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Introduction

1.1 Goals of this report

As early as 1963, a World Health Organization (WHO) Expert Committee observed that “genetic considerations add a new dimension to public health work: a concern not only for the health and well-being of persons now living, but also for (...) generations yet to come” (WHO, 1964).

Nearly 40 years later, WHO’s Advisory Committee for Health Research produced a report on *Genomics and World Health*, with the goal of providing a realistic picture of the benefits, challenges and limitations of genomics, particularly in relation to the health needs of the world’s poor.¹ The report was published shortly after the completion of the draft sequence of the human genome and at a time when both expectations and uncertainties about genomics and its likely impact on human health were high. It was therefore timely to review the science and to wade through the hyperbole surrounding public debate to consider the realistic possibilities for genomics in terms of generating practical solutions for health. Moreover, the report sought to address widespread concern that genomics had ushered in new and high-tech methods that would result in both research approaches and new interventions beyond the reach of the world’s poor.

The *Genomics and World Health* report describes the evolution of genetic science, from Mendelian genetics and the study of inherited single-gene disorders, to genomics and the comprehensive study of multiple genes and their interactions. Its authors postulate that basic molecular genetic methods could furnish means for developing skills in

genomics, in this way providing a foundation for developing public health-related services (like genetic tests) while at the same time preparing the ground for entry into a growing and promising field of biomedical study. Elsewhere it has been similarly argued that “most developing countries now urgently need to incorporate genetic approaches (including DNA diagnosis) into their health services. DNA diagnosis is relatively inexpensive, helps to develop skills in molecular biology and provides a basis for developing national expertise in genomics” (Alwan and Modell, 2003).

The Advisory Committee on Health Research (ACHR) identifies intellectual property as one of the factors affecting the accessibility of the results of genomic research and development (WHO, 2002). The present report takes up the question of *how* this may be—that is, in what ways intellectual property may affect the ability of developing countries to access genomics, both at the level of research and at the level of health interventions. It may be helpful to imagine this report as situated at the intersection of the ACHR report on *Genomics and World Health*, the Nuffield Council on Bioethics’ (2002) *Ethics of Patenting DNA*, and the United Kingdom Commission on Intellectual Property Rights (IPR Commission) report (2002) *Intellectual Property Rights and Development Policy*.² The Nuffield Council on Bioethics report “examine[s] the issues relating to genetics and intellectual property, particularly those that concern human healthcare and research related to healthcare”. Its discussion, however, is in relation

to highly industrialized countries. The last report, on the other hand, explores the relationship between intellectual property and development, including various aspects of development that relate to health. But while the concerns of developing countries³ figure prominently, the impact of DNA patents on access to effective and affordable products like genetic tests is not specifically addressed.

This report approaches the issue of intellectual property from a public health-centred perspective. It does not look to define policy; rather, its aims are to shed light on the issues as they exist in the current debate, highlight areas of contention, and suggest avenues for further investigation. The product of this deliberative process was created with the hope that it will stimulate informed dialogue among different stakeholders, and feed usefully into future processes, involving WHO and other entities, to develop policy guidance that is based on a balanced account of the issues, arguments and evidence.

1.2 Key issues

The main issues we will consider in our discussion are the following:

- the special ethical, legal, research and medical challenges raised by DNA patents, with particular reference to genomic industries;
- the response of different countries, legislative and otherwise, to the question of DNA patents, and the consequences of these actions for access to genetic diagnostics;
- the flexibilities in international frameworks, particularly the Agreement on the Trade Related Aspects of Intellectual Property Rights (TRIPS), for national policy-making relating to DNA patents; and

Box 1 DNA and genes

DNA, or deoxyribonucleic acid, is the biochemical substance that makes up genetic material. It is a double-stranded molecule comprising two linear chains made from four bases (A, C, G and T), together forming a double helix.

Genes are ordered sequences of nucleotides located in a particular position on a particular chromosome that encode a specific functional product, like a protein.

- the particular needs, both health and technological, of developing countries in relation to genetics, and what this suggests in terms of how they should structure their patent regimes.

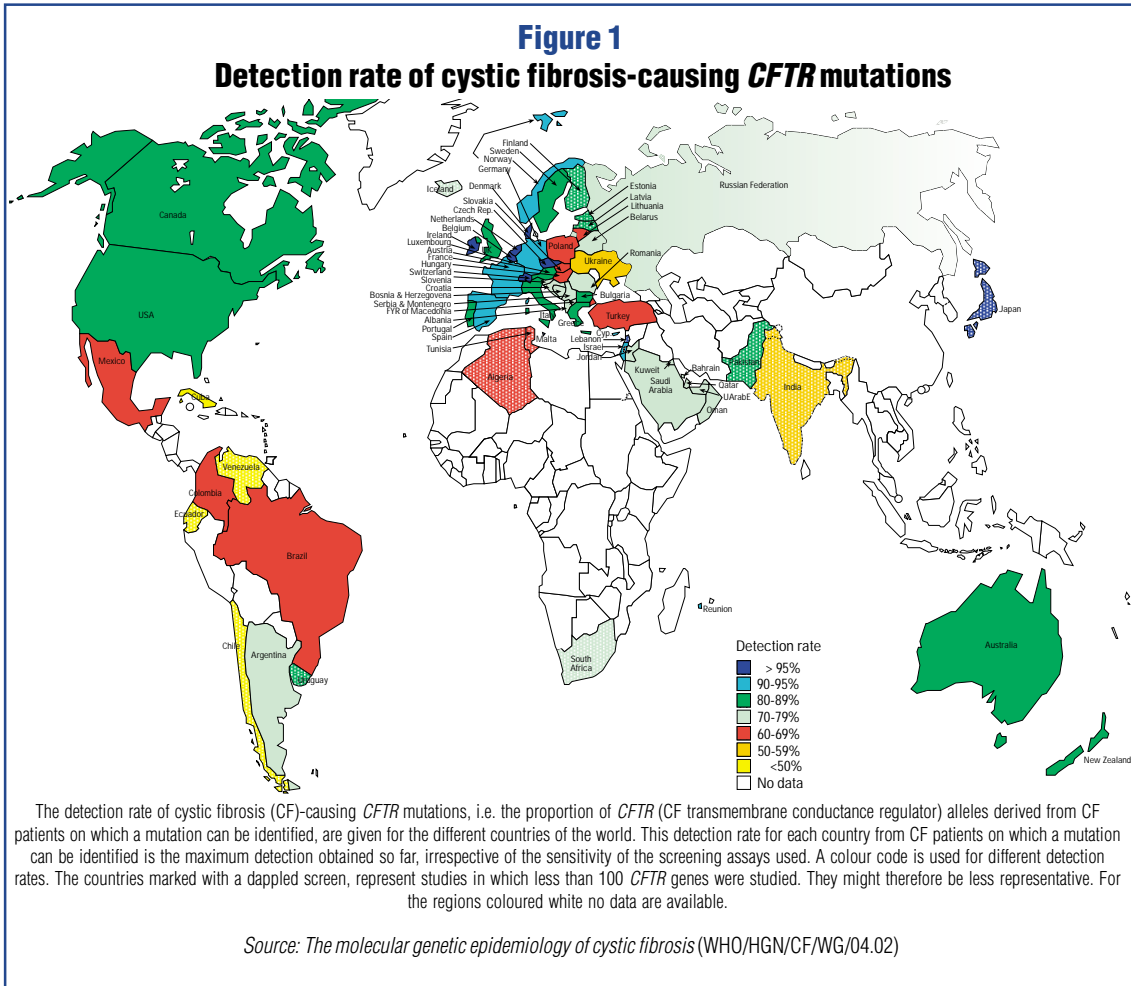
We begin by reviewing briefly the history of genomics and its impact on the biomedical sciences, as well as the relevance of genetics to the health needs of developing countries.

1.3 Genomics, genetics and health

1.3.1 Mendelian genetics and heritable disorders

One hundred and fifty years ago Mendel began his garden pea experiments, demonstrating that certain traits are passed from organisms to their progeny according to predictable patterns—and, in the process, laying the foundations of the field we now call genetics.

Disorders that are the product of so-called Mendelian inheritance are those where a specific trait is



affected by variations in a single gene inherited from one or both parents. These kinds of disorders are mostly incurable, usually severe, and though relatively rare, taken together affect millions of people globally. It is these kinds of disorders which are truly “genetic disorders”, and several developing countries are characterized by a high incidence of these. According to the *Genomics and World Health* report: “By far the commonest monogenic diseases are those involving human haemoglobin, the thalassaemias, and sickle cell disease and its variants, conditions that have a particularly high frequency in sub-Saharan Africa, the Mediterranean region, the Middle East, the India sub-continent and throughout southeast Asia” (WHO, 2002).

Having children with a genetic disorder has a particularly high cost in developing nations because parents can rarely rely upon subsidized health care or insurance to pay for often expensive therapies.

Haemoglobinopathies, of which β - and α -thalassaemias are the commonest forms, are the most prevalent genetic disorders affecting humans (WHO, 1996; Clegg and Weatherall, 1999).⁴ Treatment for thalassaemia requires children to undergo monthly blood transfusions that in turn may cause an iron overload that could bring about death in adolescence or in early adulthood. Iron-chelation therapy with deferoxamine to correct the problem of excess iron is very expensive, and

Box 2**What are DNA genetic tests and what can they tell us?**

DNA genetic testing involves the analysis of DNA in order to determine the presence of a gene associated with a particular disease. In general, there are four kinds of genetic tests:

Carrier testing determines if the person tested, who does not himself have the disease, carries a gene for the disease. If two carriers have a child together, there is a high probability that their offspring will have the disease.

Prenatal testing determines whether a foetus is affected with a genetic abnormality causing a particular condition. Embryos may also be tested during in vitro fertilization before being surgically implanted into the womb; this is called pre-implantation diagnosis. For technical reasons, the latter method is not widely practised.

Diagnostic testing determines whether the tested individual in fact has a particular genetic condition or a genetic predisposition for acquiring the condition later in life.

Predictive testing determines the presence in asymptomatic individuals of an abnormal gene that will lead to a disease in the future, or of a genetic predisposition for acquiring the condition later in life, in interaction with environmental factors.

is therefore out of reach for many poor people, like those living in Pakistan, where 5% of the healthy population carry the gene for β -thalassaemia. Some estimates put the rate of birth of affected infants at 1.3 per 1000 live births, which means about 5250 Pakistani infants are born each year with β -thalassaemia major (Ahmed et al., 2002).

Simple, inexpensive tests exist for carrier screening of this disease (WHO, 1994; WHO, 2002). (See **Box 2**.) Genetic testing of the fetus to diagnose the condition, or of the woman and her partner to determine their carrier status before conception, can provide critical information to inform choices about a condition that may have a dramatic impact on affected lives. Forms of prenatal diagnosis have been implemented, at some level, in Nigeria, Pakistan, Cuba and India (Verma et al., 2003). Prenatal diagnosis using the rapid and inexpensive polymerase chain reaction (PCR) to amplify DNA has been found to be useful in the diagnosis of sickle cell anaemia, a very serious condition associated

with a high level of mortality and morbidity. In West Africa, nearly one in four people is a carrier of the sickle cell gene (Adewole, 1999).

The efficacy of genetic approaches in the management of genetic conditions has been demonstrated in several Mediterranean countries that have implemented public health programmes to curb the devastating impact of thalassaemia in their populations (WHO, 2000; WHO, 2002; Cao et al., 2002). The enormous success of genetic screening programmes among the Ashkenazi Jewish population in the United States for Tay-Sachs disease (Kaplan, 1998), whose incidence has plummeted by 90% since testing began in the 1970s (Cohn, 2003), further testifies to the impact of a well-designed preventative strategy that incorporates genetic approaches for genetic diseases.

Because of the life-long burden of many conditions with a strong genetic component, early diagnosis or identification of carrier status provides valuable

information for making informed life choices—deeply personal choices about marriage, reproduction and lifestyle. Early testing for a range of conditions can assist patients in anticipating challenges, and in finding supportive structures and guidance early on, which often leads to improved health outcomes. Genetic tests may be particularly empowering for women, who are the child bearers and generally carry the primary responsibility of raising children and caring for the sick. But to be truly effective, it is essential that genetic testing be accompanied by appropriate counselling and support services that serve to inform patients, and to protect them from discrimination. Educational programmes are often valuable to improve community awareness, and to reduce the stigma sometimes attached to those identified as carriers of a genetic disorder (WHO, 1998).

But what role can genetic tests play in diagnosing much more common conditions, like diabetes and cardiovascular disease? In the following section, we will consider developments in genomics, and how this has provided the basis for the more elaborate study of genes and their interactions, and thus for the creation of interventions for much more complex human diseases.

1.3.2 The genome projects

Like Mendel's pea experiments, the 1953 discovery by Watson and Crick of the structure of the DNA double helix was a landmark event in the history of genetics, and in the history of the biological sciences. The event we will focus on here took place more than three decades later when, fuelled by advances in molecular biology and informatics, the Human Genome Project was initiated as an international effort to sequence the complete complement of human DNA. The Human Genome Organisation (HUGO) was the coordinating body of this effort, and at the First International Strategy Meeting on Human Genome Sequencing in 1996, partners in this initiative articulated their commitment to making their results rapidly available, and to placing them in the public domain. In March 2000, British Prime Minister Tony Blair and then-President of the United States

Bill Clinton issued a joint statement, affirming that: "To realize the full promise of this research, raw fundamental data on the human genome including the human DNA sequence and its variations, should be made freely available to scientists everywhere" (Lewis, 2000). They did not, however, rule out the patenting of DNA, later adding, "Intellectual property protection for gene-based inventions will also play an important role in stimulating the development of important new health care products".

Shortly after the start of the Human Genome Project (HGP), former president of the not-for-profit Institute for Genomic Research (TIGR) Craig Venter headed up a parallel initiative in the private sector, as leader of a new subsidiary of Applera Corporation, Celera Genomics. In 2001, the private and public sector projects announced simultaneously in different journals their respective completion of the draft sequence of the human genome (Venter et al., 2001; International Human Genome Mapping Consortium, 2001). Although the aims of the two projects intersected in a common desire to sequence the human genome, their final goals were different: the Human Genome Project sought to establish a scientific standard, namely the complete reference genome, while Celera Genomics sought primarily to sequence commercially valuable sections of the genome. The latter effort used the whole-genome shotgun sequencing method to generate short fragments that were pieced together using data from the public initiative.

The Human Genome Project, led by scientists around the world, was therefore the main driver of advances in genomics, an approach to the large-scale sequencing and analysis of DNA that continues to have an enormous impact on how biomedical research is done in laboratories around the world. Indeed, the Human Genome Project gave rise to many projects to sequence the genomes of a great many organisms, from useful laboratory animals to deadly disease-causing agents. The sequencing of the mouse (Waterston et al., 2002), rat (Gibbs et al., 2004), yeast, *C. elegans* (Wilson, 1999) and numerous pathogen genomes (Fleischmann et al., 1995; Read et al., 2000; Hall et

Box 3

Genomic medicine in Mexico

In 2004, the Mexican Institute for Genomic Medicine (INMEGEN) was launched. The genomic medicine programme is part of a strategy to improve the health of Mexicans through the development of cost-effective interventions for the prevention, diagnosis and treatment of disease.

A number of chronic, infectious and degenerative diseases currently represent significant causes of mortality in Mexico. In response to this need, the Ministry of Health (SSA), the National Autonomous University of Mexico (UNAM), the Mexican Health Foundation (FUNSALUD) and the National Council of Science and Technology jointly established a plan for the creation of INMEGEN. The Institute, which may ultimately be part of the Mexican National Institutes of Health (M-NIH), consists of an intramural research programme, including on-site laboratories and an in-patient clinical centre, and an extramural programme of collaborative research projects in Mexico and abroad.

In its current state, the Consortium for INMEGEN has already formed partnerships with three institutes in the M-NIH, and has sponsored over 40 lectures and developed three graduate-level courses on genomic medicine. In the first five years following its launch, INMEGEN will cost an estimated US\$ 190 million, or 0.82% of Mexico's annual federal health care budget.

Sources: Jimenez-Sanchez (2003), *Science*
Pharmaceutical Executive (2005)

al., 2002), have provided vast numbers of potential new targets for drug and vaccine development, and identified genes implicated in common disease. While genetic tests have been available for some time for a variety of single gene diseases (WHO, 1996),⁵ genomics has led to the creation of tests for “non-Mendelian” disorders, like various cancers, which affect a much larger proportion of people worldwide. Marrying genomics and computation has led to sophisticated microarray technologies for the diagnosis of complex disorders, which are the result of multi-gene interactions. For instance, progress has been made in genetic testing for some conditions, including familial hypercholesterolaemia, a condition that affects about 10 million people worldwide, and leads to a more than 50% risk of coronary heart disease by age 50 years in men and at least 30% in women aged 60 years (Marks et al., 2003; WHO, 1999). The study of rare but strongly genetic forms of a common disease (such as familial hypercholesterolaemia as a cause of atherosclerosis) not only provides clues about the genetic disorder, but also provides important

insights into the causal pathways leading to the more common disease (Brown & Goldstein, 1976).

So what, exactly, is the difference between genetics and genomics? As we have seen, medical genetics traditionally concerns itself with inherited single-gene (Mendelian) disorders, applying genetic tests, accompanied by non-directive counselling, to help patients in high-risk groups make decisions based on their genetic profile. What genomics brings is an approach to the large-scale study of many genes that permits sophisticated analysis of genes and their interactions. This means that genomics has applications far beyond simply genetic disorders; it can lead to greater understanding of the function of genes in more complex, multifactorial diseases and thereby to better therapies targeted more precisely at the root cause of disease.

Genomic medicine introduces a new dimension to health care—one that will rely more, rather than less, on genetic tests to determine susceptibility to various conditions and patients' likely responses

to some medications (Service, 2003). Genomics will arguably, therefore, make genetic tests more rather than less important as molecular tools become relevant to both diagnosis and prognosis of a much broader range of human diseases (Khoury, 2003; Gutmacher and Collins, 2002). Mexico presents an example of a developing country that has made a strategic decision to invest in genomic medicine. It would be valuable to assess which factors formed the basis for this decision, including the existing competence in traditional genetics approaches. Mexico's efforts over the next few years to realize this programme will provide a useful case study of an initiative in a relatively resource-poor setting to build endogenous research capacity in genomics and to generate applications relevant to the local health context.

There continues to be great optimism about the value of genomics for creating practical solutions to health problems. But despite the extraordinarily intense effort to produce a reference sequence rapidly, the resulting information cannot be immediately translated into clinical benefit. Sequencing of the human genome, while a remarkable technical achievement, was relatively straightforward when compared to the work needed to analyse the growing amount of raw data now available; this requires a level of analysis that is not easily automated. The complexity of disease causation, which involves gene–gene as well as gene–environment interactions, is particularly challenging for the study of most common human afflictions. Identifying relationships between genetic characteristics and clinically relevant features has proven extremely difficult.

So, while genomics has unquestionably generated an enormous volume of data in barely more than a decade, scientists are still in the very early stages of understanding how to transform this data into useful health applications. Nevertheless, genomics has already contributed important insights into the molecular mechanisms behind a range of conditions (Wickelgren, 2004), and provided new ways of approaching old problems, such as the control of disease vectors like mosquitoes (Brower, 2001) and vaccine development (Verma and Sharma, 2003). It is widely believed that it is only

Box 4 **Characteristics of the ideal diagnostic test—ASSURED**

Affordable by those at risk of infection

Sensitive (few false-negatives)

Specific (few false-positives)

User-friendly (simple to perform and requiring minimal training)

Rapid (to enable treatment at first visit) and **R**obust (does not require refrigerated storage)

Equipment-free

Delivered to those who need it

Source: Mabey et al., 2004

a matter of time before the promise of genomics is realized and these approaches begin to yield results (WHO, 2002). But this optimism should be tempered by the likelihood that the awaited harvest will be many years off, and the fact that there remain considerable technical and ethical challenges to surmount—including assuring the equitable distribution of its benefits.

1.4 Genetics and health in the developing world

We have seen what genetics offers to people with Mendelian disorders, and the potential that genomics has to offer those who suffer from more common human afflictions. But what does all of this mean for developing countries, where surely the issue is more one of the basic provision of health services rather than of access to sophisticated technologies?

The major argument of the *Genomics and World Health Report* is that genetics, and even genomics, should not be considered luxuries beyond the reach

of developing countries. Rather they are tools that present opportunities for addressing the specific needs of the poor, either through technology transfer or through the development of endogenous capacity. For example, besides the value of genetic tests in providing services of immediate public health benefit, the report claims that genetics has a second advantage: it lays a foundation for the development of skills and expertise in DNA-based techniques like genomics, opening the door to a powerful research platform with potentially wide applicability in the health sphere and beyond.

Although we have considered thus far genetic diagnostic tests for heritable conditions and other noncommunicable diseases, genetic tests can also be a useful tool for the diagnosis of infectious diseases. At present, for most infectious diseases, laboratory-based tests with reasonable sensitivities and specificities exist, but they are not available in peripheral health centres, which serve most of the population. Most existing tests depend on the availability of well-trained and supervised professionals, are time consuming and expensive, and rely on a constant supply of reagents and electricity. Nucleic-acid amplification technology, like the polymerase chain reaction (PCR), which can detect tiny amounts of DNA or RNA in a sample, have excellent sensitivity and specificity. This allows the use of non-invasive specimens, such as urine, for the diagnosis of some infections. Though successes have been achieved in the use of modified, simple versions of these assays, they are generally expensive and require technical expertise and equipment (Mabey et al., 2004).

Genetic tests today apply primarily to well-studied heritable conditions like those discussed above. But genomics provides an opportunity to create applications for much broader use. Because of their cost and simplicity, the use of DNA-based tests is likely to grow, and to prove directly applicable to developing countries, and to their health systems. The urgency of developing genetic tests for inherited disorders is appropriate in those regions where there is heavy burden of haemoglobinopathies or other conditions amenable to existing genetic tests. But the effort to develop technologies that are cheap and well-adapted for use in resource-poor settings

is one that has widespread utility. Achieving this will require identifying those applications that are relevant—whether PCR tests to diagnose Chagas disease, or microarrays to identify aberrant cell activity—and adapting them to local settings. Promising areas of research could even include military-driven efforts to develop ways of easily detecting biological warfare and infectious agents redirected for use in developing countries. How to bring these applications to the poor is a challenge; it is more a matter of the economics and politics of health research than any innate quality of science that makes it remote to global health challenges. Finding the right political and economic levers to turn advances in genomics into benefits for developing countries requires an open appraisal of incentives and barriers to research, including patents and other forms of intellectual property.

Genomics is in its formative stages; a great deal of information has been gathered, and the challenge is now to translate it into useful applications. Developing countries could benefit scientifically, economically and in terms of health outcomes, from being part of this foundational, dynamic and often collaborative research. There are examples of developing countries (see **Box 3**, and section 1.3) that have made the decision to invest in building capacity in genomics; it would be worthwhile to monitor their progress. Competency in genetics may, indeed, play a part in some cases in fostering this capacity; in any event, although genetics and genomics have both qualitative and quantitative differences (Khoury, 2003), they both rely fundamentally on the study and analysis of genes and their functions. Factors, including patents, that facilitate or hinder access to genetic sequences are likely to have an impact on developments in these two emergent fields.

1.5 Patents

Patents are one of several forms of intellectual property. This section will provide an overview of the basic features of patents, the rationale for the patent system, and the patenting of genetic sequences. Some of the issues raised in this section

Box 5 Australian firm patents “junk” DNA

Mervyn Jacobson, co-founder and Executive Chairman of the small Australian biotechnology firm Genetic Technologies (GTG), claims that he and his colleagues were the first to realize the value of “junk” DNA, the 98.5% of human DNA that does not code for genes.

The firm owns four broad patents on non-coding sequences, stretches of “junk” DNA, which today are known to have great value in helping researchers to identify and analyse coding regions, and in mapping haplotypes associated with common diseases like cancer and diabetes. GTG’s US patents expire between 2010 and 2016. The company has been heavily criticized in some quarters for what is seen as the aggressive enforcement of its patents, against other firms as well against academic institutions.

Applera is among three US companies now facing an in-

fringement suit from GTG for its use of non-coding DNA for a diagnostic test for cystic fibrosis. New Zealand’s Department of Health has been advised to pay US\$ 5.7 million in licence fees.

Dr Jacobson argues that “a lot of academic organizations are under pressure to generate revenue. Why should they be exempt from the rules of the market?” His company, he says, wishes to license its inventions widely for reasonable fees. In fact, GTG used its broad patents to make a deal with Myriad Genetics, negotiating the use of GTG’s patented inventions in exchange for control over the licensing of Myriad’s rights in Australia. Thanks to this agreement, GTG exercises its prerogative to permit free access to Myriad’s technology for service providers in Australia.

Source: Moukheiber (2003), *Forbes*.

will be taken up again in the analysis portion of this report (see section 3).

1.5.1 What is a patent?

Patents were created as a way to provide financial incentives for inventors to undertake research, by allowing them to exclude competitors from exploiting their invention for a specified period of time. This period gives the inventor time to commercialize her invention and recoup her investment, as well as make a profit. The resulting system is therefore justified as a means of encouraging innovation, by rewarding inventors, promoting public disclosure of inventions, inducing investment in the development of inventions, and providing the public with useful new products. The patent system is one method of addressing the problem of under-investment in those areas of innovation where the initial costs of

research and development are high compared to the costs of copying.

In order to be patentable, an invention must meet the criteria of *novelty*, *industrial applicability* (or *utility*, in the United States of America), and demonstrate an *inventive step* (or *non-obviousness*, in the United States, arguably a lower threshold that is particularly important for sequence-based patents). What is already known is called “prior art”, and a patent is intended to reward an inventor for an advance requiring a step that would not have been obvious to someone technically competent in the field.

The rights of a patent holder have been described as a fence blocking off territory, within which other parties are not allowed to tread without a licence. Those who cross the fence without permission may be found to have infringed the patent right of the

patent holder. The text of the patent includes patent *claims* that define the subject matter of the invention, as well as all the elements, features and critical aspects of the invention, so that a person trained in the relevant scientific discipline should be able to replicate the invention. Claims define the scope of the patent, or in other words, the size of territory that fits within the protected barrier of the fence.

The scope has important implications for how far the patent reaches, as it were, to encompass unforeseeable uses and applications of the patented invention. It is sometimes in the patentee's interest to draft the claim in very broad language to garner the broadest protection possible, though this strategy may make the patent more vulnerable to validity challenges. It is the role of the patent office to assure that the language does not encompass prior art, or more than what is warranted by the description of the invention. Determining the correct limits for the scope of patents for new technologies comes about through a gradual process of refinement by patent offices, and then by the courts. Case law plays an important role in defining the boundaries of the rights conferred by patents.⁶

One important feature of patents is that they may be granted on a product, a process, or a use: product patents to cover, for example, chemicals, formulations, equipment and diagnostic kits; process patents to cover a method for creating a product; and use patents to cover a specified use of a product. An invention covered by a product patent cannot be reproduced without a licence, *even if* a different method is used to make it. A process patent, on the other hand, does not hinder someone else from making the product without a licence, if a different process is used. What this means, however, is that a patent on a gene within an organism (like a plant or even a mouse, for instance) can, in effect, confer rights to the organism itself (such as in the case of the Harvard OncoMouse referred to in section 3.1.1).

In general, patents can be claimed for inventions, but not for "discoveries".⁷ This dichotomy, which turns out to be difficult to define precisely, typi-

cally amounts to a distinction between what exists "in nature", and what is the product of human labour, or at a minimum, human intervention. Patenting in biotechnology presents particular challenges to this distinction, because the subject matter in question consists of "natural" entities. Today, the condition of existing "in nature" is understood narrowly in the patent law in many countries, meaning literally what exists *in nature*; that is, what exists in its un-isolated form. But despite the fact that patents have been granted in some jurisdictions for many years, a great deal of debate continues to surround the patentability of naturally occurring substances that have been isolated using laboratory-based approaches (Eisenberg, 2002b). This has been the basis of much of the controversy surrounding the patentability of DNA and DNA methods, as well as the status of DNA vectors, cell lines, embryos, and genetically modified organisms.

According to the United States Patent and Trademark Office (USPTO), "a patent on a gene covers the isolated and purified gene but does not cover the gene as it occurs in nature" (USPTO, 2001). According to this view, what distinguishes a DNA sequence that exists naturally in a cell or organism from a patentable DNA sequence is that the former owes nothing of its existence to a human inventor, while the latter would not exist without some form, however minimal, of human intervention (Gold, 2003). The invention/discovery (or invented/natural) dichotomy is principally relevant to the novelty standard of patentability. Once the isolation of a gene sequence has been judged to meet this standard, it still must have some distinguishable utility and be shown to have demonstrated an inventive step (or non-obviousness). How to accommodate biotechnology inventions in patent law is still a hotly debated issue, and countries have not responded uniformly in the laws they have enacted regarding DNA sequences and other biological entities (see section 2.4).

In general, DNA patents claim at least one of the following four applications of DNA sequences: diagnostic testing, research tools or methods, gene therapy or methods, or the production of therapeutic proteins to be used as medicines (Nuffield, 2002).⁸

However, many patents cover more than one category—or simply claim the gene, without limitation as to its use. Various organizations, including professional associations,⁹ have articulated their positions on the patenting of human DNA. HUGO issued a statement in 1995, and later updates in 2000 and 2003, arguing against patents on short sequences of DNA (e.g. expressed sequence tags or ESTs, and single nucleotide polymorphisms or SNPs), among other things, on the grounds that they had unproven utility. In 1997, the UNESCO General Assembly unanimously adopted a *Universal Declaration on the Human Genome and Human Rights*, which stresses the importance of acknowledging human dignity, and states that no part of the human being can be subject to profit in its natural state. Because patent law standardly acknowledges that the limits of patents are entities found “in nature”, the UNESCO Declaration does not in fact challenge the current patenting of isolated sequences. In 2002, UNESCO’s International Bioethics Committee also took up the question of patents and the genome, producing a report addressing a range of ethical issues. This report proposed the adoption of an international convention on ethics, intellectual property and genomics, and a Code of Conduct as options to address public interest considerations related to TRIPS (Kirby, 2002).

1.5.2 A brief history of the patent system

The intellectual property (IP) system has been around for a long time. But its history has not been uniform or without controversy, even in its early days. In recent years, this history has been marked by dramatic changes in the way that lawmakers and courts view and interpret the system. In less than a decade, subject matter covered by intellectual property in several jurisdictions has expanded and the length of time before work gets into the public domain has lengthened. It is not only that intellectual property has changed; society has also changed, becoming increasingly “networked”. This means that copying is easier, but it also means that potential markets are considerably enlarged. As one academic has noted: “IP is now implicated

in routine, creative, communicative, and just plain consumptive acts that each of us perform everyday. The reach of the rights has been expanded just at the same moment that their practical effect has been transformed” (Boyle, 2003). The growth of genomics has paralleled—and is indeed an element of—this expansion and strengthening of IP.

The patent system has been compared to a kind of enclosure movement, not unlike the enclosure movement of eighteenth century England, when state-supported privatization conferred individual property rights on what had formerly been land with communal rights to its use. A major difference with today’s movement is that its subject is “the intangible commons of the mind”, rather than agricultural land. The economic rationale for this former movement was the need for incentives for large-scale investment and to ensure the most efficient use of resources—in other words, to guard against the “tragedies of the commons”, namely overuse and under-production (Hardin, 1968). The equivalent economic argument today is that intellectual property rights are needed to ensure that there will be those prepared to invest the time, creativity and capital needed to produce new and needed products. But the tragedies of the old commons do not apply in the same way in the context of IP. The “commons of the mind” is non-rival, which means there is no threat of overuse: unlike fisheries, my consumption of an idea does not threaten your consumption. In fact, your consumption may add value to the idea, rather than subtract value. It is also non-excludable, like clean air, which makes it hard to charge money for its use.

Today, intellectual property rights have changed from being the exception, protecting mostly downstream industrial inventions and relatively hard to infringe, to something that the courts often defend vigorously, and where courts also tend to favour property owners more than they did two decades ago (Boyle, 2003).

The rapid increase in patenting in the last decade or so is also indicative of a shift in how organizations do research. According to a recent

report by the Organisation for Economic Co-operation and Development (OECD, 2004):

Not only have new types of inventions—software, genetic, and business methods—been deemed patentable by some patent offices, but the ability of patent holders to protect and enforce their rights has also increased, leading many to call the past two decades a pro-patent policy era.

Of course, this is not the first time the patent system has had to deal with new technologies. But research in the twenty-first century is increasingly based on markets and knowledge networks, rather than on the isolated performance of individual firms. Moreover, the biotechnology, pharmaceutical and medical device markets are among the most patent-sensitive markets in the entire economy, and at the same time the most dependent on close ties to academic science for development of new products and services. These networks are more complex and partnership-dependent, as well as more global. Absorbing these changes has not been easy; indeed, patent offices and courts have struggled to keep pace, build institutional expertise, and evaluate prior art to determine the right standards for the breadth of granted patents in these rapidly evolving sectors (Cornish, Llewelyn and Adcock, 2003).

Some have suggested that these changes present fundamental challenges for the patent system itself:

The patent system is designed as a tool to provide an incentive to technical progress. The effectiveness with which it can do this will depend on the fit between the nature of the incentive and the processes by which technological development takes place. But whereas the patent system has uniform criteria to judge patent applications, the pattern of technical progress may vary significantly in different fields. The patent system fits best a model of progress where the patented product, which can be developed for sale to

consumers, is the discrete outcome of a linear research process. The safety razor and the ballpoint pen are examples, and new drugs also share some of these characteristics. By contrast in many industries, and particularly those that are knowledge-based, the process of innovation may be cumulative, and iterative, drawing on a range of prior inventions invented independently, and feeding into further independent research processes by others (IPR Commission, 2002).

In the case of new technologies marked by a more cumulative character, there are concerns that patent protection may impede innovation, in particular by limiting access to essential research tools and methods. In these instances, “too broad a protection on basic inventions can discourage follow-on inventors if the holder of a patent for an essential technology refuses access to others under reasonable conditions. This concern has often been raised for new technologies, most recently for genetic inventions” (OECD, 2004). In 2003, in its report on innovation, competition and patent policy, the United States Federal Trade Commission concluded that “in industries with incremental innovation, questionable patents can increase ‘defensive patenting’ and licensing complications”, and moreover that “questionable patents are a significant competitive concern and can harm innovation”.

Genomics-based research is inherently of a cumulative nature. As we will see in section 3.2, the networked nature of genomic research means that exclusive property rights intended to stimulate innovation may, in some cases, in fact hinder it. Developed countries are increasingly interested in the debate about genetic patents. Their experience may well be a harbinger for developing countries with relatively advanced scientific capacity, and could affect research in more developed economies that could generate interventions for the poor.

1.5.3 Licensing patented inventions

Every inventor is faced with the decision of whether or not to patent his invention (although in many cases, the patent holder and the inventor are not the same individual, because institutions will often claim rights over their staff's innovations). The decision to patent gives the patent holder at least two options as to how to exercise his rights. First, the patent holder can use the invention herself or himself and exclude all others from its manufacture,

use or sale. Alternatively, the patent holder can grant others the right to use the invention under agreed-upon terms through a licence, either exclusive to one licensee or non-exclusively to multiple licensees.¹⁰ Exclusive licences can include exemptions, for example for humanitarian or research use. In each of these cases, the patent holder is able to obtain revenue—either through the sale of his own goods and services or through royalties obtained from licensees. This is the financial incentive that undergirds patent law.

Box 6 **BRCA—The “Breast Cancer Gene”**

A much-cited example is that of Myriad Genetics, and its patenting and subsequent licensing of two genes (*BRCA1* and *BRCA2*) that are implicated in breast and ovarian cancer for women, and prostate cancer for men. Besides being the subject of many research initiatives, testing for mutations of these genes is important for genetic counselling, and recommending preventative approaches to individuals with a family history for cancer. This example has raised enormous controversy around the world, particularly in those countries in Europe and North America where patents have been issued and exclusive licensing practices exercised. Myriad's researchers sequenced the two genes and, on the basis of these discoveries, developed a sophisticated, highly automated protocol for the diagnosis of the related conditions, which costs US\$ 2500. In countries where Myriad holds patents, third parties cannot, without permission from Myriad, perform research that might refine, improve or validate the claimed genetic tests or identify new tests and diagnostic approaches.

Myriad's practice of requesting that all samples be sent to its own laboratories for analysis indirectly allows the company to build an exclusive genetic database, which could serve as a foundation for further research on the two genes and related mutations (possibly to allow some licensing, but data has to be shared). In this way, Myriad is achieving the ability to store all new information about *BRCA1* and *BRCA2* in its own laboratories, arguably extending its monopoly beyond what was granted by existing patent laws.

In Europe, numerous institutions filed an opposition to the European patents on the *BRCA* genes, and in Canada, some

provincial governments have protested by ignoring Myriad's patents and permitting the use of its patented inventions by Canadian researchers and clinicians. However, European researchers applauded in February 2004, when the European Patent Office (EPO) granted a Europe-wide patent on *BRCA2* to the charity Cancer Research UK, which published its discovery of the gene in 1995. The charity has agreed to waive fees for all public laboratories that apply to use the gene for non-profit research and clinical use.

Myriad's first patent was revoked entirely by the EPO in 2004, because it had filed its sequence with the USPTO in a rough form; by the time the correct sequence was filed, other scientists had already placed it in a public database, making it invalid for patenting. Myriad has filed an appeal against this decision. On 20 January 2005, the EPO ruled that the scope of Myriad's second patent should be dramatically limited so that it covers only a single probe, rather than any probe or nucleotide sequence that can recognize the gene. A few days later, following a public hearing, the EPO's opposition division concluded that Myriad could maintain its third patent on *BRCA*—but amended the patent so that it related *only* to the gene probe of a defined composition, and no longer included claims for therapeutic and diagnostic methods.

Sources:

Bosch (2004), *Lancet*

Lecrubier (2002), *EMBO Reports*

EPO, <http://www.european-patent-office.org>

Abbott (2005), *Nature*

Decisions as to whether and to whom to license an invention involve selection, and possibly the exclusion of some from the use of that invention. While this system can promote innovation by providing a return on investment to early innovators, there is the risk that it could hinder those conducting important research or providing needed services downstream, and can inhibit cumulative innovation. A patent holder's decision to license may impose constraints on research and even on clinical practices; if a single protocol is imposed on practitioners, it can obstruct further research and validation of the inventor's results. Discretion is left to patent holders whose prerogative it is to decide how to make use of the invention. As we will discuss in section 2.3, there are notable examples of researchers who decided not to patent their innovations but instead chose to make them freely available to third parties, and examples of others who chose to patent, but whose licensing programmes did not erect barriers to access. However, there are also examples of institutions whose patenting and licensing practices have been questioned on the grounds that they may operate against the wider public interest.

Box 6 (p. 13) describes the example of Myriad Genetics, and the impact of its patents on two genes implicated in familial breast cancer on access to genetic services.

One should, however, be wary of conclusions based on a limited number of case studies. The Myriad case demonstrates, for example, what can happen as a result of gene patenting, coupled with

restrictive licensing practices. It is also important to realize that patent holders do not have unfettered discretion. Traditionally, provisions have been included in patent law to safeguard against abuse and anti-competitive behaviour. These include instruments like compulsory licenses, which we will discuss in section 2.1 below.

One question to consider is whether the current structure of the patent system tends to encourage behaviour among patent holders that militates against the objective of promoting innovation for publicly useful purposes. For example, the nature of industry interactions may create pressure to use patents as 'anticompetitive weapons' to extend monopolies and block competitors. If this is so, and such practices are widespread, it undermines the *raison d'être* of the patent system by inhibiting cumulative innovation.

The United States National Institutes of Health (NIH), in March 2004 introduced draft guidelines on the patenting and licensing of genetic inventions. The guidelines have been criticized by some as being based more on anecdote than evidence (Surendran, 2004). In an effort to rectify this, the NIH is sponsoring a number of projects assessing the impact of university gene patents in order to gather relevant facts (Malakoff, 2004). The National Academies are, for example, conducting a study on DNA and protein patents. Efforts of this kind are valuable for elucidating current trends in patenting behaviour, and are commendable for their attempt to ground policy in empirical work.