going to be how to weigh and balance the potential benefits of great access and choice, with the harms that may arise in the interface between private companies and our health care system. We have to realize that we are increasingly dealing with a global marketplace, with companies outside our national jurisdictions. This reality calls for thinking about issues of international regulatory harmonization, and better understanding about how to use market forces to shape commercial behaviour. Importantly, we must move away from naive views of “government good, industry bad”, to understand the complexity of both government and commercial entities. For example, it is government’s own investments in biotechnology and genetic research that have paradoxically led to the likelihood of greater government costs in health care. In understanding the forces and interests at play we are more likely to form better policy. Ideally we would take a broader view of the relevant stakeholder groups and involve the public, not just as lip service, but as active participants in the development of good public policy. I believe there is hope for developing constructive public policy, and I am particularly heartened by the presentations we have heard at this conference.

## From hidden menace to certain cure: direct-to-consumer advertising of genetic tests

Barbara Mintzes

In September 2002, Myriad Genetics launched America's first direct-to-consumer television advertising campaign for genetic tests. There have been print advertisements singing the charms of genetic tests, but Myriad's pilot television campaign, which promoted predictive tests for genes associated with breast and ovarian cancer, was unprecedented.

Print advertisements in magazines and on websites promise genetic tests will bring knowledge, control, and choice over your life. Some of these advertisements include the following quotes: "We can tell you where you are weak genetically"; "A simple new test could save your baby's life"; "Ask, learn and participate in your treatment options. You have a choice"; "There is no stronger antidote for fear than information." These statements allow advertising tactics to be presented in the guise of public information. Addressing their television campaign, Myriad Genetics' president Dr. Gregory Critchfield said, "We think the public needs to know, we think the information needs to come in both directions."

To understand the future consequences of marketing genetic tests, I examined the information gleaned from 20 years of direct-to-consumer advertising (DTCA) of prescription drugs to the United States public. Myriad's argument for providing information as an instrument of power to consumers is similar to the arguments used by pharmaceutical companies about the need for direct-to-consumer drug advertising. The brand-name association, Rx & D, argued to the Romanow Commission that direct-to-consumer advertising of pharmaceuticals should be legalized in Canada: "Informed patients are best able to understand and participate in decision-making regarding management of their conditions," said an Rx & D brief to the commission. What Myriad

and Rx & D's arguments have in common is the use of the word "information" rather than "advertising," because information is a neutral word.

Internationally, the United States and New Zealand are the only countries that allow direct-to-consumer advertising of prescription drugs. The first print adverts appeared in the US in the 1980's, but a proliferation has occurred since the US Food and Drug Administration (FDA) relaxed regulations on broadcast advertising in 1997. Lately, brand-name drug companies in Canada, Europe and Australia have been lobbying governments to make print advertisements legal. A market research company's finding that \$2.51 is earned for every dollar spent on magazine adverts for prescription drugs may signal why advertising is an attractive option for brand-name drug companies. While these profit returns are not necessarily only a direct result of DTCA, there is a strong correlation between the most heavily advertised products, and annual increases in retail spending on those compared to less advertised products.

However, public understanding about the products promoted to them is a cause for concern. A study done in Sacramento by Robert Bell and colleagues at the University of California—Davis showed half the population surveyed thought the FDA pre-approved all drug advertisements.<sup>7</sup> Forty-three per cent believed only completely safe drugs were advertised to the public, and 21 per cent thought only extremely effective drugs were allowed to have advertisements. Twenty-two per cent believed the advertising of drugs with serious side effects was banned. However, all of the above statements are false.

The same University of California group examined the presence or absence of educational information in prescription drug advertisements. While the information they looked for was not required by regulations, certain facts are deemed useful for making informed choices about treatment decisions. In a selection of adverts run in major consumer magazines over a period of ten years, 91 per cent of them did not give any indication of the likelihood of treatment success. Eighty-nine per cent did not indicate how long a person needed to take the medication, and 76 per cent made no mention of

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<sup>7</sup> Bell RA, Kravitz RL, Wilkes MS. Direct-to-consumer prescription drug advertising and the public. *J Gen Intern Med* 1999;14:651-657.

other activities that could help with the condition, such as a healthy diet or exercise. These results are particularly relevant in the dawning age of genetic test advertisements: consumers should know how likely a genetic test will be to provide them with useful information. The public needs to know if the test results will make a difference to the management of their health, and what the future of their condition might be.

There is also evidence that drug advertisements alter the prescribing habits of doctors. A consumer survey by the FDA showed that 18 per cent of people have talked to their doctor about a drug they saw advertised, seven per cent of people have asked their doctor for a particular drug directly, and nearly 70 per cent of those people got a prescription for it. I performed a similar study in Vancouver and Sacramento, examining how many patients asked for drugs they had seen advertised, how many of those patients received the drugs, and how likely physicians were to prescribe such oft-requested drugs to other patients.<sup>8</sup> Patients in Sacramento were found to be more than twice as likely to ask for advertised drugs than Vancouver patients (7.3 per cent of Sacramento patients versus three per cent of Vancouver patients). In both places, 75 per cent of those who asked received the drug they requested. Physicians in both cities said giving the same drug to a patient with a similar condition was possible or unlikely, rather than likely. In addition, only one time out of eight would the physicians have prescribed the same drug as the patient requested if they had not asked for it. This raises questions about the appropriateness of prescribing in response to requests.

Another concern about the expansion of genetic test advertising is the high frequency of violations of the US regulations for prescription drug advertising. While the FDA requires the advertiser to withdraw offending adverts, very few corrections are made to consumers who have seen the adverts. In 1998, 52 per cent, or 17 out of 33 television adverts violated US regulations. The FDA sent out 94 notices of violation for direct-to-consumer advertisements between 1997 and 2001, 48 for broadcast and 46 for print. Most

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<sup>8</sup> Mintzes B, Barer ML, Kravitz RL, Bassett K, Lexchin J, Kazanjian A, et al. How Does Direct-to-Consumer Advertising (DTCA) Affect Prescribing? A Survey in Primary Care Environments With and Without Legal DTCA. *CMAJ* 2003;169(5):405-412.



of the violations cited were for inadequate risk information, exaggerated benefits, and the promotion of unapproved uses for the medication.

One example of an advertisement that was found to be in violation of the FDA regulations was the television commercial for Sarafem. Sarafem is the same drug as Prozac, but comes in a pink pill, and has been approved for the treatment of premenstrual dysphoric dysfunction. The FDA approved the drug with a new name and colour the year before Prozac's patent was due to expire in the US. Sarafem's television advertisement was found to violate regulations because it did not adequately distinguish between normal premenstrual syndrome, and the psychiatric condition of premenstrual dysphoric dysfunction for which the drug had been approved.

There are three types of prescription drug advertisements. The first is a full product advert, which states the name and function of the medication. A second type is the reminder advertisement, which indicates the brand and name of the drug, but not its function. A common reminder advert running in Canada is for Viagra, and shows a man jumping around on his route to work to the song "Good Morning." The last type of advertisement, which may become relevant when genetic test advertisements proliferate, is the help-seeking or disease-oriented advert. In these adverts, the manufacturer does not mention a specific product name, but instead suggests the person visit his or her doctor to get a test or talk about their condition. The market-leading manufacturer of drugs for the condition often produces these advertisements.

An example of a disease-oriented advertisement running in Canada is Pfizer's advert for Lipitor. Running in French and English *Chatelaine* in December 2001, the advert shows the feet of a covered corpse on a gurney with a toe tag. The caption reads, "A simple cholesterol test could have prevented this." While Lipitor falls into a class of drugs that has been shown to reduce mortality in secondary prevention of heart disease, it has not been implicated in primary prevention of mortality in women. The toe tag in the advertisement indicates the corpse is of a 52-year-old woman who is not overweight— an unusual thing to write on a toe tag.

Turning back to genetic testing, Myriad Genetics has just launched their advertising campaign for ovarian/breast cancer predictive tests. Their television advertisement piloted this fall in Denver and Atlanta, and they are also running a series of print adverts in women's magazines such as *Ladies' Home Journal*. Alongside the direct-to-consumer advertisements, Myriad are running a large-scale advertising campaign to doctors, especially in the regions where the television adverts can be seen. Myriad has a sales force of 85, but have contracted with another company for this campaign, thus employing 600 people to promote these tests.

The BC Cancer Agency has set criteria to determine those with an increased risk that justifies testing for genes linked to breast and ovarian cancer. For example, if a woman has one or more cases of breast cancer plus one or more cases of ovarian cancer in her family history, with at least one of those cases being under the age of 50, then she qualifies for the BRCA1 and 2 test. Or if a woman has two or more cases of breast cancer in her family history, with both manifesting under the age of 50, she is also at an elevated risk. However, in Myriad's television advertisement, individual women discuss getting tested after having one family member with cancer. The advertisement sends a vague message about what sort of family history indicates a high risk of developing cancer. In the time provided for the advertisement, Myriad could have indicated there is a particularly high risk for women with family histories including early-onset cases of cancer, and several close family members with breast or ovarian cancer, but it did not do so.

One concern about this advertisement is that it targets a healthy population. By showing women with one affected relative, they may stimulate testing within a population that has a different probability of illness than patients who are tested by the BC Cancer Agency. Testing a lower-risk population raises the question of whether the tests will pick up low penetrance mutations in the genes. A negative test for BRCA1 or BRCA2 does not mean the individual has no genetic mutation that could lead to breast or ovarian cancer. It's unknown whether the inability of these tests to detect low penetrance mutations will change their predictive ability. What the commercial doesn't address is that only seven

per cent of breast cancer cases are primarily genetic in origin.

Another concern about Myriad's advertisement is that it advises women to consult their primary care physician. That same physician is being targeted by another advertising campaign by Myriad. Consulting a family physician about genetic tests is a less informative situation than receiving genetic counselling through a cancer clinic or service. The advertisement mentions medical treatments are available for breast and ovarian cancer, but fails to mention those treatments are often prophylactic mastectomies or oophorectomies. As yet there is no evidence these preventative surgeries reduce mortality, so for Myriad to indicate effective treatments are available is misleading. Finally, the advertisement makes no allusion to the price of the test, which is a steep C\$3800.

The FDA regulations covering Myriad's advertisements are patchy. The BRCA1 and 2 test is categorized as a "home-brew" test, and not a commercialized test. The FDA must approve the individual chemical components of the home-brew test, but the combination of those reagents in the test itself does not undergo any pre-marketing approval process. The home-brew tests are considered a service for providing information to other labs or researchers, and not as a commercial test. Therefore, this genetic test falls into a huge regulatory gap. There are no limits on advertising this product, because there is no mandatory product labelling. No evidence has been provided to the FDA to ensure the test's usefulness under specified conditions. A commercial test would be subject to approval and regulation, but no genetic tests in the US are currently categorized as commercial, and this has been identified by many as a problem.

Over two years ago, the US Secretary of Health and Human Services set up an Advisory Committee to devise a regulatory framework for genetic tests. The committee was due to release their final recommendations in the summer of 2002, but was suddenly disbanded in August of that year, citing a new broader mandate. This raises the question of whether there were actions taken to derail the process of regulating genetic tests.

In Canada, controls over the marketing of genetic testing are similar. Direct-to-consumer marketing of prescription drugs is illegal, but Myriad's test is also classified as a home-brew test here. Health Canada says Myriad's test would not be subjected to any existing pre-approved regulations. There would be no labelling requirements describing the characteristics and qualities of the test, or an indication of who should use it. Nothing could stop Myriad from running its advertisements here, as long as their kit remains categorized as a home-brew test.

However, if the kit were classified as a commercial test, it would be subject to regulation under Class 3 medical devices. Unlike prescription drugs, medical devices can be advertised to the Canadian public. They do not require a product monograph, or an accompanying label, and there are no restrictions on the audience to which they can be advertised. Schedule A of the Canadian *Food and Drugs Act* lists a number of diseases for which preventative medicines or treatments may not be advertised to the public, but Health Canada currently doesn't include diagnostic testing in that definition. We tend to think Canadians have better protection from the aggressive marketing Americans are subjected to, but Myriad could advertise their BRCA1 and 2 genetic test here tomorrow if they wished. However, there is a possibility of future regulation in Canada through Health Canada.

In 1999, an American market researcher estimated the average television viewer sees nine prescription drug advertisements in one day. Since 1999, spending on prescription drug advertisements has risen by one third. It's uncertain whether this spending increase indicates the average viewer is now seeing 12 drug adverts per day, or if the adverts have simply become more expensive. While each commercial carries its own individual message, together they are sending a cumulative message that targets healthy audiences. Especially after seeing scare-tactic advertisements, like the Pfizer advert with the toe-tagged corpse, two major messages are being driven home. The first message is, "Think you're healthy? You've got to be kidding!" The second message is that if you are ill, you can always pop a pill.

Widespread advertising for genetic tests could have many negative consequences. Advertisements like Myriad's support a deterministic view of genetic disease risks, and fuel an exaggerated fear some people may already have about their risks. Using the mass media to advertise medicines and tests targets a healthy, rather than ill population. This targeting creates the false impression that these products are intended for a healthy population. In addition, the complex psychological and sociological effects of widespread genetic testing are poorly understood. One individual's test result can have wide-reaching implications for his or her entire family. Misconceptions about the lack of regulations for genetic tests are another cause for concern. For instance, it's unclear if the residents of Denver and Atlanta know Myriad is advertising a product that has not undergone FDA approval.

In April 2002, the *British Medical Journal* had an issue focusing on medicalization. Ray Moynihan and colleagues summarized the underlying problems behind the commercialization of medical treatments in the following quote: "There's a lot of money to be made from telling healthy people they're sick. Some forms of medicalising ordinary life may now be better described as disease mongering: widening the boundaries of treatable illness in order to expand markets for those who sell and deliver treatments."<sup>9</sup> The same can be said for those who sell and deliver genetic tests.

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<sup>9</sup> Moynihan R, Heath I, Henry D, Gøtzsche PC. Selling sickness: the pharmaceutical industry and disease mongering. *BMJ* 2002;324:886-891.

## Border crossings: language, history, culture and genetic testing for hereditary breast cancer

Patricia Kaufert

Despite current talk about interdisciplinarity or transdisciplinarity, there are still barriers to communication between disciplines. For example, in 1994 I organized a workshop that brought a range of specialties together—similar to the diversity represented at this conference. There I discovered that bioethicists do not see the world in the same way as genetics researchers; genetics researchers do not understand the language of health service researchers; health service researchers do not always want to listen to lawyers—or even anthropologists. Sometimes, language differences form barriers between these groups; other times, the problem may best be called a difference in culture.

When health professionals ask anthropologists for input, there is often an implicit expectation that the anthropologist will display some form of cultural exotica. This paper honours that tradition by using examples of the “malevolent *ogbanje*” and the *manitoch* to show how culture will influence perceptions of risk and genetic testing. But first, it is important to distinguish between language, culture, and social context.

### Language and culture

An example from Rayna Rapp’s work in studying prenatal testing in the city of New York illustrates some of the issues raised by language and culture differences. Rapp is a medical anthropologist; she interviewed clinical geneticists, genetic counsellors and laboratory technicians, but most importantly she talked with women. These women came from very diverse racial, ethnic, class, and religious backgrounds—an unusual situation for genetic testing.

Some of the counsellors spoke Spanish as either their first or second language, but none spoke French, so Rapp was occasionally asked to interpret for genetic counselling sessions with French-speaking Haitian women. In this setting, Rapp discovered that no word for Down syndrome existed in Creole. She also discovered that the Haitian woman for whom she was interpreting had no knowledge or understanding of the condition. Obviously, the possibility of a child with Down syndrome existed in a very real sense for everyone in the genetics clinic—the counsellor, the technician, the clinical geneticist, even the anthropologist, but not for the Haitian woman. Think of that woman sitting there, listening to Rapp’s translation, trying to understand what the genetic counsellor is saying about the risk of being over 35 and pregnant, finding that none of it makes sense. The barriers between her and the counsellor are linguistic, but they are also social and cultural.

There are a number of approaches that might be taken. One solution might be to replace Rayna Rapp with a French-speaking medical interpreter. This would overcome the language barrier and, given that this is New York, it would protect the hospital against being sued for not having ensured that a client had understood the risks of the procedures offered to her, such as amniocentesis. (Fortunately or not, this is not a risk a Canadian hospital administrator must face.) Language translation would not deal, however, with the issue of whether or not Down syndrome exists as a meaningful concept in the Haitian community to which the woman belongs.

An alternative solution is to hire a bi-lingual counsellor, preferably from the Haitian community, and to introduce cultural sensitivity training for all the counselling staff. This solution is essentially the one advocated in the genetic counselling literature. Hopefully, such an approach would ensure that the counsellor had read Rayna Rapp’s book and knew enough to recognize the possibility of a communication problem and whether she or he should consult an anthropologist or a bioethicist. An anthropologist might talk about culture, but a bioethicist might want to engage her in a discussion of Haitian moral values and Haitian concepts of what constitutes a viable human life. A social worker with

a more public health/activist orientation might question the whole enterprise of genetic testing.

The following quotation is taken from an interview with a counsellor:

How do we convey a chromosome risk when a low-income Afro Puerto Rican woman experiences a 100 per cent chance of running out of food stamps this month, a 25 per cent chance of having a son or brother die in street violence, and an 80 per cent chance of being evicted by the end of the year? A one-in-180 chance of having a child with a chromosome abnormality at age 35 is probably the best odds she is facing.<sup>10</sup>

Yet the situation described by Rayna Rapp is not simply a matter of social deprivation and whether testing can be relevant in the context of being poor, a woman, and living in New York. It also addresses communication across barriers of language and culture.

Without some form of common language, nothing can be explained and nothing can be understood. Understanding, however, requires more than the ability on the part of the counsellor to “convey chromosome risk” to the woman. The woman must also be able to speak about her life, her values, and the meaning for her of this particular pregnancy.

Culture and genetic testing: The malevolent *ogbanje*

Speaking at a conference in the early 1990s on culture, kinship, and genes, Marilyn Strathern, a British anthropologist, suggested that many of the people listening to her probably thought of culture as a barrier to medical care, something that may be seen to “get in the way” of scientific understanding. A person’s failure to endorse something could be put down to a cultural block, especially if that person belonged to an ethnic group. Strathern proposed that with this view, culture is seen as a handicap that needs to be overcome - if these people just changed their customs, they would be more open to accepting medical care.

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<sup>10</sup> Rapp R. *Testing Women, Testing the Fetus: The Social Impact of Amniocentesis in America*. New York: Routledge; 1999. p. 69.



The “malevolent ogbanje”, borrowed from a study done by Esther Nzewi among the Igbo in South-Eastern Nigeria, illustrates culture as a block or a barrier to genetic testing. The Igbo believe in reincarnation; the word ogbanje means one who has engaged in repeated incarnations, and the malevolent ogbanje are a sub-group within this larger category.

Malevolent *ogbanje* are believed to be born with weak, disease-ridden bodies and to remain chronically ill. They are described as *akpa oya* (‘a bag of diseases’)... Their death is self-willed and often occurs in infancy, early childhood or early adulthood.<sup>11</sup>

As their name implies, the malevolent ogbanje are not victims but aggressors, motivated by the desire to punish their families and humiliate their parents over some wrong committed against them in a previous life. Seemingly unappeasable, a malevolent ogbanje is repeatedly reborn, often to the same parents, always within the same family and sometimes returning generation after generation.

Esther Nzewi was testing the hypothesis that the malevolent ogbanje are actually children with sickle cell disease. Having recruited a sample of children below the age of five, all of whom had been identified as malevolent ogbanje by their parents or village elders, she tested eighty for sickle cell disease and reported that seventy tested positive. Sickle cell disease occurs when a child inherits the mutation from both parents; it is frequent in this area of Nigeria. According to the Food and Drug Administration website for this disease, the implications of sickle cell disease include repeated disruptions in the blood flow to the major organs including the lungs, kidneys, liver, bones, and other organs and tissues. While they last, these disruptions cause extreme pain and are often fatal. Prenatal testing is available in the United States, although neonatal testing is more common. There is no cure for someone born with sickle cell disease, but survival has improved in the United States largely through early detection and the use of prophylactic antibiotics.

In Nigeria, children with sickle cell disease often die between the ages of six to twelve months and the majority do not live much beyond five years of age. Noting a decline in

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<sup>11</sup> Nzewi E. Malevolent Ogbanje: Recurrent Reincarnation or Sickle Cell Hemoglobinopathy? Soc Sci Med 2001;52(9):1403-1416.

the number of children born with sickle cell disease, Esther Nzewi concludes that some of the Nigerians are making use of carrier testing. Carrier testing for sickle cell disease has a troubled and controversial history in the United States, yet may well have seemed the option for an area which is relatively poor, relatively limited in terms of access to health care services and in which the burden of this disease is very high. By reporting back her study results to the community, Esther Nzewi hopes that her research will convince more people to have carrier testing. However, given the reception to her findings by the elders and more traditional families, she is convinced that many will refuse.

Neither the parents nor the elders had any problems with accepting that the children had sickle cell disease and they fully recognized the harsh and terrible nature of what was happening to them. Their response, however, was that having sickle cell disease was the choice of the *ogbanje*. The latter were exercising their rights to revenge and using this disease as their weapon of punishment. Carrier testing would provide no protection against malevolent *ogbanje* as they can choose when to be born and to whomever they wish.

In thinking about this situation, it is important to recognize that there are costs to carrier testing, as there are with many other forms of genetic testing. Those who are identified as carriers before marriage are likely to have difficulty finding a partner. If carriers marry before being identified as carriers, their choices would be to separate and find a partner who is not a carrier, stay together but without children (a very difficult decision in a society in which children are highly valued), or risk having another child with sickle cell disease but now knowing that they, not the spirits, are responsible. In communities in which social capital is built through marriages and children, these consequences are not minor. Neither is the spiritual and cultural impact. Denying the existence of malevolent *ogbanje* would call into question the whole cosmological order as related to birth, death, and the linkage between the human and spirit world.

The malevolent ogbanje is a relatively extreme example of a cultural belief, largely incomprehensible in Canadian terms, blocking what would seem on balance, and from a health provider perspective, to be a very worthwhile use of genetic testing. It also appears to confirm the definition of culture as something that “others” have—the term “others” being defined in terms of class, race or ethnicity.

Marilyn Strathern offered an alternative definition of culture, which envisages culture as drawing attention to the way things are formulated and conceptualized as a matter of practice or technique. In this definition, people’s values are based on their ideas about the world, and conversely, ideas shape how people think and react. So everyone has “culture” in the sense of values and ideas that shape what they think and how they behave. Some of the debates that take place over genetic testing, even among health professionals, are about cultural differences, but also about cultural similarities, ideas, and values shared or disputed.

### The *manitoch*

A culture-based experience of cancer is illustrated by Fiola Hart-Wasekeesikaw’s study of cancer in First Nations communities in Manitoba.<sup>12</sup> The word *manitoch* is Saulteaux and translates as “cancer-as-worm.”

*Manitoch* can enter peoples’ bodies through open areas on their skin. It grows and breeds by consuming the flesh and bone of its hosts. Cancer-as-worm is manifested by pain and other signs of decay and devastation. The incurable nature of cancer is depicted in the worms’ hair-like legs, which grow to enormous lengths within a body. Since cutting one of its tentacle-like projections is likely, it is impossible to surgically remove cancer in its entirety. The remaining worm pieces migrate to different parts of the body. These remnants may lie or begin to grow.

Remembering Susan Sontag’s work on metaphors of cancer, then the *manitoch* is both real, but also a metaphor of cancer, but not only of cancer. The elders drew a powerful parallel between the eating away of the physical body by cancer and the eating away of

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<sup>12</sup> Hart-Wasekeesikaw F. First Nations peoples’ perspectives and experiences with cancer [thesis (M.N.)]. Winnipeg (MB): University of Manitoba; 1996.

the spiritual and political body of their communities by environmental degradation and social change.

The image of the manitoch is very powerful, but the elders had other things to say about cancer. Talking about the causes of cancer, the elders told Hart-Wasekeesikaw that cancer, like diabetes, was a “white man’s sickness”, rarely seen in traditional society. They argued that the increase in rates of cancer in their communities was caused by changes in diet, particularly the shift from eating “wild food” to the dependence on store-bought foods high in chemical additives. They described the contamination of the river that was their water supply by an upstream paper mill, and the contamination of fish by chemicals from the same mill. They blamed lung cancer on smoking and breast cancer on women not breast-feeding.

The manitoch may seem a strange and fantastical creature, yet these other causes of cancer listed by the elders are familiar to anyone who has read the determinants of health literature. Recently, John Frank, scientific director of the CIHR Institute of Population and Public Health, discussed the factors that determine health, including eating and activity patterns, physical and chemical exposures, steep socioeconomic status gradients, and persistent organic/other pollutants. He attributed increasing rates of breast cancer to “the iatrogenic and social destruction of breast-feeding traditions.” It should be noted that John Frank described genetic testing as one of the “multiple and tragic consequences” of the risk prediction industry. Is there, perhaps, some cultural incompatibility between the determinants of health model of disease and the genetic model? Are we perhaps looking at a clash of cultures, a problem of languages?

To determine the value of genetic testing for a people and a disease, it is important to remember what to measure that value against. Two or three years ago I took part in a session on health policy, which was part of a larger meeting on genetics. A well-known Canadian geneticist was at the same session. Absolutely convinced of the merits of genetic testing for hereditary breast cancer, he wanted the session to focus on how best to convince health policy makers to fund testing. I tried to explain the principles of

evidence-based decision making. The final report of the National Forum on Health says that the acid test for judging a health measure is “whether or not it had improved health beyond what could have been achieved by doing something else with the same resources or doing nothing at all.”<sup>13</sup> I pointed out the merits of cost-benefit analyses, the necessity of developing pre-determined outcome measures, the virtues of rigorous evaluation techniques, and the righteousness of technology assessment. I might as well have been speaking a foreign language. In a sense, I was speaking a foreign language. Like the Haitian woman who had no concept of Down syndrome, he had no concept of health policy.

The terms interdisciplinarity or transdisciplinarity imply that bringing different disciplines together is relatively simple and necessarily good. This paper presents the idea that there are a number of different cultures and languages vying for place in the field known as the “new genetics”, and that we do not all have the same ideas about the world of genetics and genetic testing.

Even the definition of gene is under dispute. For the past several months, doing work on a report on genetic testing for hereditary breast cancer, I started keeping tally of some of the different definitions used in the various literatures. A favourite item came from a brief guide to genetics produced by the British Medical Research Council, which characterized genes as simple-minded cogs in the sophisticated machinery of our bodies. The juxtaposition between the very old eighteenth and nineteenth century images of the body as a machine with the equally iconic, currently somewhat overused, image of the double helix was almost as interesting as the figure of the manitoch.

The list of gene definitions also includes one by a philosopher of science, who claims that a gene is anything that a competent biologist chooses to call a gene, and that rather than being physical objects, genes are merely concepts. Reading the patent application for the BRCA1 gene made to the Canadian Patent Office in 2001, genes are inventions and they have owners; in this case, they are Myriad Genetics, the University of Utah and the

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<sup>13</sup> National Forum on Health. Final Report of the National Forum on Health. Ottawa: Health Canada; 1997. p. 17.

Government of the United States. Peter Meldrun, President of Myriad Genetics, once referred to the gene as the “intellectual property estate surrounding our breast cancer disposition test, *BRCAAnalysis*”.<sup>14</sup> For epidemiologists and health care bureaucrats, BRCA1 and 2 are entities with physical locations and concrete functions. Health Canada, for example, defines genes “as the physical and functional units of heredity. They are composed of DNA sequences and are located in the cellular structures known as chromosomes.” Yet seen by a woman with a strong family history of breast cancer, genes are not simply “units of heredity”; they are carriers of death from one generation to the next.

The cultures and languages that support each of these definitions are barriers to easy communication between geneticists and patent lawyers, philosophers of science and venture capitalists, and between women and policy makers. We must be careful to recognize such cultural discordance and the nuances of language that we use.

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<sup>14</sup> Myriad Genetics. Myriad Genetics Awarded Three U.S. Patents And Eight International Patents [press release]. Salt Lake City: Myriad Genetics; 2001 May 15.

## Genetic testing for hereditary cancer: implications from practice

Mary McCullum

The title of this conference poses the question, “Genetic testing: help, hope or hype?” My answer is “yes” to all these. Using examples from the literature and the BC Cancer Agency’s Hereditary Cancer Program, I will illustrate the help, the hype, and the hope that increased availability of genetic testing can offer patients in a clinical setting, and I will also highlight some gaps in our current capacity to respond to these issues. Although the examples I use focus on testing for hereditary cancer, they also raise issues relevant to testing for hereditary conditions more generally.

The explosion of genetic knowledge in recent years has given hereditary cancer a lot of attention, some of which has generated misconceptions that should be corrected. The first is the impression that most cancers are hereditary. In fact, only five to ten per cent of cancer diagnoses are related to a specific hereditary cancer syndrome. Of these, hereditary breast and ovarian cancer (related to the BRCA 1 and 2 genes) and hereditary nonpolyposis colorectal cancer (related to the MSH2, MLH1 and other genes) are the most common. Others, such as retinoblastoma and multiple endocrine neoplasia are much less common.

A second misconception, which contributes to the hype of genetic testing, is the idea that genetic testing is appropriate for anyone with a family history of cancer, simply because family history is recognized as a risk factor for many cancers. This is not true—only certain *patterns* of cancer in a family suggest that a cancer is hereditary, or indicate genetic testing should be used.

The complex array of types and causes of cancer are part of the reason why specific family patterns of cancer must be present to indicate hereditary disease. Cancer is really

hundreds of different diseases, all of which result from DNA damage that allows a cell to divide and to reproduce when it is not supposed to. In the case of hereditary cancer, a person is born with a mutation in every cell in their body—but only one copy of the critical allele is damaged. To develop cancer, the other copy of that gene must also be damaged in a cell where the gene functions. Family histories of cancer resulting from this scenario are not common.

Genetic counsellors look for several red flags in a family history that may indicate a hereditary cancer. The first is a history of cancers that were diagnosed at an earlier age than usual; for instance, people who were diagnosed with breast or colon cancer in their 30s. Another flag is the presence of several close relatives on one side of the family with the same type of cancer, or multiple cases with different types of cancer that are all related to the same syndrome, such as breast and ovarian cancer, or colon and endometrial cancer. A third is a history of multiple cancer diagnoses in one individual. Testing patients for hereditary cancer risk whose family histories do not exhibit these characteristics would be similar to performing any other medical test without specific indication. An apparently negative result could provide false reassurance to someone, potentially making them think that they have no cancer risk; anxiety and confusion could result if the test yields results that are more difficult to interpret.

For patients whose family histories of cancer do suggest an increased risk of hereditary cancer, the next step is genetic counselling. The goal of cancer genetic counselling is to enhance the person's understanding of his or her inherited cancer risk in order to facilitate informed decision-making. It requires specialized skills and knowledge, and can be a complex and time-consuming series of interactions between the counsellor, the person, and the person's family members—especially if they pursue genetic testing.

Before genetic testing is considered, the genetic counselling session will cover assessment and interpretation of the family history and the likelihood of a specific hereditary syndrome, which often requires some exploratory review of genes, chromosomes and inheritance. The counsellor will review which cancer risks are



associated with that syndrome, and may suggest related screening. They will also explore the person's cancer risk perception and their experience of living with a significant family history of cancer.

After these concerns have been dealt with, the test's availability, and its possible results, risks, benefits, and limitations are discussed, as well as how to talk about genetic testing within the person's family.

## Help

I want first to discuss instances where genetic testing and the process of genetic counselling are a source of some help to individuals. For instance, by discovering that a cancer susceptibility gene is responsible for a family's pattern of cancer—what some families describe as their curse—the family may be able to make sense of the devastation that cancer has caused for them. Positive results may validate a person's concerns about being at high risk to develop cancer, and justify his or her requests for enhanced cancer screening or risk-reducing surgery.

Genetic testing can also identify individuals in a family who have not inherited the family gene mutation, which may reduce their anxiety and spare them from unnecessary medical interventions. This also reduces the associated health care costs that would have accompanied enhanced screening, surgical interventions, or other procedures. For some, however, receiving a negative result doesn't actually feel like good news. A woman may feel additional anxiety if she wonders why she was spared instead of her sister. People with negative results may feel like they are no longer part of the family "club" that existed when they all shared a common risk.

A dramatic example of a family helped by genetic testing was first published in the *New England Journal of Medicine* in June 2001.<sup>15</sup> An individual, Linda, went to a genetics clinic when she was diagnosed with gastric cancer at the age of 24. Her mother had died

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<sup>15</sup> Huntsman DG, Carneiro F, Lewis FR, MacLeod PM, Hayashi A, Monaghan KG, et al. Early Gastric Cancer in Young, Asymptomatic Carriers of Germ-Line E-Cadherin Mutations. *N Engl J Med* 2001; 344(25):1904-1909.

of gastric cancer at age 29, preceded by the maternal grandmother who died at 32, a great-aunt who died at 39 and the great-grandfather at 43—all from gastric cancer.

Even without a genetics background, it is easy to see that this is a very striking family history for a not very common cancer. So researchers stored a sample of Linda's DNA for possible future work. Unfortunately, Linda died within a few months of her diagnosis. Her identical twin sister was so worried about her risk, despite normal results of prescribed endoscopy screening, that she requested prophylactic gastrectomy surgery (stomach removal). The surgery was done, and review of her stomach tissue after surgery found microscopic evidence of gastric cancer, so Linda's sister felt that she had made the right decision: eight years later she has not had further evidence of cancer.

This family became involved in the research on the relationship between the CDH1 gene and hereditary diffuse gastric cancer. A genetic test found a mutation in the twins' CDH1 genes, making gene testing possible for the other sisters. One of the sisters was found to carry the same mutation that was found in the twins. She chose to have prophylactic gastrectomy, which revealed that she already had microscopic evidence of cancer. The other sister did not have the mutation. This indicated that she was not at high risk for gastric cancer. This result enabled her to stop having endoscopic screening, and gave her family hope that there was at least one branch of their family where their legacy of cancer might end.

This example could also be about a family with hereditary breast and ovarian cancer, or hereditary colon cancer. Although the results may not have been as dramatic, they would similarly illustrate the potential for genetic testing results to save lives and help families.

We know that not everyone who might be eligible for such testing, however, will actually choose to have it done. For instance, although a positive genetic test result indicates only an elevated—not 100 per cent—probability of developing cancer, some people would or could not cope with the level of certainty they think this result delivers.

Others are concerned that learning they are at high risk will have too great an emotional impact on them. However, a recently published meta-analysis of studies on the effect of hereditary breast cancer genetic counselling on patients found significant decreases in generalized anxiety, improved accuracy of perceived risk, and a trend towards reduced psychological distress. Much more still needs to be learned about the psychosocial impact of hereditary cancer susceptibility testing on individuals and families.

Many factors influence whether an individual or family feels genetic testing is helpful for them. At the individual level, the ability to make informed choices, based on the results of testing, about cancer screening and risk reduction is important. At the family level, there may be a sense of responsibility for informing all relatives, or for having passed the gene mutation on to children. There is also the possibility for coercion of some family members to participate in genetic testing, either because of the need for a living, affected family member to provide the first blood sample, or out of concern that additional relatives should make the same choices that other relatives have made about testing and interventions. Outside of the family, there is also the possibility of insurance or employment discrimination.

## Hype

The hype surrounding genetic testing for hereditary cancer can be seen in the unrealistic expectations that the public and some health care professionals seem to have for these tests. People expect that results will be similar to other medical tests—black or white. In most cases, however, genetic test results can only be presented in terms of increased probability of developing a disease; they cannot predict when this will happen, or how severe the disease will be.

People also expect that if a genetic test exists, it must be a good thing to use. As described above, only certain family histories indicate the use of genetic testing for hereditary cancer risk. However, there is demand for genetic testing from people without

the described family histories. This demand is likely to intensify with ongoing media attention on genetic discoveries and advertising campaigns by genetic testing companies.

Part of the demand may also stem from people's perception of breast cancer risk and heritability. In 2001, the Canadian Breast Cancer Foundation did a survey of women in BC and found that women perceived breast cancer as their greatest health risk. Women also believed that breast cancer risk was primarily inherited, when in fact only five to ten per cent of breast cancer is strongly hereditary, and more women die of heart disease than breast cancer.

These misperceptions about health risks contribute to the number of callers that clinics receive, who ask, "How do I get that cancer gene test that I read about in the paper yesterday?" However, when these people receive information about genetic testing in the context of a personal risk assessment, they do appear to understand why it is not appropriate for everyone.

Also, there is a lack of knowledge among health care professionals about hereditary cancer and genetic testing that limits their ability to provide accurate, individual information. For example, a recent survey of Canadian health care providers conducted by Joan Bottorff found that the majority of nurses and doctors surveyed are now in their mid-40s. They report having no specific education in genetics since their basic professional education, which was on average 20-25 years ago and is thus likely to be inadequate and inaccurate given the pace of genetics research. Therefore, health care providers may actually contribute to people's misconceptions of their hereditary cancer risk by making well-intentioned, but sometimes inappropriate, referrals. As genetics becomes a more important aspect of health care, the BC Hereditary Cancer Program and other agencies and organizations have a lot of work to do regarding professional education about the new genetics and hereditary risks for diseases.

But even with adequate knowledge among health professionals, there are limits to the attention that genetics can currently receive from primary care providers. The BRCA1

and 2 genetic test provides a useful example of the need for these services, which is likely to increase. A limitation of this test is that a significant proportion of results will actually be considered uninformative. In BRCA1 and 2 testing, a mutation must first be identified in a living affected family member. This is called the index case, and if a mutation is found it is considered to be a true positive result. A positive index case makes carrier testing possible for other family members; their results will either be positive or negative, and will be considered true results.

However, even with a strong family history and an index-case blood sample from a woman who has already had cancer, a mutation is not always found. That result is not a true “negative result” for the presence of hereditary cancer in that family. It only shows that we have not yet been able to find a genetic explanation for their family history, so we consider this result to be inconclusive or uninformative. The failure to find a mutation may be caused by technical limitations: perhaps there is a mutation in BRCA1 or 2 but in an area that current technology can’t test. Or, this family’s cancer may be related to another gene that hasn’t yet been discovered—BRCA3, for example. A third possibility is that the index case actually had a sporadic cancer, despite the family history, and if another relative had been tested, a mutation indicating hereditary cancer would have been found. Sometimes, the last scenario can be ruled out by testing multiple family members or by trying to start with the person who is most likely to have a mutation, such as the person with multiple primary cancers or at the youngest age of cancer diagnosis. Given the array of causes for an uninformative result, it is important for people to understand its implications—that hereditary cancer has not been ruled out.

Another type of uninformative result is the identification of a genetic variant of uncertain significance—that is, a mutation that may or may not lead to cancer. Even genetic experts differ on how to interpret such results in the clinical setting. It is very difficult to explain to patients, who then pass the information on to family members. Studies of physicians have demonstrated that even straightforward results can be misunderstood. Thus, these ambiguous results hold great possibility for confusion, especially if the responsibility for

providing the results becomes shifted from specialized genetic counsellors to busy physicians in the middle of a hectic office.

There is already a gap between the growing demand and limited supply of specialized genetic counselling services. In BC, the average wait from date of referral to an appointment with the hereditary cancer program is about 12 months. Although hereditary cancer risk assessment is rarely an urgent situation, this is not an acceptable waiting time. Currently, these referrals rarely include people who live in remote parts of BC. If genetic counselling and testing services were more accessible to people in these areas, the demand for them would likely be even greater.

## Hope

But there is hope for the future amidst the help and hype of genetic testing. For instance, people who were adopted sometimes ask about genetic testing, hoping to learn about their health risks in the absence of any information about their birth family's medical history. Current approaches are limited by the need for family medical history, but further developments may open previously closed doors for genetic testing of adopted people.

Another hope is that as genetic testing becomes a more standard part of medical care, legal or other protections can be put in place so concerns about genetic discrimination should decrease. Currently, individuals who have been identified as having a genetic predisposition for a disease face the possibility that insurance companies will use this information against them, even though this knowledge can allow the person to make choices that will actually lower their risk of developing the disease. If everyone eventually learns that they are at risk for something, perhaps the playing field will become more level.

Another area of hope for genetic testing in the clinical setting is the development of effective and acceptable strategies to prevent cancer and other inherited diseases from developing in those at high risk. A concern with current genetic testing is that our ability

to identify those at risk for inherited disease has preceded our ability to mitigate or prevent the disease. This is a common reason given by people who choose not to pursue genetic testing when it is available to them. They ask, “Why would I want to know if I can’t do anything to prevent it?” If new cancer treatments and prevention strategies are developed, this could reduce the burden of the disease on future generations in families who participate in genetic testing.

This hope—to understand and prevent cancer—is one of the reasons that many people give when they choose to participate in genetic testing and related research. As research yields increased understanding of the genetic basis of some diseases and some differing responses to treatments, it may allow for the individualization or “tailoring” of treatment, something that is already being applied in areas of cancer care. Ultimately, a person’s genetic profile may become a key component of prescribing interventions for the prevention or treatment of some diseases. Despite associated complexities, this possibility is very exciting at a clinical level.

Researchers in labs and clinical settings are learning more each day about the genetic contribution to diseases and the impact of genetic testing on individuals and families. Although health policy is not made by individuals and individual families, my hope is that the current hype associated with genetic testing will be replaced by an understanding of the ways in which it can help promote the health of individuals, families and communities.

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## Predisposition testing for common diseases: implications for populations

Lisa Madlensky

Most of the research on genetic disease and predisposition testing has been done on high-risk families and individuals. The families who first came forward for genetic testing research had histories of hereditary disease, and were identified as being at the highest risk. But the impact that predisposition testing could have on a population basis, where there is a wide range of family histories and various levels of risk, is still unknown.

Eligibility criteria are currently used to restrict access to genetic testing to people with some increased risk of a genetic disease, in order to mitigate the potential negative impact of genetic testing at a population level. However, the criteria vary by setting and by gatekeeper. Some areas have restrictive criteria, while others have broad criteria that make genetic testing more widely available. Also, patients with a lower priority risk level may still receive genetic testing, depending on the view of the gatekeeper to testing. “Patient anxiety,” an unwritten clause in genetic testing, may encourage primary care physicians—or even steadfast genetic counsellors—to allow patients to bypass normal eligibility criteria for genetic testing.

Even strict eligibility criteria may not be easy to interpret. For instance, the Ontario Medical Review has a clear list of criteria for BRCA1 and 2 testing that are similar to those of the BC Cancer Agency. Persons need a certain number of cases of disease in the family history, with family members affected at a younger age, with multiple primary cancers, or multiple cancers in the same person. But there is also a caveat that states, “In exceptional cases, testing may be offered to a first-degree relative [of a cancer patient where the] risk of carrying a mutation is greater than ten per cent.”<sup>16</sup> Now the situation is

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<sup>16</sup> Predictive Cancer Genetics Steering Committee, Ontario Medical Association. Ontario physicians' guide to referral of patients with family history of cancer to a familial cancer genetics clinic or genetics clinic. Ontario Med Rev 2001;68(11):24. [cited June 28, 2004] Available at: <http://www.oma.org/pcomm/omr/nov/01genetics.htm>



muddled: when does risk exceed ten per cent, and what significance does ten per cent have as a risk estimate? Risk estimates can be calculated from a family history using a variety of software programs and risk assessment models; however, each of these programs may deliver a somewhat different number from the same family history. Furthermore, there is a danger of people arriving at their primary care provider with a self-assessment of risk that exceeds ten per cent and demanding the test.

What would happen if these eligibility criteria were not used and the door were opened to genetic testing for the general population? This paper discusses the impact that widespread genetic testing could have at a population level if genetic tests were made available to people without an increased risk of hereditary disease.

### Model for population-based testing

Consider a hypothetical population where everyone is eligible for predisposition testing; neither a family history of disease nor a blood sample from an affected relative is required. There are four possible outcomes of genetic testing for any individual. A person may have the mutation and eventually get the disease, which will be called a true-positive result. A person could have the mutation and never develop the disease (false-positive). The third possibility is that a person does not have the mutation, but will still get the disease (false-negative), which is more likely in the case of common diseases, such as cancer and heart disease. The final possibility, of course, is a person who does not have the mutation and will not develop the disease (true-negative).

Despite current real-world caveats regarding genetic testing and mutation identification, this model is simplified to assume that genetic testing can accurately identify mutation carriers. However, the test cannot predict disease status. Of the people who test positive, no one knows who will develop the disease. Likewise, until the disease develops in an individual with a negative result, no one can tell whether that result was true or false.

## Harms and benefits of testing

Each of the groups in this hypothetical population will experience different potential harms and benefits from receiving predisposition testing. The true-positive group—mutation carriers who will develop the disease—is arguably the group that has the most potential to benefit from testing. This is also the group seen traditionally in genetic counselling, as exemplified by the gastric cancer family discussed in McCullum’s paper. For that family, testing was beneficial and potentially decreased mortality from cancer.

However, the benefit of genetic testing for people with true positive results also depends on a variety of factors. It is influenced by the person’s reasons for undergoing testing—whether that person was coerced by other family members, and whether the reason was altruistic or personal, are important issues to consider. The utility of genetic testing, at least in terms of impact on mortality, depends on the willingness of identified persons to undergo interventions. Yet not all the people who want as much information as possible wish to act on that information. For instance, carriers of the gene for hereditary breast and ovarian cancer risk (BRCA1 and 2) may not choose to undergo prophylactic surgery or chemo prevention regimens. Hereditary colorectal cancer risk gene carriers may not choose to have regular colonoscopy. Given a positive genetic testing result, these interventions have the potential to change the course or risk of a disease—if acted upon.

The true-negatives are the largest segment of the population. These are people who do not have the mutation and who ultimately do not develop the disease. For people in this group, there is a possible benefit of reassurance, as the negative result indicates that they are not at high risk for the disease. However, there is also the potential for harm—if the reassurance causes a person to reduce healthy behaviours such as diet moderation, exercise and not smoking. There is a tendency to think in terms of the context of a single disease, but it is also important to consider how risk perception and risk behaviours may not affect just one disease but many. Breast cancer, colon cancer and Alzheimer’s disease all have the same common risk factors: an unhealthy diet, smoking, and lack of exercise. Thus, making lifestyle changes either because of general health campaigns or because of

the results of one genetic test can actually affect a person's risk for developing other diseases.

Of course, the more worrisome groups are the false-positive and false-negative segments of the population. One potential for harm in the false-positive group is from unnecessarily undertaking radical risk reduction treatment. This is a complex issue, as there may even be psychological benefit from radical interventions in some individuals. For instance, there are women who make decisions to undergo prophylactic surgeries who are satisfied with that decision, even accepting that they might not have been the one to develop breast cancer in their family.

Among individuals with false-positive results in the general population, however, negative psychosocial sequelae may occur even where the person did not have an elevated perception of risk. People who do not have a family history of a hereditary disease can still, although rarely, test positive for a disease risk gene; this result comes unexpectedly for them. Not having seen the disease in their family or felt at particular risk, the person may not be prepared to deal with this result, especially if they haven't had adequate counselling beforehand.

The group who arguably has the greatest potential for harm from genetic testing is the false-negatives, people without a mutation who will still develop the disease. For common complex diseases this is likely to be a frequent occurrence, as few people in the general population will have a "genetic" basis for their disease. As with the true-negative group, the result can bring reassurance that then leads to a reduction in healthy behaviours or ignoring other disease risk factors. Compared to the true-negative group, however, this process is more harmful because the reassurance is false.

#### Colorectal cancer: Testing at a population level

The size of these four groups—and thus, to some extent, the impact of genetic testing—depends on the risk of getting a disease that is associated with a mutation in a particular

gene. This is called the gene's penetrance. For instance, in a disease with a very highly penetrant gene, the chances that a mutation carrier will develop the disease are high. On a population level, there will be a higher proportion of true-positives. If the penetrance of a disease risk gene is low, then there will be a higher proportion of false-positives at the population level. The breakdown of these groups can also be complicated by the extent to which interventions based on genetic testing results alter disease progression. That is, some true positives will appear to be false-positives because due to the interventions they never developed the disease.

Most people with a common disease do not carry one of these highly penetrant mutations. This means that, though the positive impact of genetic testing can be very real at the family and individual level, it is very small at the population level. An example using real numbers for hereditary colorectal cancer can demonstrate this. Assume that five per cent of Canadians will develop colorectal cancer. Genetic testing for hereditary colorectal cancer risk looks for mutations in hereditary non-polyposis colorectal cancer (HNPCC) genes. Currently, the proportion of colorectal cancer cases that are actually related to a mutation in these genes is estimated at two per cent. That is, a person with colorectal cancer has a two per cent chance of carrying an HNPCC mutation. For this model, the penetrance of hereditary colon cancer gene mutations will be assumed to be 50 per cent; that is, a person with an HNPCC mutation has a 50 per cent chance of developing colorectal cancer.

Parenthetically, it should be noted that with additional research both of these estimates have dropped over time. When the HNPCC genes were first identified, they were estimated to account for five to ten per cent of colorectal cases; later, three to five per cent. The estimate may drop below two per cent with ongoing research on population-based cancer registries. Likewise, early estimates of penetrance were very high because the first families to be tested were the very strongly affected families. As testing becomes more widespread, it is performed on families with genes that appear less penetrant, causing the overall estimate of penetrance for the disease risk gene to decrease.

The example of colorectal cancer is less controversial than other genetic diseases such as breast cancer, because there is evidence that interventions actually lead to prevention of colorectal cancer. The primary intervention is colonoscopy; people who carry mutations in the HNPCC genes are advised to have regular colonoscopies starting at an earlier age than otherwise would be recommended. This practice is effective because it identifies pre-malignant lesions or polyps in the colon, which can be removed before they develop into cancer. Other possible interventions on higher risk people, but where the effects are not yet clear, are chemo prevention (aspirin, non-steroidal anti-inflammatories), and changes in general health behaviour such as diet and exercise. In rare cases in the United States, prophylactic colectomy has been done at the patient's request.

Returning to our hypothetical example illustrating the effects of genetic testing for HNPCC genes, the results in a population of 1000 people with the assumptions described above would be as follows. The great majority of the population—nearly 95 per cent—will not develop the disease or carry the gene mutation (true-negatives). Five per cent—50 people—of the 1000 will develop the disease. Since only two per cent of colorectal cancers are associated with a mutation in the HNPCC genes, just one of the 50 with the disease will carry a gene mutation (true-positive). That leaves 49 people who will develop the disease who did not carry the mutation (false-negative). Thus it is clear that the impact that genetic testing can make on decreasing the occurrence of colorectal cancer at the population level is very, very small. Only two people in 1000 are identified as being gene carriers, and only one of those developed colorectal cancer. Based on these assumptions, the number of people identified as mutation carriers is very small, the number without mutations is very large, and the great majority of people who develop the disease are *not* in the mutation-carrying group.

In addition, for every one individual who benefits from the test, the majority of the population has the potential for harm from a negative result, if reassurance negatively changes their health behaviours. As well, harm is possible to the one individual who has the mutation but would never develop the disease if he or she chooses interventions that are unnecessary but carry risk. For instance, with every colonoscopic procedure there is a

risk of colon perforations. Chemo preventive agents carry other risks, including bleeding. The most extreme example is unnecessary surgery. Quite apart from harm from such interventions, there is the potential for negative psychosocial consequences for someone who is told that he or she is a carrier of a gene that causes or increases the risk of disease. And, finally, for the group of 49 people with the greatest potential for harm, the false reassurance of a negative result could exacerbate their already high risk of disease by changing their health behaviours.

A false-negative result may not only have consequences for the 49 individuals themselves, but for their families as well. Someone may say to family members, “Guess what? I don’t have the gene for this particular disease, so chances are none of you kids have it or none of my relatives have it,” passing on false reassurance through the family. This is particularly harmful in a family that has a higher risk of disease because of lifestyle factors that family members share—where they live, the food they eat, or any other risk factor that is “inherited” through social and family mechanisms rather than genetic ones.

### Disease penetrance and prevalence

As outlined above, the size of these four groups differs according to disease and gene considered. The penetrance of the mutation, the prevalence of the mutation, and the prevalence of the disease itself can all affect the outcome of genetic testing in a population. Using a combination of these three concepts, it is possible to rank the value of genetic testing for a particular disease along a spectrum. With a less prevalent disease with a highly penetrant gene mutation, genetic testing becomes more predictive of disease state. This is traditional genetic testing, where the presence of a mutation essentially indicates the eventual development of a disease. Huntington’s disease and familial polyposis, are two rare conditions that fit this pattern, and for which genetic testing can provide useful information.

Further down the spectrum are diseases which are more prevalent, such as cancer and heart disease, but for which the genes are only moderately prevalent. The example of hereditary colorectal cancer falls into this grey area, as do many examples discussed in papers from this conference. For these diseases, finding a mutation by genetic testing might identify an increase in a person's risk of disease, but it is no guarantee that the person will get the disease. In fact, as illustrated with colorectal cancer, most of the people who develop the disease do not have a predisposing gene mutation.

At the far end of the spectrum are disease conditions with low prevalence genes. In these diseases, the hypothetically simple gene-disease relationship is complicated by such things as modifier genes, polymorphisms, or gene-environment interactions. This is an active area of research that will likely further our understanding of these diseases' natural histories. But at present, we suspect these very common diseases are caused by a number of interacting factors, both genetic and environmental. Thus, genetic testing for such diseases in a clinical setting is of very questionable utility.

The model I have described has demonstrated the potential harm of genetic testing if given to the general population in the absence of strict eligibility criteria. Most genetic test results are negative or uninterpretable. False reassurance and inappropriate interpretation of negative results can both be sources of harm, since the absence of the disease risk gene does not mean the absence of the disease. Even in programs looking at families at higher risk, the yield of a positive test result is quite low—the highest potential for positive results is about 50 per cent. Therefore, we should not necessarily be preparing people for a positive test result, but for cancer prevention and good health regardless of their genetic test result.

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## Genomics and publicly-funded health care: opportunities and risks

Phil Jackson

The popular media often talks about the revolution that genetics information will bring within our lifetimes. Antonio Gramsci, an Italian writer and theorist, once said that revolution could be characterized in two ways: as a war of attrition or as a war of manoeuvre. A war of attrition is a slow, gradual build-up of force that eventually breaks through on a series of fronts simultaneously, whereas a war of manoeuvre is a rapid advance. The popular press tends to represent genetics research as a war of manoeuvre—a storming of the Bastille. Advances will come quickly, and the test will soon be available at your corner store.

But comparing the past decade of claims about genomics to actual genomics developments, we can see that the future will likely bring both types of revolution. Certain areas will advance by manoeuvre. In drug development and oncology, for instance, there may be unanticipated discoveries that change the way in which treatment is organized and drugs are developed. But overall, it is probably more appropriate to consider a war of attrition. The gradual build-up of investment and research knowledge will begin to translate into treatment, slowly changing the face of medicine.

The term “genomics” is used in this paper in order to extend the discussion beyond genetic testing, as development in genetics will not be simply the explosion of predictive testing that was anticipated five years ago. This paper will address the role that genetic information, single nucleotide polymorphism (SNP) information, and expressed sequence tag (EST) information will play in the whole broader paradigm of health care delivery. In ten to fifteen years, this may also include a new understanding of the pathways of disease and the development of genetically-tailored drugs, or pharmacogenomics. This is a key area of the pharmaceutical trade literature now, and millions of dollars have been poured



into pharmacogenomic research—in the United States, much more is being spent on this than on genetic testing. To date, this research has yielded hundreds of thousands of potential drug targets, but brought very few drugs to market. Over time, the “revolution” will be made of simultaneous moves on different fronts.

As advances are made in new genetic medicine, they are transferred from the labs into the physician’s office, which poses a whole series of health policy questions. It is important, however, to be very clear in health policy dialogue about what is understood by the term “new genetic medicine.” Much of what falls under the “new genetics” label is not new at all. For instance, Mendelian genetics and inheritance have been informing medicine for some time, as has the development and expansion of single gene testing.

There is a genetic isolationism at play in health care discourse, which tends to place anything genetic on a higher pedestal of risk and challenge than other health issues. In fact, many of the ideas and problems posed by genetics are not new—they are repetitions of old problems, cast in a new light. This paper will discuss several areas of concern that are emphasized by genetic medicine—including genetic patents—and outline some recommendations to address these concerns.

Health human resources, or the availability of adequate personnel to address the needs of health care provision, is one of these old problems made new by the specialized nature of genetics knowledge. Currently only three Canadian universities have programs for genetic counsellors. Last year, the total enrolment in McGill’s program was two students; this is one of the larger programs in Canada. For a sense of perspective, there was also a doubling of enrolment in Ontario’s specialized program in medical genetics to a grand total of two.

This illustrates our limited capacity, at present, to deliver on the hype and claims that are being made about the impact of genomics on health care. Projecting into the unknown to plan for future health human resources needs is a problem we are currently engaged with at the federal and provincial levels. That is, how do we anticipate and respond to what we

know will be a chronic demand for geneticists, lab technicians and genetic counsellors? Staff at Ministry of Health in Ontario have canvassed other jurisdictions, such as the United States and United Kingdom, for their approaches to this problem.

Every jurisdiction interviewed recognized that health human resources pose a problem—increased enrolment and training of genetic counsellors is necessary. But at present, we lack well-tailored tools for predicting how many new genetic counsellors will be needed. To make these predictions, several groups are using the World Health Organization's (WHO) 2001 revised guidelines on the number of geneticists per 100,000 patients required to meet future demand. Data from 2001 may appear to be up-to-date; however, the data on which WHO's guidelines are based was collected in 1968 and published in 1972. This was before the human genome had been decoded, at a time when only a small number of genetic tests were being delivered. Thus, the current WHO standard for geneticist need per patient is likely to be a significant underestimate.

Even so, few Canadian jurisdictions meet the WHO guidelines. In the meantime, we can decide not to accept 1972 figures to make 2008 projections about future health human resource needs. Independent research is required to develop a robust method for our provinces and territories to assess their requirements.

### Health care provider training and awareness

Even with specialized genetic counsellors, we still require that primary care providers have the language and tools necessary to make proper referrals. Again, adequate training and awareness among primary care providers is a health policy challenge that goes beyond genetics medicine. There is an expanse of literature on the challenges of changing physician behaviour; genetics simply requires different physician changes, so some of this research can be applied.

In the case of genetic medicine, primary care providers must generate an informed perception of risk and be able to convey that more appropriately and accurately to

patients. For them to do this effectively, the gap must close between patients' increased need and demand for information, and the current ability of providers to meet that demand. This will require more health care provider training. To determine the size of this gap, we must examine their present level of training and the current literature on physicians' comfort and awareness levels with respect to genetic medicine.

A lack of comfort and awareness can be particularly problematic in the case of direct-to-physician marketing, where a trained sales force is sent by a company to pitch the test du jour to individual physicians. The salesperson likely has more confidence, knowledge and training about the offered test than the physician does. The long-term danger of this situation, without a more coherent approach to training in genomics for primary care providers, may lead to a breakdown in the ability of physicians to be appropriate gatekeepers to genetic test access. They may simply lack the confidence and training to challenge the claims of the salesperson, or the demands of their patients. In this scenario, direct-to-physician marketing in tandem with direct-to-consumer marketing poses a serious threat to ensuring appropriate access to genetic medicine.

#### Direct-to-consumer marketing

Direct-to-consumer (DTC) marketing is another problem that did not originate with the development of genetics, but has been exacerbated by it. Canada is next door and a major trading partner of the United States, which has allowed DTC marketing of prescription therapies for a long time. In the case of pharmaceutical marketing, considerable research has been done on the effects of DTC advertising. But DTC is expected to increase with the projected expansion of genetic testing in the United States—from US\$319 million in 2000 to about US\$1.17 billion in 2007.

As described in Mintzes' paper in these proceedings, Myriad Genetics is already advertising their test for BRCA1 and 2 to consumers. It is not likely to be the only test advertised this way, and this will raise a series of challenges for the publicly funded Canadian health care system.

One of these challenges is how patient demand for genetic medicine will change the broader patterns of health care utilization. Compared to these large-scale changes, the cost of the test itself is insignificant. Imagine an individual identified as “at risk” for cardiac disease by some sort of predictive test. Of his or her own accord, the person may make several decisions about medical management, the use of pharmaceuticals, other screening tools, and physician time. Cumulatively, those costs are immense. For a more detailed discussion of this issue, see the work of Jerry Hurley and Fiona Miller at McMaster University.

Direct-to-consumer testing may also challenge jurisdictions like Ontario to examine its system, which allows any lab with a license to provide testing according to certain quality assurance standards. With DTC advertising, the public desire for a test may be brand-specific; for instance, preferring Myriad’s patented *BRCAAnalysis*<sup>TM</sup> test over the generic BRCA1 and 2 test offered by Ontario.

### Health technology assessment

Health technology assessment (HTA) is already a challenge, but the introduction of new waves of testing will highlight existing weaknesses in our overall system and approach to assessing health technology. The major problem is to weave together cost-benefit analysis, risk analysis, and—which is increasingly important in predictive testing—population utilization analysis. From these, we can achieve a potential system impact analysis. This is not done well with old technologies, and new technologies are likely to highlight areas for further change.

To date, it has been a significant challenge for decision makers and policy makers to obtain accurate, quick HTAs, especially in the area of new genetic testing. Adequate resources and coordination play a role in this, but conflicting timelines pose additional problems. The turn-around time for a comprehensive HTA is currently 18 to 24 months, but policy makers must often make decisions on the introduction of key tests in a much shorter timeframe. Cutting down the time required for an HTA would help close the gap

between information and policy, as would an improvement in the coordination and information sharing between jurisdictions about HTAs.

Politicians and policy makers are not immune to the hype in newspapers, or pressure from patient groups, so it is extremely important for us to balance this by providing them with well-considered evidence on new genetic medicine. Without that tool, policy makers may lack the ability to give considered responses to the direct-to-consumer and direct-to-physician approaches that companies employ.

### Privacy and confidentiality

Genetic information raises some unique privacy considerations. But it is important to remember that if there were adequate health privacy legislation in place that covered all forms of health information—including an individual's DNA—then people would largely be protected from health privacy concerns. This has not been a major policy issue yet in Canada, but a look to the United States shows that privacy issues will eventually be a major item on the Canadian policy agenda.

Across the United States and Europe, health privacy has already taken centre stage. As of 2001, 44 US states prohibit the collection of genetic test information by insurers, which is a significant move given their private health insurance system. Genetic privacy is still an important issue in the Canadian context because of the implications that genetic information can have for family members. Only one major case will have to make it to court or to the privacy commissioner on the inappropriate use of genetic information, for the issue to rapidly assume national significance here.

### Coordination

In Canada, national coordination between provincial and territorial organizations in any realm of health care is rare. For this to happen in genetics would be something of a

miracle. The relationship between federal and provincial governments is one part of the coordination problem, as is the distance between these jurisdictions.

The first challenge for policy makers who have the task of regulating the new genetics is to know what is going on. In Canada, genetic testing has developed in different ways in each province. The mechanisms for referral of samples are not formalized, but are based on relationships that have developed over the years between various labs and centres for testing. The result is that there may be internal coordination within each jurisdiction, but there is not organized care and testing across the country. This is one area where current work at the national level is essential for efficient use of resources. Canada has some of the most advanced testing centres in the world, but coordination is necessary to take full advantage of the resource base and expertise present in each of the separate genetic testing facilities. There is a greater range of tests available in laboratories across Canada than any one lab can offer. By integrating some of the key testing centres with the key referral centres at a national level, patients could have greater access to testing, and the centres could benefit residents outside a single jurisdiction. According to a major national survey done by our staff recently, such coordination could also limit the number of tests that are being inappropriately or unnecessarily sent out of the country.

Such coordination is a huge challenge. It will require assessing the current practices in each jurisdiction; documenting what is being done to deliver testing, where those tests are going and why. Following these steps, a more appropriate and informed method of coordination could be proposed.

## Regulation

With the regulation of genetic medicine comes also the question of patents—a question that has been discussed much more since Myriad Genetics issued an order to Canadian and European labs to stop genetic testing for hereditary breast cancer because it violated their patent on the BRCA genes (see also Caulfield’s paper herein). One thing that Myriad can be thanked for is rapidly creating an international community of policy

makers that is significantly more informed about patent law than they have ever been. McGill University law professor Richard Gold recently suggested that the Myriad case has accomplished what months and years of negotiation could never have achieved. For instance, our ministers have established links within Canada, and with the United Kingdom, France, and Australia.

The common problem faced by these jurisdictions is how to maintain a high quality standard of genetic testing and keep the test accessible for the individuals that need it. The Myriad case highlights the seriousness of the potential implications for health care delivery, for decreased access to genetic testing in the future because of monopoly pricing by patent holders. It also has raised awareness internationally that the innovation agenda must engage with the broader health care agenda to maintain patient access.

Reconciling policies to support innovation and/or gene patents with equitable health care policies is a unique challenge for Canada. Canada's patent law is very closely aligned with the United States, and there is pressure to keep it so. However, our health care system is far closer to the European model. With one foot in each world, it is difficult to create consistent government policy—one arm of government supports commercialization of gene discoveries, while another supports broad equitable access to health care and has to pay the costs of commercialization.

## Recommendations

To address the patent problem, Ontario has compiled a series of recommendations—many of which are based on European patent law—in a report called “Genetics, Testing and Gene Patenting: Charting New Territory in Health Care”,<sup>17</sup> which was presented to Canada's premiers at a special meeting in Vancouver in January 2002. One of these recommendations is to adopt an oppositions period, which would allow individuals to challenge the validity or breadth of a patent without incurring a patent violation lawsuit.

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<sup>17</sup> Ontario Ministry of Health and Long Term Care. Genetics, Testing & Gene Patenting: Charting New Territory in Healthcare. Toronto: Government of Ontario; 2002. [cited July 7, 2003] Available at [http://www.health.gov.on.ca/english/public/pub/ministry\\_reports/geneticsrep02/genetics.html](http://www.health.gov.on.ca/english/public/pub/ministry_reports/geneticsrep02/genetics.html)

This is currently utilized in France and a number of other European jurisdictions. The opposition period is built into the French European patent acts.

Another aspect of European patent law we should consider is “improvement privilege.” This allows for the use of patented material in order to improve on or build upon an invention, such as a genetic test, that is currently available. This is a very significant allowance and would mitigate the impact of patenting on future testing, and is an area that we have been pushing nationally for change.

A third aspect of European patent law that may be useful in Canada is the *ordre publique*, or morality, clause. In Canada, patents are granted for inventions on the basis of that invention being novel and useful. However, in European patent law there is a built-in capacity for individuals to launch an appeal or oppose a patent even if it is new and useful, on the grounds of public order or morality.

Taking the social and health effects of patents into account, health policy makers must also consider whether genetic tests should be patentable at all. Many jurisdictions do not allow methods of medical treatment to be patented. For instance, patents and monopolies cannot be had on a surgical technique. Although Canadian patent law is said to be amoral, it has always recognized medical treatments as non-patentable, and has also always allowed generic drugs. One of the questions the Ontario report has asked is whether this logic should also apply to aspects of diagnostics where human DNA is involved.

Utility standards, or how useful a new invention must be for it to be patentable, may also need to be raised in Canada. In 2001, the United States raised their utility standards, but not to the extent that some may have expected. One of the new standards actually read, “The description of the use of a transgenically altered mouse as snake food will no longer be acceptable as a utility.” Likewise, stating that a substance may burn is also no longer acceptable as a utility. Thus, “utility” is still loosely defined, and still a low bar to reach.



Once a patent has been granted, it is also important to consider how that patent is licensed—that is, who has access to the patented invention. Many genetic patents, including Myriad’s breast cancer patents, give them the exclusive rights to use the gene. Health care jurisdictions have been most annoyed and worried by the company’s ability—as allowed by the exclusive license patent—to tell them where, when, how and under what conditions a test should be delivered. This is, implicitly, where, when, how and under what conditions an individual’s personal health information shall be shipped.

This raises the questions: Should an individual patent holder have exclusive rights to test at a single site? How should health policy respond if this site does not have high quality standards? In the present example this is not the case: Myriad Genetics happens to provide a very thorough and accurate test. However, if a company held a monopoly on a gene and used the same marketing approach *without* high quality standards it could be very dangerous. Limiting licenses is an issue that the Ontario Ministry of Health is strongly pushing the federal government to examine.

Many of the issues discussed here are being addressed by the Coordinating Committee on Genetics and Health, which involves nearly all Canadian jurisdictions, either as a corresponding member or as a formal member. As part of this work, there has been a formal protocol developed with the CIHR Institute for Genetics and the Institute of Health Services and Policy Research. Other aspects are being completed by the Advisory Committee on Health Information. These include a comprehensive scan of the genetic testing that exists and the development of principles and protocols for a coordinated system of testing across Canada; also, work on privacy principles and a new tool for health human resources planning is underway. Linkages have been developed with the UK National Health Service, health services in Australia and France, and increasingly the OECD, to be more aware of some of the developments and learn from other jurisdictions. There is ongoing pressure for patent reform, which is beginning to yield results in terms of discussions.

Whatever form the genetics revolution takes, it will challenge the health care system. It is important to remember, however, that solving these problems is not solely the task of government policy makers. Researchers and health care providers should engage in the debate with policy makers, and meet the challenge together.

## Slips trips and avoiding the GATTACA fall: Some near-term considerations for predictive genetic testing for Canada

Terry Sullivan

I will touch on five areas to pull together some of the key items that have been referred to over the course of this conference. Topics addressed in this presentation include the population context and some limiting of the hype around the subject. It also highlights some of the challenges in meeting the industry innovation and trade-related obligations that the country imagines it has, and reconciling those perceived obligations with some of the health policy and health care organizational issues which are presented by predictive genetic testing. I will discuss my experience during the last 13 months with the very active program of predictive genetic testing in Ontario, where there has been a rapid escalation from a research program to a service program, with full coverage of the cost of testing. My remarks conclude with some comments on key research policy issues, and hopes for the future in this area.

One theme heard throughout the conference is that we need to moderate the “hype” about the scale of benefits that can be expected from predictive genetic testing. Testing has generally served well to inform diagnoses and treatment of diseases in families with predominantly single gene disorders. However, the burden of disease from single gene inherited conditions is small compared with the chronic diseases of modern life. Public health policies aimed at preventing diseases in entire populations are governed by other considerations and many of us spend a lot of time during our working days trying to push back patterns of average risk in the population. So in industrialized countries, which are really only a small part of the world, there are patterns of chronic disease that are quite distinct when compared to the rest of the world. Many of the concerns we are talking about are fairly arcane to the most advanced economies.

The contribution of genes and environment to health is not universal or fixed. The effects vary by setting and population studied and by the interaction of genes and environment over the course of a lifetime. So, for example, if one examines variation in height and the predictions of environment and gene, the outcome depends on the time period and the country being considered. In Northern Europe, genes seem to play a high role because the environmental effects appear to have plateaued. In sub-Saharan Africa, it is a much different picture. The context of the time period and the geographical location will give quite a different picture of the contribution of genes and environmental factors to particular health endpoints. This interaction is illustrated in patterns of disease in migrant populations, such as the study of heart disease in Japanese populations who have migrated to North America or Europe.

One key reference is that most of the major chronic diseases that form the big burden of disease in our population are multi-factorial, they are culturally and socially interpreted, and these factors interact over the course of a lifetime of an individual. If one examines the distribution, for example, of global cervical cancer incidence, as in Max Parkin's work in 2002, you see a tenfold variation. This variation is almost certainly not related to genetic predisposition. It has a lot to do with exposure to human papilloma virus and its global distribution, as well as the conditions in which people live and the amount of money and per-capita GDP of the country in which they are living. Colorectal cancer also highlights this point. Colorectal cancer is largely preventable in our population, although we are missing many opportunities to reduce the condition and to detect it early in every population. A very small proportion of colorectal cancer is tied to a couple of specific genetic predispositions; another significant proportion is associated with family history; and a much larger proportion, perhaps 80 per cent, does not appear to have any particular family patterns.

Going back to the question of population benefit, researchers are not sure yet if results obtained from predictive genetic testing are true positives. The likelihood is that a significant number of them will be, because of the eligibility criteria and the filtration. However, it is apparent that even in high-risk individuals, few of them may actually

become clinically affected. In contrast, we have been involved in a program called Cancer 2020 to simulate the effects of various preventive interventions on the population, mapping them over the next 15 years and basing them on the Ontario population. The simulation looks at the effects of modest changes in diet and physical activity, as well as oral contraception in women. The amount of avoidable, preventable death jumps up to about 6000 individuals if the effects of those changes are projected into the next 15 years, compared to the small number of people who may have a benefit from early predictive genetic testing related to colorectal cancer.

That does not mean that we should not be proceeding very actively and carefully in the area of predictive genetic testing. In fact, we are doing so. It's just to highlight the point that the benefits from a population-based approach are always going to eclipse the benefits from predictive genetic testing, particularly for single gene heritable disorders. We always have to keep this balance in mind when we are talking about the promise of predictive genetic testing. Indeed, in about six to eight weeks time, a national consensus panel will release a report on organized screening for colorectal cancer, recommending that every province in Canada begin organized screening for colorectal cancer—which could have dramatic effects in terms of reduced mortality in the population. It is not certain how that proposal will be received in Canada. We have been trying for some time in Ontario to get a pilot underway and are hopeful that we will actually have one in progress shortly. The benefits from an organized screening in average-risk individuals would be quite dramatic, based on the simulations that we have done.

We have heard a lot about industry and trade concerns, the question of intellectual property and patent protection for genes, and genetic testing procedures over the course of the conference. Many people are assuming that at the end of the day there will be a solution to this problem through the World Trade Organization. It may not be tomorrow, it may not be next week, but it will be sometime in the next couple of years. France has taken a courageous—some might say foolhardy—approach to this issue, but France is an exception. Frankly, the United States is also an exception. So this is one area where Canada is in the position to forge a unique solution, and we should stop wringing our

hands and looking for the referee, and get on with doing something original. Canada can do something unique to get around the challenges that we are facing with respect to patents, whether that is dealing with Industry Canada, or the Health Canada taking their own pre-emptive moves, or a series of federal measures that could be undertaken to deal with this question.

There are big commercialization pressures from bio-industry. Here in Canada, the last Throne Speech contained promises to cure breast and prostate cancer, and these promises are, in some ways, similar to promising to land a man on the moon. The former president of the University of Toronto travelled around talking to everybody in the university sector and the cancer sector on the subject. Many who heard him became agitated because one to three billion dollars will be disbursed to this aggressive business of curing cancer (or at least launching a large-scale assault) motivated by the promise of biotechnology to solve our problems. In this there is no mention of the consideration of non-genetic factors that contribute to the distribution of cancer in the population.

Governments are very susceptible to this sort of enterprise, because it holds the promise that we are all going to become rich with patents and life will be good. We have to be careful in our advice to government about the promises of a “lunar landing” in this whole area of biotechnology, and the realistic role of a small country like Canada in a world market. Despite the indicators that were pointed to earlier in this conference, we do have real competitive pressures related to growth and wealth creation, not only for biotechnology. Whether biotechnology is going to bring us there is another question. One of the good provisions in the mandate outlined in the CIHR legislation is that while there may be an economic development reference, there is also a reference to improving the health of Canadians. Balancing economic development and health outcomes is a big challenge. It is playing itself out in the departments of the federal government as we speak, so we should knock on doors. I know many of us are.

There are a whole set of issues for health policy and health care organization in Canada, and there is a question about who pays for these procedures. Canada has a different mix

of practices going on across the country. The BRCA1 and 2 case, for example, shines a light on this problem in an explicit way and has received a lot of attention. There are important questions around the opportunity costs and benefits of such testing, and which tests do more harm than good. But for those specific tests that have some established benefits, the question about how it gets paid for is at the back of everyone's mind. There are significant questions about the matter of disclosure and how families are dealt with. Even researchers are struggling with setting out proper guidance for dealing with family-related disclosure and how to approach disclosure in a sensitive way, while protecting the privacy of all other individuals.

There are also key questions that we have not yet addressed around privacy in predictive genetic testing related to insurance and employment. Canadians can be quite naïve on the employment aspect, perhaps because there has not yet been a lot of adverse selection in the labour market. Canadians are more cautious about disclosure to private insurers. There has been considerable discussion about regulating the claims of advertising and direct consumer marketing of a variety of materials and “home-brews.”. There has also been a lot of concern about the “Wild West of the Web” and whether people are on the Internet sending their tissue or their blood to offshore or even onshore organizations that promise things they cannot deliver. Some regulation in this area is probably necessary. Most people in Canada do not actually know who regulates this area, because it is not well regulated. But the need for regulation to protect against harm must be balanced with a consumer's right to buy rubbish if they so choose. There must be an informed disclosure of the benefits of testing, and recognition of *caveat emptor*, but the health sector has always been more carefully regulated than other sectors, as consumers in this arena are not well equipped to make informed choices.

Nine in ten Canadians believe that insurers should not have the right to refuse insurance if a disease gene is present but the disease is not. There is some regional variation in this opinion by age in Canada, Britain, France, and other European jurisdictions. Six in ten Canadians say that employers need not be told of genetic danger, meaning that 40% presume that it's okay to do so. There is some, perhaps misplaced, trust, apparent in this

presentation. When a population in Ontario was asked whether they would take genetic tests for illnesses that have no cure, a little more than a third said they would be very likely to take the test. Of course, being asked the question and then being faced with the reality may be quite different. Another 33% said they would be somewhat likely to take the test. This response may seem irrational or counterintuitive, but people have a tremendous appetite for this information. When people in Ontario were asked if they knew who regulates genetic tests, a bout one-fifth of them thought that governments do, a tenth believed that doctors do, and the majority, just a slim majority, either had no idea or did not know or refused to answer. So they do not know, because we do not know, who is regulating these tests. The real answer is that nobody is regulating the testing, but that was not one of the choices.

There are additional issues related to health care organization and health policy that I'd like to touch on from the perspective of my involvement in a network for cancer prevention. This network has been built up in Ontario through the active work of a large group investigating BRCA1 and2 and heritable colorectal cancer. The consequence of this work is the rapid evolution, over the course of the last five plus years, of a system of testing and counselling. We have gone from a research-based approach to a service-based approach that is still tied to the research enterprise, which may not be a bad model. Among other things, this model has kept in the public sphere much of the data that has been collected and linked to the cancer registry. So we are moving out of the Iron Age, from research to case finding, and potentially an approach to organized high-risk screening. There are points of service, there are referral pathways, the testing is paid for, and the quality of the testing is reasonably high quality. Small numbers of real people, with real and immediate risk and a difficult set of choices to face, are getting real benefit from the testing. We underestimate the complexity of the calculus for risk and benefit in this population. There is a whole research program around what people who are faced with the possibility of family risk in this area would value. A colleague this morning pointed to a recent set of papers in the *New England Journal of Medicine* on prophylactic oophorectomy, and this is one indication of early benefit for some people who may be



identified in the course of testing. It is at least an option at that particular moment in the lives of such women.

As a consequence, we need the elaboration of screening and intervention cascades based on evidence in order to respond to some of these developments. Some research is developing in the early stages, and there is some practice building from this research, but it is not systematically well organized. There was a paper in *The Lancet* in June 2003, discussing adaptation of traditional screening eligibility criteria to high-risk populations for cancer genetic screening. There may be a way of adapting some traditional criteria to deal with matters of eligibility, to deal with the problems of prevalence and penetrance and how you trade off these issues. In Canada, we have not organized ourselves well to do this yet, and we have approaches building in each of the provinces without any ideal models for how we might best do this.

Lastly, we have not elaborated the relationship between medical genetics, genetic counselling, and specialty care provision. For example, in Ontario we have decided to segregate these areas. If the main points of initial contact are through medical genetics, then patients who would be high-risk for heritable cancers go first. We have done an adequate job of splicing together the specialty care on the cancer side with medical genetics, but the point is that there is no clear road map in this area. Organizing an approach to high-risk screening, for example, requires that models are developed and evaluated for the best ways of doing this. Primary care providers can have problems coping with the complexity of these issues. For the more common heritable cancers, the challenge will be to ensure that there are specialty centres that act as knowledge repositories for these particular conditions, and ideally an approach from a population base that sketches out a sensible program model. Another possibility is to evaluate several different program models for the purposes of responding to high-risk cancers and other heritable conditions.

In the research policies, a number of challenges were identified. Firstly, there are the distorting effects of biotechnology on public institutions and the "lunar landing" reality

that we are dealing with in Ontario of having everybody reorient their priorities. Happily, researchers being good game players, if this turns out not to happen, everybody will reorient to whatever the next set of funding opportunities may be. But over time this approach certainly has had a steering effect on universities and on research institutes, and many of us are concerned about the impact on population-oriented science.

A second challenge raised was the anti-commons or secrecy of industry-sponsored work. This issue of intellectual property rights is important but Canada does not have any particular unique or imaginative solutions.

Thirdly, we need better methods to evaluate these technologies, linking the evaluation to feedback into the regulatory process. Once again, since there is no formally organized approach to technology evaluation in Canada, other than a few luminary centres that are largely organized provincially and one national effort, there is no clear method for accomplishing this linkage.

Lastly, with respect to the human genome, there is a need for a parallel map—one that encompasses social and environmental pathways to disease with the same large ambitions. This map would somehow balance out, at least in public institutions, the focus on predictive genetic testing with other non-genetic approaches. It would also examine the social, behavioural and cultural impacts of this testing, and some of this work has begun. In fact, in our own group in Ontario there has been a large NIH grant focusing on cultural issues in the understanding and interpretation of predictive genetic testing.

So, hope and help. Two thoughts. Firstly, we really need some national leadership in this area, and national leadership in Canada has often become a hiding place for governments who do not want to take jurisdictional roles. The federal government is responsible for dealing with patent issues. In my opinion, former Ontario Premier Mike Harris was very courageous and did a great job of standing up and making a public noise about BRCA1 and 2. But national leadership is needed in this area. The federal government will have to deal with patent harms at the level of multi-lateral tribunals.

Secondly, either at the national or the provincial level, government will have to deal with advertising claims for a range of predictive tests, at least where those tests originate in this country. Yet I'm not sure if this issue is even being considered, given that 60% of Ontarians do not even know who, if anyone, is regulating the industry. Ontario had a very creative solution to introducing non-discrimination provisions into the provincial legislation. Unfortunately, the Ontario Bill seems to be floating in limbo at the moment but this may be one pathway. I'm not able to say if there is a federal pathway through this same set of challenges and again it highlights this area as one where discussion is needed. This is a significant issue, and the Canadian life and health insurers have made it clear that they will be using predictive genetic testing as a basis for determining insurance premiums and coverage. Discussions are taking place, but the insurance industry representatives are in business and they will select for risk unless there is some regulatory wedge. In my opinion, we are sleeping at the wheel on this, while the rest of the world is trying to do something about it.

It may be possible to select one type of testing, for example testing for heritable cancer, such as BRCA1 and 2, or maybe colorectal cancer, as a prototype for building a made-in-Canada approach to these issues. That is, to identify optimal programs and to evaluate them so that there is a working prototype for how to manage the whole spectrum of new technologies on the horizon. If potential tests are increasing from 1,500 to 35,000, then there are enormous challenges out there. Finding a way of prototyping particular kinds of testing for heritable disease seems a good way of managing these challenges, including the whole mix of human resource issues that have been discussed. Of course there must be different models configured for different disease conditions, but if we can start with those where the disease burden is higher, maybe we will find a way of building useful policy.

## About the authors

**Patricia Baird** is a pediatrician and medical geneticist, and while Head of the Department of Medical Genetics at UBC for over a decade was extensively involved in developing services for families with genetic diseases. She has been a member of many national and international bodies, among them the National Advisory Board on Science and Technology chaired by the Prime Minister; the Medical Research Council of Canada; chair of the Federal Royal Commission on New Reproductive Technologies. She has served as an advisor to the WHO in genetics in recent years, and has published extensively on the policy implications of new genetic and reproductive technologies.

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**Phil Jackson** is currently the director, Health Information and Sciences Branch, in the Integrated Policy and Planning Division of the Ontario Ministry of Health and Long-Term Care. Previously, he was the director of the Strategic Health Policy Branch, and also the manager of the Population Health Strategies Unit in the Strategic Health Policy Branch. Prior to this position, he served as the coordinator of the Aboriginal Health Office. Phil Jackson has played a significant role in the recent drafting of the Ontario report “Charting New Territory in Healthcare”, which examines genetic testing, gene patenting, and the implications of developments in genomics for the future of health care. This report was adopted by all premiers at the recent Premiers Health Conference in Vancouver. He is currently chairing the Federal/Provincial Coordinating Committee on Genetics and Health. The committee is developing the long term plans to implement the recommendations of the Premiers Report.

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**Helen Wallace** is deputy director of GeneWatch UK, a science-policy research group whose aim is to ensure that genetic technologies are used in the public interest. She studied physics and mathematics and has a doctorate in oceanography. Prior to joining GeneWatch she spent four years as an environmental modeller in a consultancy firm and seven years as senior scientist with Greenpeace UK. She is the author of a recent report for the World Health Organisation entitled “Human Genetic Technologies: Implications for Preventative Health Care”.

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