Genetics, genomics and the patenting of DNA

Review of potential implications for health in developing countries

Human Genetics Programme
Chronic Diseases and Health Promotion
World Health Organization

2005

WHO Library Cataloguing-in-Publication Data

Genetics, genomics and the patenting of DNA : review of potential implications for health in developing countries.

1.Genomics - legislation 2.DNA - therapeutic use 3.Patents - ethics 4.Patents - legislation 5.Genetic research - legislation 6.Review literature 7.Developing countries I.World Health Organization.

ISBN 92 4 159259 1 (LC/NLM classification: QU 33.1)

Cover by WHO Graphics

Printed in Switzerland

Contents

Boxes, figures and tables

Acknowledgements

The present document grew out of a WHO Consultation in April 2002, organized and hosted by the University of Toronto's Joint Centre for Bioethics, a WHO Collaborating Centre. The meeting was organized to respond to the recommendations of The Advisory Committee on Health Research (ACHR) report on Genomics and World Health (2002), and aimed to develop a strategy to promote genetic services and to strengthen discussion on genetic ethics. Its recommendations emphasized the importance of an ELSI (ethical, legal and social implications) perspective in considering the implications of genomics for health.

This document benefited from the input and guidance of numerous individuals. The Human Genetics Programme would like to express its thanks to the University of Toronto Joint Centre for Bioethics, for its support for this and other ethics-related initiatives of the Programme, as well as to **Louise Bernier**, **Karen Durell**, and **E. Richard Gold**, of the Centre for Intellectual Property Policy, McGill University, Montreal, Canada, for drafting the background paper that formed the basis for the review process, and the development of this final report. Thanks are also due to the following staff from WHO Headquarters for their helpful feedback on earlier drafts of this document: **Alexander M. Capron** and **Jason Sigurdson**, of the Department of Ethics, Trade Human Rights and Law; and **Charles Clift**, of the Secretariat for the Commission on Intellectual Property Rights, Innovation and Public Health. In addition to members of WHO, several others generously contributed comments on drafts: **R. Cook-Deegan** (United States of America), **R. Eisenberg** (United States), **A. Rai** (United States) **and P.A. Singer** (Canada). A special thank you also to **Eduardo Sabate** (Venezuela), for his valuable advice and to **Rafael Bengoa** for his support throughout the entire process.

Preparation of the document was undertaken by the Human Genetics Programme headed by **Victor Boulyjenkov.** Principal responsibility for writing and editing rested on **Alyna Smith**, assisted by **Angela Ballantyne**. The Programme is particularly grateful to members of the Scientific Review Panel, for their commentary and advice throughout the development of this report: **Shaikha Al-Arrayed** (Bahrain), **Amir Attaran** (United States), **John Barton** (United States), **Kare Berg** (Norway), **José Maria Cantu** (Mexico), **Jean-Jacques Cassiman** (Belgium), **Mildred Cho** (United States), **Carlos Correa** (Argentina), **Abdallah Daar** (Canada), **Prabuddha Ganguli** (India), **Cathy Garner** (United Kingdom of Great Britain and Northern Ireland), **E. Richard Gold** (Canada), **Vladimir Ivanov** (Russian Federation), **Patricia Kameri-Mbote** (Kenya), **Darryl Macer** (Japan), **Patricia Aguilar-Martinez** (France), **Sisule Musungu** (Switzerland), **Victor Penchaszadeh** (United States), **Sandy Thomas** (United Kingdom), **Lap-Chee Tsui** (China), **Ishwar Verma** (India), **Huanming Yang** (China). A complete list of names, including institutional affiliations, of the members of the Scientific Review Panel can be found in Appendix 2.

Foreword

Rapid advances in genetic technology and human genome research make it almost certain that genetics and genomics will become more and more important for health improvement. If used appropriately, this knowledge will provide many exciting future opportunities to achieve better health for all people. However, it is clear that many individuals, groups and nations have concerns about the use and exploitation of genetic data and genome technology. Biomedical research in human genetics can lead to the development of diagnostic and pharmaceutical products. Patents may be necessary to raise funding to develop such products commercially, but patenting also has the potential to impede access to genetic materials, to the ultimate detriment of service delivery to those with genetic disorders, especially in developing countries.

While governments have long relied on patents and other forms of intellectual property to foster innovation, in recent years there has been some concern that patents on genes may hinder research in the public sector, and push costs too high for widespread access to medical products and services, particularly for complex diseases such as heart disease, cancer, diabetes and asthma. However, the extent of the impact of patents on genomics innovation and on access to genetic services continues to be a matter about which there is great disagreement. The Human Genetics Programme, with this initiative, aims to draw together existing arguments and evidence to present a picture of the current landscape of the debate, from a pubic health perspective.

Genetics differs from many areas of research in that important new knowledge can come from an individual, a family, or an ethnic group with a particular genetic variant. Genetic material, and the information it encodes, therefore has the dual quality of being both personal and communal. The human genome and the segments of DNA that constitute it likewise would appear to have conflicting status of being both proprietary, and a common heritage. Intellectual property is a system developed with the ultimate end of promoting the public good by fostering the creation of useful new products. An important challenge is how to square the seemingly competing needs of inventors and communities to ensure an equitable distribution of benefits.

This report does not look to define policy, but to highlight areas of contention, suggest avenues for further investigation and stimulate dialogue among different stakeholders. Thus, the report may serve as a point of departure for professionals and public health officials to develop policies and appropriate practices. It expresses the view of the authors and does not necessarily represent the policies of the World Health Organization.

Dr V. Boulyjenkov, Ph.D, D.Sc.,

Human Genetics Programme

Acronyms

ABS	access and benefit sharing
ACHR	Advisory Committee on Health Research
AIPPI	International Association for the Protection of Intellectual Property
ARIPO	African Regional Industrial Property Organization
BGI	Beijing Genomics Institute
BRCA	breast cancer gene
CAS	Chinese Academy of Science
CBD	Convention on Biological Diversity
CHGC	Chinese National Human Genome Centre
CVC	citrus variegated chlorosis
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
EMR	exclusive marketing right
EPO	European Patent Office
EU	European Union
EST	expressed sequence tag
FAPESP	State of São Paulo Science Foundation
HGP	Human Genome Project
HUGO	Human Genome Organisation
IP	intellectual property
IPR Commission	Commission on Intellectual Property Rights
IPRs	intellectual property rights
JPO	Japan Patent Office
LDCs	least developed countries
MCH	Miami Children's Hospital
OECD	Organisation for Economic Cooperation and Development
ONSA	Organisation for Nucleotide Sequencing and Analysis
PCR	polymerase chain reaction

1 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 countries[3] 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
- 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.

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.

1.3 Genomics, genetics and health

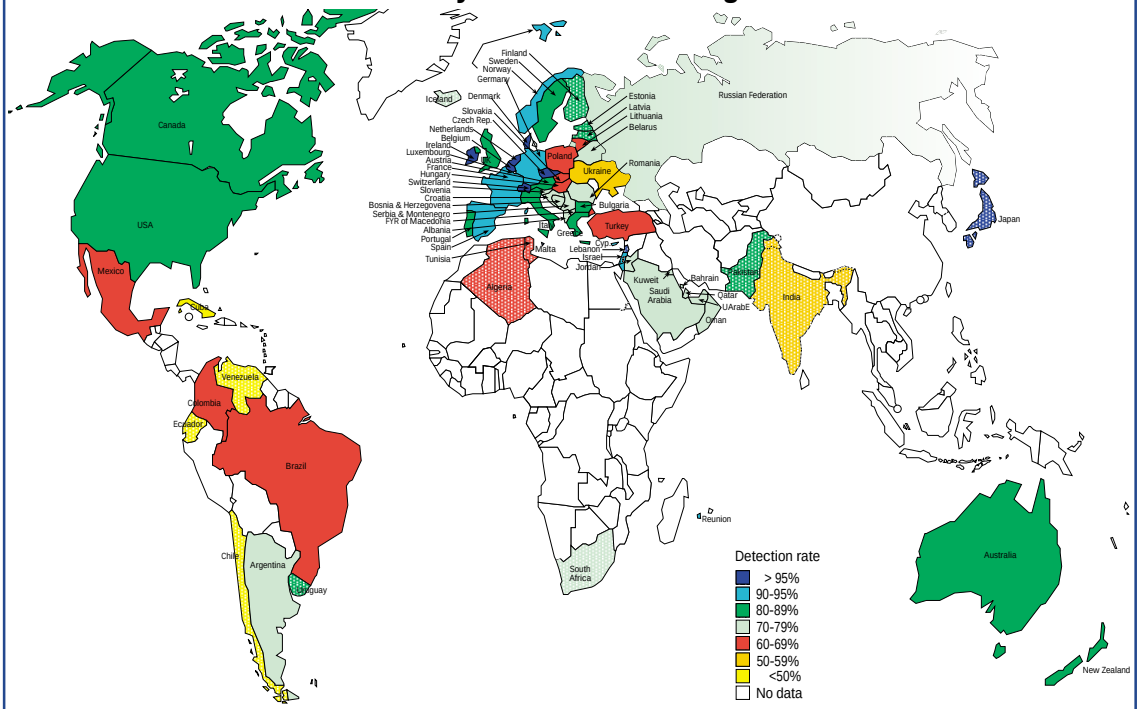
1.3.1 Mendelian genetics and heritable disorders

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

Figure 1

Detection rate of cystic fibrosis-causing *CFTR* mutations



The detection rate of cystic fibrosis (CF)-causing *CFTR* mutations, i.e. the proportion of *CFTR* (CF transmembrane conductance regulator) alleles derived from CF patients on which a mutation can be identified, are given for the different countries of the world. This detection rate for each country from CF patients on which a mutation can be identified is the maximum detection obtained so far, irrespective of the sensitivity of the screening assays used. A colour code is used for different detection rates. The countries marked with a dappled screen, represent studies in which less than 100 *CFTR* genes were studied. They might therefore be less representative. For the regions coloured white no data are available.

Source: The molecular genetic epidemiology of cystic fibrosis (WHO/HGN/CF/WG/04.02)

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 thalassemias, 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 subcontinent 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; Guttmacher 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 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.

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 Robust (does not required refrigerated storage)

Equipment-free

Delivered to those who need it

Source: Mabey et al., 2004

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 infringement 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, typically 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.

2

The current landscape

2.1 Intellectual property systems

A patent is valid only within a particular jurisdiction. For instance, a patent granted by the USPTO provides rights over a given invention within the United States of America. Third parties are excluded from making, using or selling the invention within the borders of the United States and its territories, including importing the invention into the country.

An inventor can seek patent protection in multiple jurisdictions through a single application. The African Regional Industrial Property Office (ARIPO), an organization of eastern and southern African countries, is an example; a single application can provide patent protection across all 15 countries that belong to ARIPO, although national offices still need to register patents in accordance with national law. By contrast, in the African Intellectual Property Organization (OAPI), an organization of West African countries, there is a truly regional patent. In Europe, an applicant can apply to one or more national patent offices, or can apply for a patent from the EPO, which is recognized in countries party to the European Patent Convention. A national patent is valid in that country; an EPO patent can be recognized in multiple countries designated by the inventor. Infringement actions, however, must be litigated in national courts. The EPO is the administrative body of the European Patent Convention, which covers all European Union (EU) Member States as well as some non-EU countries. Since 1975, there has been discussion about creating a single patent (the Community Patent) for the whole of the EU.[11] The Patent Cooperation Treaty (PCT) permits inventors to apply through the World Intellectual Property Organization (WIPO) for patent protection in 123 countries, but patents are only actually granted at the national level.

Globally, the EPO, USPTO, and Japanese Patent Office (JPO) are the most influential actors in international patent policy, and regularly meet in trilateral discussions.[12] WIPO plays a major role in the administration of international agreements, and the WTO has become a key institution as a result of the 1995 Agreement on the Trade-Related Aspects of Intellectual Property Rights, which emerged from the Uruguay Round of trade negotiations of 1994 that also established the World Trade Organization.

Despite the creation of various international frameworks, and the streamlining of patent application processing across some jurisdictions, patent legislation is nevertheless designed and applied principally at the national level. It is therefore important that each country weigh domestic factors when constructing its patent regime. However, national patent regulation is heavily constrained by the requirements of TRIPS.

Under TRIPS, WTO Members are obliged to provide minimum standards of protection for a wide range of intellectual property rights, incorporating many of the provisions from existing agreements administered by WIPO, like the Paris Convention of 1883 and the Berne Convention of 1886. With regard to pharmaceutical patents specifically, TRIPS requires that all nations (except least developed countries) adopt the practice of accepting pharmaceutical product claims as patentable by 2005 at the latest. The WTO Doha Declaration of 2001 reaffirmed that the TRIPS Agreement "can and should be interpreted and implemented in a manner supportive of WTO Members' rights to protect public health and, in particular, to promote access to medicines for all" (WTO, 2001; WT/MIN(01)/DEC/2).

However, the implementation of the Doha Declaration was contentious, in particular resolving the issue identified in paragraph 6 of the Declaration. Article 31(f) of TRIPS states that products made under compulsory licensing must be "predominantly for the supply of the domestic market". A compulsory license is a government-authorized use of a patented invention without the patent holder's consent, and is permissible under Article 31 of TRIPS, provided that certain conditions are met. In paragraph 6 of Doha, the WTO recognizes that WTO Members with insufficient or no manufacturing capacity in the pharmaceutical sector could have difficulty making effective use of the compulsory licence safeguard, originally expressed in TRIPS and clarified in the Doha Declaration (WTO, 2001; WT/MIN(01)/DEC/2).

On 30 August 2003, after protracted negotiations, member countries finally agreed "to allow any member country to export pharmaceutical products made under compulsory licences" (WTO, 2003; WTO Press/350/Rev.1). Eligible developing countries now have the option of importing generic drugs produced under compulsory licences overseas, which they would not be in a position to produce domestically, in order to address local public health challenges.[16] All compulsory licences would be required to comply with the agreed terms and it was understood among the members that the decision would be "used in good faith in order to deal with public health problems and not for industrial or commercial policy objectives" (WTO, 2003; WTO Press/350/Rev.1).

The present reality is that many developing countries lack not only sufficient scientific capacity to manufacture patentable products but also the necessary infrastructure and capacity to construct and implement finely balanced patent systems (Carroll, 1995). There is concern that they may be obliged to institute "TRIPS plus" legislation nationally (e.g. as a result of bilateral trade agreements), which does not take advantage of the flexibility and public health safeguards within TRIPS (Musungu and Dutfield, 2003).[14]

2.2 TRIPS and DNA patents

In relation to DNA patents specifically, there is contention as to whether TRIPS requires countries to grant patents on DNA sequences. While the TRIPS Agreement does not explicitly obligate its members to declare DNA sequences to be patentable inventions, Article 27(3) does not list DNA or genes among the acceptable exceptions from patentability. According to Article 27, "patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application". However, it stipulates that:

> 3. Members may also exclude from patentability:
>
> (a) diagnostic, therapeutic and surgical methods for the treatment of humans or animals;

Box 7
Research exemptions

TRIPS, in section 30, states that members can provide limited exceptions to the exclusive rights conferred by a patent. Section 8 of TRIPS permits members to adopt measures necessary to protect public health and nutrition and to promote the public interest in sectors of vital importance to their socioeconomic and technological development.

Some countries have adopted research exceptions (also called research exemptions) in their patent legislation, which grant a limited right to researchers to experiment on a patented invention. They may also enable researchers to undertake studies to gain a fuller understanding of the invention itself without having to pay royalties to the patentee. But there is sometimes uncertainty about the scope of a project permitted by a research exception clause, especially in the case of research dealing with genetic material. In the United States of America, a recent case (*Madey v. Duke,* 2002) has severely limited the research exemption in the country's universities.

Some developing countries have also integrated a research exception clause into their patent legislation. For example, the Brazilian Patent Law states that "experimental working for scientific or technological research purposes" qualifies as a research exception (Brazil: Patent Law 9.279 of 1997).

In India, section 47(3) of the Patent Act of 1970 excludes from the exclusive patent right "any machine or other article in respect of which the patent is granted and any process in respect of which the patent is granted may be made or used by any person, for the purpose merely of experiment or research including the imparting of instructions to pupils". Amendments to the India Law in 1999 and 2002 have retained section 47(3) as crafted in 1970.

The Patent Law of the People's Republic of China states in section 62 that using the patent concerned solely for the purposes of scientific research and experimentation is not considered to be an infringement of the patent right.

A number of recent reports have expressed the need for greater clarity regarding what is covered by research exemptions, particularly in relation to clinical and preclinical research (OECD, 2004; Nuffield, 2002). This environment creates significant uncertainty for researchers who may become hesitant to undertake projects where they need to rely on ill-defined exemptions. Researchers may rightly fear having to face patent infringement suits, which could be very expensive.

(b) plants and animals other than micro-organisms, and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes. However, Members shall provide for the protection of plant varieties either by patents or by an effective *sui generis* system or by any combination thereof. The provisions of this sub-paragraph shall be reviewed four years after the date of entry into force of the WTO Agreement.

What is relevant for our purposes is that nowhere in paragraph 27.3(b) is reference made to genes or DNA. This means that countries are free to judge for themselves whether the excludability of DNA is inferred, and how strictly to apply the three criteria of patentability. Brazil, for example, has chosen not to permit the patenting of "the genome or germ plasm of any natural living being, when found in nature or isolated therefrom, and natural biological processes" (Section 1, Article 10 IX of Industrial Property Law No.9279/96). On the other hand, Brazil will allow use of patents based on gene sequences.

By contrast, DNA patents have been permitted in Europe and the United States of America for many years. The European Parliament and Council *Directive on the Legal Protection of Biotechnological Inventions 1998* or the EU Biotechnology Directive *(EC, 1998; 98/44/EC)*, adopted after a 10-year debate in the Council and European Parliament, requires that biotechnological inventions that meet the criteria of novelty, utility and non-obviousness be deemed patentable, with few exceptions. However, most EU Member States are still to implement the Directive, because of widespread concern about the implications of patenting biological substances. In Article 5, the Directive states:

> 1. The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions.
>
> 2. An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.
>
> 3. The industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application.

While some countries' reluctance to implement the Directive may, in principle, speak of hesitance or opposition, it arguably has little consequence in practice; the majority of patent applications go through the EPO, which has incorporated the Directive, and these patents may be validated by national patent offices, even in those countries that have not yet implemented the Directive.

This debate reflects a fundamental controversy about whether DNA ought to be treated specially, or the same as any other molecule. Many naturally occurring chemicals, like erythropoietin, have been patented by companies that have succeeded in isolating them in the laboratory.[15] In section 3.1 we will consider some of the concerns about the eligibility of DNA as patentable subject matter. As we saw above with Brazil, developing countries have responded differently to the issue of how to treat DNA, in the context of patent law. We will explore some of these differences in section 2.4.

2.3 The genomics industry and patenting

Genomic industries are those that employ genomics approaches—namely, sequencing, high-throughput screening, DNA microarrays, other DNA methods, bioinformatics and data mining—as an important part of their business model. Firms in this category may be engaged in a range of activities, from drug discovery and development, through the creation of diagnostics to producing research tools and methods. In this section, we will identify the major actors in this field, both public and private, and consider how DNA patents are implicated in their activities.

2.3.1 Who is doing the work and where

When the Human Genome Project got under way in the late 1980s, investment in genomics from the private sector was very low. However, by 1993, public and private funding of genomics in the United States had reached nearly equivalent levels. According to an international survey conducted in 2000, the private sector is now the predominant source of funding for genomics, and the United States accounts for the lion's share of this investment. Indeed, the six biggest players in

genomics are United States firms (Cook-Deegan, Chan and Johnson, 2000).

Like biotechnology, genomics is an approach, rather than a specific field. And like biotechnology, genomics has infiltrated many fields that use its large-scale, highly automated methods for the study of DNA. Firms engaged in genomics activities include service firms that sequence or analyse DNA for research laboratories; firms that carry out genetic testing or forensics; firms that make instruments; and firms that develop analytical software used to analyse entire genomes, mine DNA databases, or interpret data. The top four genomics firms in the United States, which include Celera Genomics, have different business models, and are therefore engaged in varying combinations of the above activities (Cook-Deegan, Chan and Johnson, 2000). Genomics firms like Myriad Genetics and Quest Diagnostics, for instance, are involved in developing genetic tests. In general, "diagnostics firms" invest considerable capital into the development of highly systematized, automated methods for the accurate diagnosis of particular diseases.[16]

In contrast to companies that are centred on the sequencing and analysis of genomic DNA, some companies have complex business strategies that require the large-scale sequencing of genes, as well as the production of proteins whose medical value must be assessed in order to develop new genomic pharmaceutical products. Though their work is "gene-based", as it were, these companies are in the business of creating not only diagnostics, but also therapeutics. They may face, therefore, high front-end costs of research and development similar to those confronted by traditional pharmaceutical firms.

In the pharmaceutical sector, innovation costs are generally very high (DiMasi, Harsen and Gatowski, 2003), and there may be on average 8 to 12 years between patenting a new product and bringing it to market. Average costs are high because only a small proportion of investigated products gives rise to marketed drugs. In this setting, patents are considered a critical factor in providing incentives for research and development (R&D), as well as protecting competitive advantage. They are also prized by start-ups and university spin-off companies in the biomedical field, whose main asset for attracting venture capital is protected intellectual property (OECD, 2004).

By contrast, in-house genetic tests can often be developed with relatively little expense, using existing and accessible methods from biotechnology, once the relationship between the gene and the disease has been established. These laboratories are often proficient at producing low-cost diagnostics based on published information, and do not require the high front-end investment in product development of commercial firms. Consequently, examples exist of straightforward, reliable methods for testing for genetic disorders like sickle cell disease and cystic fibrosis. But while these tests fill an immediate need, by providing simple-to-use and inexpensive diagnostic tests for locally relevant conditions, they vary widely in terms of their protocols and safety testing, because in-house tests are also generally subject to less rigorous standards (Cox et al., 2003).

The link between diagnostics and therapeutics is increasingly strong, which could mean that the economics of diagnostics and therapeutics will converge in the coming years. We discussed in section 1.3 the advent of genomic medicine. This employs genomic information to provide more personalized care for patients, which is based on evidence that some patients respond more poorly to certain treatments. In December 2003, the worldwide vice-president of genetics at GlaxoSmithKline stated: "The vast majority of drugs—more than 90 per cent—only work in 30 or 50 per cent of the people" (Connor, 2003). Some companies are already exploiting such pharmacogenetic indicators to develop genetic tests to determine if patients will benefit from specific drugs, or will have unusual toxic reactions to them (Service, 2003). For now, this work is directed towards only a few conditions, including some forms of breast and colon cancer, and some drug classes for pain control. As understanding of the genetic basis for drug responses grows, genetic tests may precede use of many therapies to increase the likelihood of a positive outcome or to reduce side

effects. This is particularly important for expensive treatments, and when several possible therapies are available, with varying costs and side-effects. The 2003 Nuffield Council on Bioethics report on pharmacogenomics claims: "It is not clear that the private sector will be motivated to pursue pharmacogenetics research in relation to medicines not covered by patent protection".

The report further recommends that:

> Efforts should be made to encourage pharmacogenetics research on existing medicines, where there is reason to believe that such research could significantly improve efficacy or safety. Funding within the public sector and public–private partnerships should be encouraged.

2.3.2 Trends in patenting

Entities from industrialized countries currently hold 97% of all patents worldwide. More than 80% of the patents granted in developing countries belong to residents of industrialized countries, usually multinational corporations from the most advanced economies. 70% of global royalty and licensing fee payments are made between parents and affiliates of multinational corporations (UNDP, 1999). Developing countries do not represent a significant percentage of patent applicants. It is estimated that only 0.1% of the total number of patents issued by the USPTO, including all varieties of patents, were filed by sub-Saharan African applicants (Ogbu, 2002).

The rise in patents in biotechnology has been particularly dramatic, climbing by 15% per annum from 1990 to 2000 at the UPTO and 10.5% per annum at the EPO, compared with a 5% per annum increase in overall patents (OECD, 2004), though there has been a notable drop in the past three years in the number of DNA patents granted. As of 2003, more than 5000 applications for patents on human genes had been filed with the USPTO and from those applications more than 1500 patents were granted (Kluge, 2003). Inventors from the United States have filed more international patents on DNA sequences than inventors anywhere else in the world, and more than the combined total of inventors in the European Union. Japanese and British inventors are the next most prolific patentees in this field (Rausch, 2002).

The public sector has played an important role in the growth of patents for biotechnological inventions. For example, public institutions in Europe and the United States own 30% of all the patents for DNA sequences filed between 1996 and 1999. And start-up companies have a higher share of biotechnology patents than do large, established pharmaceutical companies (OECD, 2004). In the United States, the Bayh-Dole Act of 1980 introduced incentives to universities receiving federal funding to patent the products of their research, in order to encourage technology transfer, and the commercialization of inventions into useful products. The result is that some universities today own more DNA patents than do large private firms (Cook-Deegan, Chan and Johnson, 2000). There is ambiguity for those centres that provide diagnostic testing services. To improve existing techniques and test efficacy, research requires that tests be used on patients, which amounts to providing clinical services. While a number of countries provide a research exemption (see section 2.3.3) that permits the use of patented subject matter for strictly research purposes, it is not clear to what extent this exemption applies to institutions whose research involves the use of patient samples and thus overlaps with clinical practice (Walsh, Arora and Cohen, 2003; Cornish, Llewelyn and Adcock, 2003).

One of the difficulties in cases where university laboratories are among the chief providers is that universities are increasingly viewed as pursuing commercial ends, being actively engaged in profit-making activities and in widespread patenting and licensing (Howard, 2004). Consequently, some have judged it a double standard that universities would be spared having to pay licensing fees for

services provided, when they themselves are likely holders of rent-earning patents. Although this is not the case with all universities, their supposed immunity because of their status as academic centres may be in danger of disintegrating in the face of increasingly profit-making agendas.

Traditionally, governments have had the role of filling the gaps; of addressing market failure by allocating funds to areas of research that draw little funding from private sources. However, if those institutions receiving public funding are increasingly tied to the private sector and are licensing their inventions exclusively to companies, public money may be generating products that are not readily accessible to the public (e.g. because of high prices). Products may not be developed for needy populations as these generally do not constitute lucrative markets. Given that the effectivenes of the patent system relies on market mechanisms, this situation, at least in principle, presents a tension between the aims of government-funded research and the incentives that underpin the patent system; and the further challenge is that publicly funded research does not always find its way into the public domain. However, licensing practices and policies may in future play an important role in leaving open avenues of research relevant to developing countries. For example, research-use exemptions or humanitarian-use exemptions, which protect from litigation research in areas of primarily humanitarian rather than commercial interest (such as adapted tools for use in low-resource settings) are being explored by several groups. The idea behind such work is to develop ways of changing norms around licensing, so that innovation in areas outside of market interest is not impeded.

Developing countries stand to gain from taking advantage of the flexibility within TRIPS that allows members to protect researchers from infringing patents used in research. Such clauses can encourage research activity, and foster the development of scientific capacity. However, they should be careful to avoid ambiguity in defining the scope of the research exemption, because a lack of clarity may chill research. In the face of uncertainty, researchers are reluctant to risk patent infringement and possible litigation. It is therefore particularly important to clarify how the research exemption applies to preclinical and clinical research that has the dual aim of advancing knowledge and producing or providing goods and services.

2.3.3 Opportunities and challenges for developing countries

In most cases, companies do not bother to take out patents on DNA sequences in developing countries, because the market in those countries is not lucrative enough to warrant protecting. What is at stake is the development of cheap technologies suitable for use in the developing world, given the current make-up and emphasis of the genomics industry. Endogenous research within most developing countries may not be hindered by patents; however, research may be hindered in those countries with adequate technological capacity and research capital to generate the products of relevance to their poorer neighbours. These countries include the United States, where, as we have seen, the bulk of genomics-related research is taking place. They could also include Brazil and India, developing countries with well-advanced science and health technology sectors, which are well placed to generate appropriate health-related products to address local and more global needs.

An interesting place where advances are being made in genomics is in bioterror-related research. As genomics provides tools for studying pathogens and developing ways of diagnosing them quickly and simply, it can do the same for "bioterror" agents and therefore holds great interest for some defence programmes. Platform technologies used for bioterror research can be relatively easily adapted to create applications relevant to developing countries. Some academic researchers interested in creating such tools have capitalized on grants for biodefence research to create technologies for the diagnosis and monitoring of infectious diseases, like HIV/AIDS.

Much of the promise in genomics and biotechnology for developing countries depends

on using platform tools and technologies, modified for use in poorer settings. The work of Dr Eva Harris is a well known example of technology transfer of biotechnology tools to low-resource settings, primarily in Latin America. She is free to teach local laboratory technicians and health care workers how to create low-cost alternatives to technologies used in her own laboratory at the University of California at Berkeley, because patents on the technologies do not tend to exist in those countries. Whether she would have the same liberty to work in poor countries with more well-developed biotechnology sectors where patents on genetics tools may be more likely, is less clear. Dr Harris must carry out most of her teaching on-site because she risks patent infringement doing the same work at home. Likewise, work in universities using platform technologies can be modified for use in developing countries. A research technology, developed through a collaboration between the Sustainable Sciences Institute (SSI) and the University of California at Berkeley's Department of Electrical Engineering and its School of Public Health, has generated a low-cost point-of-care tool for diagnosing dengue fever. According to its creators:

> The ImmunoSensor is a platform technology, thus it can be adapted for virtually any disease that is currently diagnosed by an immunological assay. The prototype application of the ImmunoSensor is diagnosis of dengue, the most prevalent mosquito-borne viral illness, with 100 million cases of dengue fever annually worldwide. SSI is coordinating field trials for dengue diagnosis using the ImmunoSensor in Nicaragua, Ecuador and Sri Lanka. In addition, efforts are being spearheaded to adapt this technology for HIV diagnosis. [17]

SSI is presently negotiating rights to ImmunoSensor technology from the University for use in developing countries, and will develop a business strategy so that disease-endemic regions can use and market the product to serve their own needs. The underlying IP of platform technologies could be safeguarded for applications such as this.

As for pharmacogenetic approaches for personalized treatment, it will likely be an important part of the way medicine is practised in the future. There are a few examples today of its successful use, though there remain big questions about when, and if, it will come into widespread use. What is important to remark is that pharmacogenetics presents a further example indicating that as medicine continues to evolve, it is likely that the importance of genetic tests will grow, and their usefulness expand considerably beyond tests for genetic disease. Competency in the development and delivery of genetic tests could therefore provide a foundation for continuing benefit from medical advances based on genomics. However, ensuring that personalized medicine will be an affordable option in general, and for developing countries in particular, presents a major future challenge. Moreover, the application of pharmacogenomics in developing countries is likely to be quite different from in Europe and Japan, for instance. The disease burden in poorer countries is not identical—for example, infectious disease is still a major problem—and health systems require adapted methods. The direction of genomic research today is the direction that current incentives encourage—and is one that does not show any signs today of targeting the needs of those outside of wealthy markets. We will consider in later sections in more detail the role of patents in guiding the shape of today's research landscape.

2.3.4 Availability of genomic data

The availability of fundamental genetic data is not solely dependent on public funding. For example, the SNP Consortium was a collaborative venture among 10 private sector companies and the Wellcome Trust. It was "founded on the premise that genetic information related to SNPs is accelerated when research findings are freely

available to all researchers and companies" (http://snp.cshl.org). The Consortium was a not-for-profit group working to compile a database of mapped SNP, whose contents are freely available through free public databases. SNPs are common DNA sequence variations among individuals, which scientists hope will improve their ability to understand and treat human disease. According to the Ontario Ministry of Health and Long-Term Care (2002), this project "treats SNP information (non-patented) as primarily an informational input freely available, and yet, still providing a vital contribution to downstream product development".

One commentator has argued that large companies, in fact, see it as being in their interest to free up raw data:

> Although it may seem extraordinary for firms that usually sing the praises of the patent system to collaborate in a concerted effort to put new discoveries in the public domain, it makes perfect sense from the perspective of the pharmaceutical industry. The patents that matter to pharmaceutical firms are the drug patents that secure the revenues that fill the pharmaceutical feeding trough. Patents on the many prior discoveries that facilitate drug development look like siphons, diverting those revenues to the troughs of other firms (Eisenberg, 2001).

This suggests that big companies may not all be opposed to liberating research tools from patent protection.

Intellectual property rights covering databases represent the second major way in which proprietary rights may be exercised over DNA sequences. In some countries, databases are protected by copyright or *sui generis* database rights, though in the United States, unlike in the EU and elsewhere, they are protected mainly by contract law—agreements signed by users to gain access to databases.

As previously noted in section 1.3, the Human Genome Project exemplifies the fact that by no means all genetic inventions are protected by patent rights. In fact, the HGP has been used as an example of precisely the kind of scientific effort that did not require the incentives of patents to promote innovation, and indeed actively discouraged patenting on the pathway to producing the reference sequence. The project, which was entirely publicly funded, was characterized by both openness with respect to the sharing of results, and competition among laboratories.

The HapMap project, which aims to "determine the common patterns of DNA sequence variation in the human genome and to make this information freely available to the public" (International HapMap Consortium, 2003), has adopted a different approach, applying the software model of open-source access, which permits others to use its products on condition that they too agree to keep them in the public domain (Cukier, 2003). While the HapMap project allows process patents, it does not allow product patents on DNA sequences. It is less open than the HGP, but aims to protect the products generated from its work from being used by private entities that could make proprietary claims, limiting access to communal resources.

Despite the SNP Consortium and other similar examples, there were in the late 1990s a number of firms that charged for access to databases of genomic sequences. But lately the relative value of private versus public databases has been called into question by the announcement that Incyte Corp., the largest genomics firm in the United States, is closing its headquarters and paring more than half of its workforce. According to a brief in *Science*:

> The gene discovery firm [Incyte] pioneered the notion of turning profits by selling genetic data to drug discovery firms and academics. The strategy seemed promising for a while, and the company's stock bolted to the dizzying high of $144 a share during the technol-

> ogy bubble days of 2000. But the company faced the stiffest competition possible: free genomic data supplied by public gene-sequencing efforts financed by governments around the globe…. Like other one-time genomics companies such as Celera and Myriad Genetics, Incyte has refashioned itself as a drug discovery firm (Service, 2004).

This suggests not only that efforts to generate genomic data have been highly productive to date, but that the resulting publicly available data is generating arguably more useful follow-on research by companies that have turned to drug discovery, unable to sustain a business model based on privately-owned data. While the race to sequence the human genome was a fruitful and largely efficient one, translating this wealth of knowledge into applications has been much slower—though, arguably, it has been facilitated by largely free access to sequence data. Whether the lag in generating useful products is due to the unavoidable complexity of the work involved, reflects fundamental flaws in the research and development chain, or a combination of both, has yet to be elucidated.

What is clear is that, thanks to the abundant success of the HGP and other initiatives, there is a growing repository of publicly available genomic data. Researchers in developing countries can benefit from access to these resources. Existing strategies to develop indigenous capacity in bioinformatics and data mining in low-resource settings, including through international partnerships, should be identified and assessed, and initiatives considered to encourage these efforts.

The Human Genome Project was characterized by competition, openness in the sharing of results, and efficiency. The international HapMap project, for its part, has adopted an open source approach for providing access to genomic data, while preventing third parties from making proprietary claims that could restrict access. This approach, while promising, has yet to prove itself; moreover, while the HGP and HapMap models are arguably effective ways for encouraging and sharing the fruits of basic research, it remains very unclear whether they provide the right kind of incentives for the work required to translate this research into applications. Large companies have shown their willingness, in some instances, to engage in more open science when it involves the generation of raw data.

The open source model for genomics has been advanced by several scholars. We will consider it, and various other models, in section 3.2.2 below.

2.4 What some developing countries are doing

There is great diversity among developing countries, including wide diversity in scientific capacity and infrastructure to support health research and health delivery, as well as varying patent systems. Although they are different in a number of respects, Brazil, China and India are all examples of developing countries with comparatively well developed gene-based industries. In this section, we will consider the capacity of each of these countries to harness gene-based approaches to address the needs of their populations. We will also look at the patent systems that have developed over time and helped to shape their present circumstances.

2.4.1 Brazil

Genomics in Brazil

The State of São Paulo Science Foundation or FAPESP, was founded in 1962 in São Paulo, Brazil's richest and most populous state (37 million people). In 1997, FAPESP, established the Organization for Nucleotide Sequencing and Analysis (ONSA), a virtual community including 35 laboratories across the state (*Economist*, 2000), which was charged with boosting Brazilian competence in genomics. ONSA's first project was to sequence

X. fastidiosa, a bacterium that causes citrus variegated chlorosis (CVC), which results in fruit that are small, hard and of no commercial value. CVC was first recorded in Brazil in 1987; it affects all varieties of sweet orange (Simpson, 2000) and has a significant economic impact, costing Brazilian growers an estimated US$ 100 million per year (*Economist*, 2000).

The successful sequencing of *X. fastidiosa* provided FAPESP with both a team of skilled sequencers who were then able to move on to sequencing genes relating to human diseases, and international recognition that has resulted in external funding for human-related sequencing projects. The *X. fastidiosa* genome was the first complete sequence to come from outside the United States, the United Kingdom or Japan and the first ever sequencing of the complete genome of plant-disease-causing organism (Yoon, 2000). FAPESP's approach was novel because it created a virtual research community rather than investing in building a physical genomics centre (Trafford, 2001). FAPESP's statute prohibits it from assembling its own corps of scientists. The institute must, therefore, invest widely in existing centres within the state rather than confining resources to a small subset of the research population. This results in the sharing of knowledge among a large number of researchers and a sustainable investment in the industry.

The virtual network strategy allowed ONSA to maximize the value of the funding provided by FAPESP, to overcome geographical isolation and to nurture a critical mass of trained geneticists. The success of the *X. fastidiosa* project catapulted Brazil into the international spotlight. As a result ONSA has developed international partnerships to fund further sequencing projects that are expected to make a significant contribution towards better understanding of leading causes of ill health globally. For example, ONSA is sequencing human cancer-related genes in collaboration with the Ludwig Institute in Switzerland (Rother, 2001), which is paying half of the US$ 10 million cost of the project (*Economist*, 2000).

In 2000 the Federal Government of Brazil decided to expand São Paulo's genome project to the national level; it launched the Brazilian Genome Project, which comprises a network of 25 sequencing laboratories. The growth and strength of genomics industry in Brazil indicate the results of these initiatives. For example, the number of scientific publications from Brazilian researchers increased 300% between 1987 and 2002, now accounting for about 1.2% of global scientific papers. Brazil is now an undisputed leader in plant genomics (WHO, 2002).

Brazil's patent law

In 1809 Brazil became the fourth country in the world to enact a patent law. Brazil became a founding member of the Paris Convention in 1882 (Barbosa, 2004). On 14 May 1996, Brazil introduced Law No. 9.279 to Regulate Rights and Obligations Relating to Industrial Property (Brazil Law, 1996), which was intended to fulfil Brazil's obligations under TRIPS to enact minimum patent standards (Barbosa, 2004).[18]

Brazil signed the Convention on Biological Diversity (CBD) in 1992 and ratified it in 1994. Brazil has been a vocal and active supporter of benefit sharing in relation to the commercialization of research based on natural products and of introducing an internationally recognized certificate of origin for genetic samples (GRAIN, 2002). After extensive negotiations at the Seventh Meeting of the Conference of Parties to the Convention on Biological Diversity in Kuala Lumpur in February 2004, country representatives agreed to include the certificate of origin as a topic to be addressed in the guidelines to be prepared by the next conference in Brazil in 2006 (Dalton, 2004). As we will see in section 3.1.2, CBD specifically excludes human genetic resources.

In 2001, the United States filed a complaint with the WTO arguing that Article 68 of Brazil's patent law No. 9.279 was in breach of Articles 27 and 28 of TRIPS. Article 68 allows Brazil to issue a compulsory licence to a local producer if, after

three years, the patent holder has not begun manufacturing the product in Brazil. This measure is designed to encourage technology transfer and support a strong domestic generics industry, in addition to strengthening the Brazilian Government's bargaining position in relation to the cost of drugs (Oxfam, 2001) and, ultimately, helping the Brazilian Government to ensure affordable access to vital medicines (Cooper, 2001).[19] Though the case involving drugs has become the prototype for considering compulsory licences, particularly in the context of developing countries, it is important to recognize that compulsory licences are not limited to use against drug companies. For instance, in France, opponents to restrictive licensing of genetic tests threatened to opt for *ex officio* licences, permitted by French law on grounds that practices are contrary to public health (Lecrubier, 2002).

Gene patenting

According to a report prepared by the Brazilian Group of the International Association for the Protection of Intellectual Property (AIPPI), there is ambiguity as to whether the Brazilian patent law No. 9.279 excludes genes from patentability. Both Article 18, item III, and Article 10, item IX, suggest that genes should not be considered patentable material. On the other hand, the law does allow for the patenting of chemical products, provided they fulfil the criteria of novelty, inventive activity and industrial application. If Brazil were to conclude that DNA is not merely a large polymer, it could permit chemical product patents while blocking patents on genes.[20] At the time of writing of the Brazilian Group's report there was no case law to resolve this issue of interpretation.[21] However, a number of commentators have concluded that DNA is not patentable under current Brazilian law—except for certain specific uses.[22]

2.4.2 China

Genomics in China

China has adopted a policy of actively supporting and encouraging biotechnology and genomics-related industries. In 1998 the Ministry of Science and Technology established both the Chinese National Human Genome Centres (CHGC) in Shanghai and Beijing to specialize in genome sequencing and analysis (WHO, 2002). In 1999, the Chinese Academy of Sciences established the Beijing Genomics Institute (BGI). China was then in a position to join the International Human Genome Sequencing Consortium in 1999. China not only played a significant role in the sequencing itself, characterizing 1% of the human genome, but was able to develop advanced bioinformatics and supercomputing facilities to support further genome-sequencing research. This research has included sequencing the silkworm genome, establishing the Super Hybrid Rice Genome Project and collaboration with Danish scientists to sequence the pig genome (Porcine Genome Sequencing Project).[23]

BGI's latest achievement was announced on 1 March 2004, when BGI reported the construction of a chicken genome variation map, based on DNA from three strains of chicken and identifying two million SNPs. This work is part of a larger project to sequence the chicken genome, conducted by an international team and lead by BGI.

China supports collaboration with foreign researchers, but recognizes the need to protect Chinese genetic resources from exploitation and biopiracy (WHO, 2002). In 1998 the Ministry of Health and the Ministry of Science and Technology jointly established the Chinese Human Genetic

Resources Management Office. It is responsible for managing all matters dealing with Chinese human genetic resources, including human gene groups, blood, genes, organs, cells and other DNA materials of human beings (Feng, 2003).

China is keen to ensure that some of the benefits of international genetic research, based on Chinese genetic samples, flow back to the Chinese community. Yu Xiucheng, director of the Division of Health Technology Management of the Department of Sciences, Technology and Education of the Ministry of Health has stated that all cooperative international projects based in China and working with Chinese human genetic resources should follow the principles of equality, mutual benefit and joint participation; and that the achievements and patents must be owned and shared by both the foreign and domestic researchers (Feng, 2003).

China's patent law

China first introduced a patent law in 1985, which was subsequently revised in 1992. Further amendments to bring the patent law in line with international standards and TRIPS requirements were passed at the 17th Session of the Standing Committee of the Ninth National People's Congress, and took effect on 1 July 2003.[24] For example, the amended law will, in accordance with TRIPS, allow patent holders who believe their rights are being infringed to ask the courts to intervene.[25]

During the same period, as China prepared to join the WTO, the overall number of patent applications increased. By the end of July 2001, the State Intellectual Property Office of China had accepted 99 550 patent applications from China and abroad, a 24% increase from 2000.[26]

Gene patents

Chang Mao, an officer from the State Intellectual Property Office, has stated that China does not allow companies or research institutes to patent life forms; however patenting genes is permissible (Wang, 2001).

In 2001, Shanghai Joint Gene Technology Co. Ltd, the largest gene technology company in China, applied for more than 3700 gene patents, including patents for genes dealing with cancer, obesity, high blood pressure and senile dementia, which are expected to be of high value for clinical diagnosis and the development of new medicines. "Owning intellectual property is one of our company's fundamental goals. If we had not owned intellectual property, we would not have our own gene industry after WTO accession", said Qin Yilong, the company's vice-president in 2001.[27]

The concept of *international patent families* [28] provides a basis for comparing the research and technological activity of different countries, in terms of resulting products intended for international use. A *patent family* consists of all the patent documents associated with a single invention that are published in one country. From 1980 to 1999, China, which had filed a total of 145 patent families in human DNA sequences, had only filed 17 international patent families.[29] The United States, by comparison, had 5610 international patent families (accounting for 72% of the total world figure of 7810).[30] Brazil had only 1 international patent family.

2.4.3 India

Genomics in India

The growth in the biotechnology industry in India is built upon its existing internationally recognized information-technology industry, a large pool of trained scientists and a dynamic generic pharmaceutical industry (BioSpectrum, 2003). In the international market, India's highly qualified, English speaking but comparatively low-cost workforce offers a significant competitive advantage (Thorold, 2001). The Indian Government has invested substantially in building the industry. The Department of Biotechnology (the Department) was established by the Indian Government in 1986 and receives an annual budget of approximately US$ 30 million (WHO, 2002).

The Department has established a programme in Human Genetics and Genomic Analysis, which includes projects in genetics diagnosis and counselling, functional genomics, research into human genome diversity, and biocomputing. There are 16 Genetic Diagnosis and Counselling Units throughout India, which have provided genetic testing and counselling services for over 18 000 patients and families affected by genetic disorders such as thalassaemia, sickle cell disease, Duchenne muscular dystrophy(DMD), haemophilia, and cystic fibrosis.[31]

In recognition of the connection between information technology and biotechnology, the Department initiated a bioinformatics programme in 1986. This programme gave rise to the Biotechnology Information System Network, which operates throughout India, and has resulted in the development of state of the art computational and communication resources that are used to support sophisticated bioinformatics research. India now operates as a "major regional nodal point for genomic-related databanks and networks" (WHO, 2002). In addition, the Indian Government recently approved a programme in molecular genetics and genomics with an annual budget of US$ 4 million, to be administered through the Indian Council of Medical Research (WHO, 2002). Furthermore, the Indian Ministry for Science and Technology has invested in a number of centres of excellence in the field with world-class infrastructure and staff, such as the Plant Genomics Centre, New Delhi, and the Centre for Human Genetics, Bangalore.[32]

States like Andhra Pradesh, Karnataka, Maharashtra, Kerala, Tamil Nadu and Himachal Pradesh are developing biotech parks and biotech-friendly policies, which include a number of concessions for foreign industry partners.[33] Two highly successful biotech firms are Shanta Biotech and Bharat Biotech. Shanta Biotech produces India's first genetically engineered vaccine called Shanvac (BioSpectrum, 2003), which vaccinates against hepatitis B. Shanvac retails for US$ 4 which is less than half the price of similar vaccine sold by multinational companies.

Patent law in India

India's original Patent Act was passed into law in 1970 (Singh and Agarwal, 2003). TRIPS entered into force in 1995. The Patent (First Amendment) Act 1999 provides transitional patent protection, as a step towards becoming fully TRIPS compliant, by implementing Exclusive Marketing Rights (EMRs). EMRs are particularly important in relation to drugs and food, because India will not allow product patents until 2005. EMRs provide exclusive rights to *sell* one's patented products, whereas full product patents grant exclusive rights to *both* manufacture and sell the products. The EMRs protection period is five years.[34] Under the 1999 Amendment, it is now possible to make an application for product patents, including substances intended for use or capable of being used as a medicine or drug, but excluding the intermediate for the preparation of drug. However, because India has until 2005 before its patent legislation must be fully TRIPS compliant, product claims for medicines or drugs will not be processed until the end of 2004.[35]

The Patent (Second Amendment) Act 2002 and the Patent Rules 2003, which came into force on 20 May 2003, include provisions for extending the patent term to 20 years and emergency provisions

to protect public health. These amendments will bring the Indian patent regime further in line with TRIPS. Indian law used to provide a standard period of 14 years protection (from the date of sealing) and 5 years protection (again from the date of sealing) for food and medicinal products. This has been increased to a protection period of 20 years.

In order to protect indigenous knowledge, an exemption for products based on Indian systems of medicine has been granted. Section 3 of the Patents Act explains that an invention that is in fact traditional knowledge is not patentable. Nor does the Indian patent system appear to allow patents on genes or cells.[36]

2.5 Some early lessons for developing countries

Each of three countries described above has achieved a level of competence in gene-based research and its applications. Though there are diverse and complex economic, historical and cultural factors at work, it may be useful to highlight those features that are common to all three countries:

- political commitment to building strong national biotech industries, supported by financial resources;
- a clearly defined project, highly relevant to local needs around which to mobilize efforts;
- an emphasis on building sustainable networks across the country;[37]
- capitalizing on international partnerships, and timely entry into the industry; and
- vocal and active participation in international negotiations on trade and benefit sharing, and domestic structures and policy created to protect indigenous resources.

One area of divergence of particular relevance to the present discussion is on the issue of DNA patents; there is no common approach among the three countries on how to address human DNA within patent law.

It is not clear if, and how, the status of DNA as reflected in the patent law of developing countries has affected or may in the future affect the ability of developing countries with relatively strong research and technology bases to harness genetic approaches to improve the health of their populations. It also remains to be seen how these issues will interact with the overall changes to their patent systems as a result of TRIPS coming into force in these countries in 2005.

3

Analysis: impact of DNA patents on access to genetic tests and genomic science

3.1 Ethical, legal and social challenges to the patenting of DNA

3.1.1 Ethical objections

Despite the fact that patent offices in the United States and Europe have been granting patents on DNA, there continues to be wide debate about the acceptability of this practice, both on ethical and legal grounds. In this section, we will sketch some of the broad issues and concerns that have been consistently raised in the course of this debate.

Commodification

Intellectual property is a system that confers proprietary rights not on real objects, but on the "intangible commons of the mind" (Boyle, 2003). As we saw in section 1.5.2, the trend in some of the most influential countries over the last two decades has been toward a pro-patent policy, one that favours patent owners and the expansion of what is deemed patentable subject matter. Patents on genetic sequences present a case that falls at the intersection of two controversies: the patenting, and thus the commodification, of biological entities, and the patenting of raw data. Concerns have been expressed about the commodification of persons and their biological material.[38] It has been claimed that it is unacceptable for people to have "proprietary rights in living beings and tissues" (Gold, 2003), and that market logic now holds sway over the use of living organisms (or their component parts). The court case of *Diamond versus Chakrabarty* of 1980 in the United States confirmed the patentability of micro-organisms, arguably catalysing the growth of patents in the biotechnology sector. More recently Harvard University's successful patenting of the OncoMouse demonstrated that in the United States and Europe the courts judge that organisms are likewise patentable subject matter. Notably, the OncoMouse patent was narrowly rejected by the Supreme Court of Canada, in a 5-4 ruling (Check, 2002; Scassa, 2003). And, as we saw in section 2.1, there continues to be much dispute in Europe about whether this is in contradiction to the EU Directive of 1998 that requires patent protection for biotechnological inventions. Besides the objections to the patenting of DNA and other biological entities, there are objections that patents now permit the commodification of ideas. Both objections are argued on two fronts: the first claims that extending property rights to biological entities or to ideas is wrong in itself; the second is utilitarian, and judges that such practices are wrong because they generate unacceptable consequences.

Policy debates often tend to focus on the latter types of argument, because they circumvent difficult discussions that often arise from varying world views, religious or intellectual. However, objections to the broader patent system and to patenting of genetic sequences should not be brushed aside; these questions do merit inclusion in policy discourse. Often, decisions about changes to the intellectual property system, which of late have tended towards strengthening and extending its reach, have been made on the basis of economic arguments that have not been conclusively proven. Given the lack of definitive economic justification for the expansion of IP rights, it is particularly important to take account of objections based on a fundamental uneasiness with the system—which in several cases have been expressed articulately and soberly by critics. Though it is doubtless easier said than done, this suggests that moves to expand IP into new and controversial territory—particularly in the absence of incontrovertible economic arguments—should not proceed in the absence of public dialogue.

The TRIPS Agreement leaves space for countries to do precisely this. According to Article 27 of TRIPS:

> 2. Members may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect *ordre public* or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law.

Some countries have rejected the patentability of land mines on these grounds (IPR Commission, 2002). But while the *ordre public* provision, in theory, constitutes a "morality filter" of sorts for determining patentable subject matter, and therefore suggests a route to opponents for protesting the patentability of DNA, in practice, it has been invoked only in unusual and extreme cases (Nicol and Nielsen, 2003).

"Common heritage of mankind"

A further position, articulated in UNESCO's Declaration on the Human Genome and Human Rights (AIRES/53/152), claims that the human genome is the common heritage of humankind. This implies that DNA has a special character, beyond that of ordinary biological molecules. Human DNA is common to all human beings (DNA itself is common to all living things), past and present, and is therefore in some sense foundational, imbued with not only biological, but also historical and even moral significance. On the other hand, it has been argued that such a view borders on "genetic essentialism" (Suter, 2001), a kind of reductionism that grants exaggerated value to the contribution of genetics to human behaviour, identity and culture, minimizing the importance of non-biological factors. UNESCO's Declaration was unanimously adopted by the UN Assembly in 1997, and has been widely cited. While the Declaration affirms that "the human genome in its natural state shall not give rise to financial gains" (UNESCO, 1997), it does not explicitly preclude financial gain obtained by the patenting of genes, or of isolated genetic sequences. Despite widespread controversy, it is noteworthy that, to date, "the shared status of the genome at the 'collective' universal level has only been specifically addressed by international and regional policymaking bodies" (Knoppers, 1999). It is not precisely clear what this claim amounts to, in practice. More than likely the argument sets the stage for one of the following assertions.

Public good

A public good is one that is non-rivalrous and inappropriable. A classic example is air: my breathing it does not stop you from breathing it, and it would be very difficult for anyone to charge money for its consumption. It has been argued that DNA has this character (Devanand et al., 2003).

> Genomics is principally about knowledge, which is commonly conceived to be the archetypal public good. Genomics knowledge is non-rivalrous in consumption (not depleted by use), and is usually made public by genomics databases on the internet and journal publication, as was the case with the malaria and mosquito genome. It is a global public good in the sense of the knowledge not being bound by national border, in discovery, transmission, or use. Further, the global public-good nature of genomics is reflected in the way in which the Human Genome Project was funded and undertaken (Thorsteinsdóttir et al., 2003).

To call something a "public good" is not simply to describe how it is; it is to make a normative claim about what would be in the public's interest. In the case of air, it is a public good because its appropriation would make everyone worse off. To say that genomics, or more specifically genomic data, is a public good is to say that people would be better off if everyone had access to it.

But as we have seen, the generation of genomic data requires a different set of institutional and analytic tools than the translation of this data into practical applications. The latter work looks more like drug development and less like basic science, and may therefore require the financial incentives of the patent system to justify the investment of time and capital. If this is true, then it could well be the case that permitting some level of appropriation would introduce more benefits to the public than costs.

Some commentators have not argued so much against property rights per se—rather they have argued against the misappropriation of goods from those who were their rightful owners. Often these arguments are a background to further claims about distributive justice, so that the benefits of research reach back to those who were the "source" of the raw material. In most cases, the source is a community whose members share various genetic traits in common, whose DNA is tapped for scientific, clinical or commercial gain. In essence, such arguments express a concern about the distribution of benefits, and use the question of ownership as a means of ensuring that those with unequal power but desirable resources, and who contribute in some way (whether intellectual or biological) to research that generates useful results, get their due.

3.1.2 Benefit sharing

Some discussion of benefit sharing in relation to genetic resources has taken place within the context of the United Nations Convention on Biological Diversity, adopted at the 1992 Earth Summit in Rio de Janeiro. Among the Convention's three primary goals is the fair and equitable sharing of the benefits from the use of genetic resources. In 2002, the Bonn Guidelines on Access and Benefit Sharing were adopted under the CBD;[39] however, their application to human health is limited because, as section C/9 of the guidelines lays out, the scope of the guidelines is defined so as to explicitly exclude *human* genetic resources.

The earliest discussions of human genomics and fairness arose apart from deliberations in the UN, and were in relation to families of patients with debilitating genetic illnesses, such as Canavan disease, who participated actively in fruitful research ventures. Indigenous peoples' rights, in context of participating in human population genetics as opposed to biodiversity, is an issue that arose later, and was principally catalysed by the Human Genome Project. In 2000, the HUGO Ethics Committee, in its statement on benefit sharing, considered benefit sharing specifically in the context of research involving the human genome. The Statement recommends, among other things, "that profit-making entities dedicate a percentage (e.g. 1%–3%) of their annual net profit to healthcare infrastructure and/or humanitarian efforts". In an editorial for *Science* published in the same year, members of the HUGO Ethics Committee offered three arguments to justify benefit sharing (Berg et al., 2000):

- 99.9% of the human genome is common to all humans. This entails a responsibility, grounded on human solidarity, to share in the benefits of research based on this common good.

- There is a long legal history of viewing global resources, such as the sea, air and space, as common goods, to be equitably available to all humans, and protected for future generations. The human genome can equally be regarded as a common heritage.

- Vast differences in power and wealth between those conducting human genetic research and those providing genetic samples for such research, as well as the potential for substantial profits, raise concerns of exploitation. The HUGO Ethics Committee sees benefit sharing as a way to address these concerns.

It has been argued that the discovery of disease-related genes is increasingly the result of fruitful partnerships between researchers and those afflicted with the condition (Merz et al., 2002). To a growing extent, research participants not only take part in studies; they are also integrally involved with broader aspects of the research, including identifying and obtaining samples from other affected individuals, and even with securing research funds. This was the case for the more than 150 families worldwide that participated in a collaborative initiative with researchers at Miami Children's Hospital (MCH), which led to the 1993 discovery of the gene linked with Canavan disease. Canavan disease is an inherited, fatal neurodegenerative disease largely affecting Ashkenazi Jewish people. In 2000, several of these families as well as various patient associations sued MCH, which had patented the gene without the knowledge of the research participants, for what they judged to be an unacceptably restrictive and costly licensing strategy. Following the issuance of the patent for the disease-related gene, one in four laboratories in the United States stopped offering a test for Canavan disease because of the conditions that MCH attempted to impose on them (Cahill, 2001; Brower, 2000). The Canavan Foundation had at one time offered genetic testing free of charge, but ended this practice after it was advised that the patentee would require payment of royalties to MCH, and compliance with specific licence terms if it wished to continue offering the test (Marshall, 2000). This case was settled out of court, on terms that have not been made public.

Among the players involved in the development of genetic tests—including patients and patient organizations, universities, companies, and government agencies—some "believe that [patients and advocacy groups] are the best situated to represent, protect and serve the interests of those most affected" (Merz et al., 2002). Providing compensation or property interests for those whose samples are studied, or at the very least giving them a say in how the patented invention should be used, may be strategies for mitigating purely commercial motives that could hinder access. In some cases, this would mean going against the grain, and seeing "sources" as more than just exploitable founts of "raw" material, with legitimate interests in sharing in the benefit of research in which they have made a contribution, intellectually or materially.[40]

There are examples of companies that have incorporated benefit sharing into their strategies, most notably: the Canadian firm Newfound Genomics, which donates 1% of its net profits to a charitable trust for the general population (http://www.newfound-genomics.com/); deCODE Genetics, which was granted the exclusive use of a centrally compiled population health database in Iceland in exchange for paying all related expenses incurred by the government for its building and maintenance, in addition to an approximately US$ 700 000 annual payment, and 6% of its gross profit; and the University of Hawaii, whose researchers discovered a gene mutation responsible for a rare genetic disorder called pseudoxanthoma elasticum (PXE), and subsequently filed for and obtained the first patent in the United States with one of the patients' parents as co-inventor (Altonn, 2002; Marshall, 2004; Terry and Boyd, 2001). According to Patrick Terry, chairman of the advocacy group PXE International: "With the

heavy stick of holding a patent on the gene, we can accelerate the research process, control royalty and licence fees and eliminate turf wars between researchers" (Coghlan, 2001). This presents another example of how patents can sometimes be used strategically to secure access to proprietary technologies.

The International Treaty on Plant Genetic Resources for Food and Agriculture, which took effect on 29 June 2004, could prove an important precedent for benefit sharing in the context of human genetics. This Treaty is the product of seven years of negotiations among governments, farmers' and consumer groups, research organizations and companies. According to Article 13.2:

> (ii) The Contracting Parties agree that the standard Material Transfer Agreement referred to in Article 12.4 shall include a requirement that a recipient who commercializes a product that is a plant genetic resource for food and agriculture and that incorporates material accessed from the Multilateral System, shall pay to the mechanism referred to in Article 19.3f, an equitable share of the benefits arising from the commercialization of that product, except whenever such a product is available without restriction to others for further research and breeding, in which case the recipient who commercializes shall be encouraged to make such payment.

Furthermore, Article 12.3 states:

> (d) Recipients shall not claim any intellectual property or other rights that limit the facilitated access to the plant genetic resources for food and agriculture, or their genetic parts or components, in the form received from the Multilateral System (ftp://ext-ftp.fao.org/ag/cgrfa/it/ITPGRe.pdf).

Although its subject matter is plant genetic resources, the Treaty tries to address very similar issues to those raised in the context of human genetic resources. The Treaty does not attempt to circumvent existing intellectual property laws, or to confer intellectual property rights to sources; rather it is an effort to generate a more equitable distribution of benefits through explicit agreements between parties.

Certificates of origin for (non-human) genetic resources are also being discussed as tools for global distributive justice. Certificates of origin disclose the country of origin of genetic material and proof of prior informed consent. Countries rich in biodiversity and genetic resources like Brazil, the Dominican Republic and Peru have insisted that certificates of origin be legally enforced. A legal requirement of informed consent procedures, along the lines of the Bonn Guidelines, could help ensure that developing countries benefit from international genetic research by encouraging a discussion about the distribution of expected benefits with the test population prior to the initiation of research. Such benefits, as suggested in Appendix II of the Bonn Guidelines, could include technology transfers, joint collaborations or joint ownership of intellectual property rights, and might contribute to building capacity in genomic industries. However, the suggestion to include certificates of origin as a legal requirement for patent applications has been fiercely opposed by patent offices in industrialized countries (Dalton, 2004).

It remains contentious whether resolving the question of benefit sharing requires making changes to the patent system, or whether there may be other methods of achieving greater equity through policies and approaches outside of patent law. Ultimately, most commentators arguing for benefit sharing are not arguing against the ownership of genetic knowledge, but against its misappropriation and subsequent failure to fairly compensate sources.

Developing countries should consider establishing policies that encourage entities involved in commercial aspects of research to negotiate openly with foundations and disease-associated advocacy groups or local community leaders for equitable benefit sharing. These countries should contemplate creating standards to guide such negotiation, in addition to carefully assessing mechanisms for negotiating the distribution of benefits resulting from international human genetic research.

3.1.3 Legal issues

In addition to ethical and social concerns, a number of commentators have argued that DNA, at least in certain cases, does not meet the legal criteria of patentability when applied strictly, and that it is not suitable as patentable subject matter.

One set of concerns turns on the view that DNA's value lies principally in its informational content, rather than its material qualities. In the case of diagnostics, what is discovered is a particular relationship between the presence of a particular gene or genetic sequence, and a particular illness.[41] According to this view, what has been identified looks more like information than physical material (Nuffield, 2002). According to some critics, this represents a departure not only from patent practice, but from patent doctrine, which is based on an agreement to disclose information in exchange for giving the inventor rights over the material invention. If DNA itself has value not only as material, but also, if not primarily, as information, this moves away from the usual range of patentable material and presents a new challenge for those who need access to the information (Eisenberg, 2002a).

A second set of concerns relates more specifically to the application of the criteria for patentability by patent offices. A general worry is that these criteria have been interpreted loosely in some jurisdictions in the context of DNA, and moreover that patents of broad scope have been granted. In the first instance, there has been concern about the requirement of an "inventive step", given that the sequencing of DNA, once a laborious manual task, has become a highly automated and routine part of laboratory practice. In the United States, the Court of Appeals for the Federal Circuit's interpretation of the "non-obviousness" standard has explicitly denied that the difficulty or complexity of invention matters at all in the determination of patentability (Rai, 1999). According to this ruling, as long as DNA has not been identified before (in other words, is novel), it meets the non-obviousness test. This ruling distinguishes the United States from Europe and Japan, which maintain a more robust standard ("inventive step") that considers the scientific difficulty of the work behind the invention. Additionally, there has been questioning of the granting of patents for sequences of questionable or limited utility. Some of this controversy has abated with the USPTO's 2001 guidelines on expressed sequence tags (ESTs, short pieces of DNA that help to identify when particular genes are being expressed in cells), which tighten the specifications regarding what constitutes "utility".[42]

A third set of concerns relates to the traditional distinction between inventions and discoveries. While it might be argued that this is an esoteric question with little import in patent law, for many it is fundamental to the question of what constitutes genuine innovation—the very thing intellectual property seeks to stimulate. As we have seen, most legal documents stipulate that entities, as they exist in nature, may not be patented. However, the European Directive, for example, permits the patenting of biological entities that have been isolated from their natural state, which have been shown to have a certain utility, or industrial application.

It may be useful to consider an example. We can imagine a researcher who, by experiment, learns that a plant growing in its natural habitat is able to take up toxins in the soil. A second researcher takes the plant and moves it into contaminated soil, demonstrating its utility to clean up the environment. At least intuitively, this latter person did something one might be prepared to call "innovative"; his colleague's achievement, on the other hand, while useful in generating scientific

knowledge, was less obviously "innovative". Knowledge is the quintessential public good; in increasingly knowledge-based industries, innovation in many cases is driven by the very thing that typifies common ownership. But whether or not one is prepared to view the first person's efforts as truly innovative may well depend on the degree of creative energy and technical capability needed to acquire the knowledge in question. In the case of genetic information, it has been argued that the sequencing and isolation of genetic sequences is no longer a demonstration of more than basic competence. By contrast, identifying the link between a particular gene (or set of genes) and the development of disease, depending on the complexity of the interactions involved, is unlikely to be a straightforward matter. What seems clear is that the question of what is "obvious" depends on the state of the technology and of the science at a given point in its evolution.

It is also clear that sometimes the degree of obviousness is not a good proxy for the social value of patenting. This has long been the case in small molecule patenting for drugs. What this suggests is that in some cases non-obviousness is becoming a place-holder for valuations about the amount of time and investment behind innovation, rather than about the degree of ingenuity behind an invention. Patents, in this case, are principally to *induce investment* rather than to encourage innovation. Though they may both be important, they are not the same.

As one author notes:

> The presumption against patenting basic information about natural phenomena might be overcome if the prospect of securing exclusive property rights in scientific discoveries for a limited period of time served as a necessary or important incentive to making investments in scientific research, in particular, if it served to elicit discoveries that would not otherwise be made or to accelerate the pace at which scientific knowledge advances (Scherer, 2002).

We will explore in section 3.2 below whether or not these justificatory conditions in fact hold true.

Given the nature and extent of arguments on both sides of this debate, it is important for developing countries to recognize the *ambiguity* in TRIPS, which does not explicitly require that countries include DNA among patentable substances. At the same time, they should be aware that it cannot be confidently said that TRIPS *permits* the exclusion of DNA, because this ambiguity has also been argued by some to suggest an implicit requirement to grant patent protection on DNA, if the invention is deemed to meet the standard criteria for patentability. For the moment, while it may be optimistic to describe the available room for manoeuvre in TRIPS as flexibility, the present ambiguity arguably permits a degree of manoeuvre and debate for countries on this issue.

Many practical difficulties with the system may be a product of the struggle of patent offices to keep pace with new technologies, and also of courts in some cases lacking the institutional capacity to stay on top of scientific advances (Rai, 1999). Challenges include keeping up with the state-of-the-art of rapidly advancing fields like genomics, and applying the standard criteria appropriately so as to reward genuine invention. While it may be the case that patent offices and courts, left on their own, will find the appropriate equilibrium, this will no doubt be an extraordinarily lengthy process. It may be of benefit for countries with common interests and circumstances to share experiences, and work together to strengthen the capacity of patent offices to respond to the challenges of emerging fields.

3.2 Ways in which the patent system may affect access to genetics and genomics

In general, patents can adversely affect access in at least two ways: by hindering access to the *products* of innovation in genomics in the short term; and, indirectly, hindering genomics *innovation*, particularly in areas relevant to developing countries, by creating barriers to research. It can also positively affect access by inciting investigation in complex and expensive research of social value.

3.2.1 Patents and access to genetic tests

Patents can affect access to useful genomics products like genetic tests in at least three ways:

- improving incentives to develop useful tests;
- increasing the cost of available services;
- imposing transaction costs and inconvenience on research and development;
- impeding the transfer of existing tools and technologies.

We will consider each of these effects below.

Improving incentives to develop useful tests

The *raison d'être* of the patent system is to encourage innovation—or, more precisely, to encourage the investment of the time, creativity and capital necessary to bring about socially useful advances. In such industries as pharmaceuticals, where research and development costs are reportedly very high, there is a strong dependency on patents as a mechanism for recovering up-front investment.

While the HGP is hailed as a success in public non-proprietary research, patents may have contributed indirectly to the pace of research through the competition provided by Celera Genomics. Even so, while the sequencing effort has been held up by some as a prototype for collaborative public initiatives driven primarily by non-proprietary incentives, it is far from clear that the work to translate the now-abundant raw genomic data into clinically useful applications can rely on the same model. The complexity of gene–gene and gene–environment interactions makes the task of turning promising targets into concrete applications a challenging one (Wirth, 2001). This means that creating tests for common diseases, and interventions for some more intractable infectious diseases like malaria and HIV/AIDS, will surely require considerable investment of both time and resources. By contrast, simple DNA-based diagnostic tests for single-gene disorders and for many infectious diseases depend less on a high front-end investment because they are relatively easy to make.

In the case of common conditions that tend to affect people in both economically developed and poor countries—such as cancers, diabetes and heart disease—patents will provide an incentive for investment, because firms can be assured that if they produce a useful product, they will have protected access to wealthy markets to repay their initial investment. The main question in these instances is how to ensure that these products are applicable and available in low-resource settings.

In the case of diseases that characterize poor populations, firms have little incentive to invest. In these instances, patents will rarely provide an incentive for research and development. However, patents may still be useful to developing countries in at least two ways: first, firms within developing countries that succeed in obtaining patents in lucrative markets on an endogenous innovation could earn rents that lift them into viability; and second, patents could be used by those doing research relevant to developing countries as tools to negotiate access to other technologies or services (see **Box 5**, for instance). The latter is precisely what is done by many private companies, which see patents as assets to be traded in exchange for other assets of value. The possibility of developing country institutions obtaining rents from patented tools and technologies exists, of course, only where

Box 8
Haemochromatosis

Hereditary haemochromatosis is a genetic disease that results in an overload of iron in the body, and can lead to arthritis, diabetes, liver cirrhosis, liver cancer, and heart failure. Early diagnosis and treatment can prevent these serious complications.

Mutations of the HFE gene (*C282Y* and *H63D*) have been linked to the disease. In 1998, patents were granted on these mutations in the United States. An exclusive licence to perform diagnostic genetic testing was issued by the patent holder to Smith Kline Beecham Clinical Laboratories, which subsequently contacted a number of laboratories in the United States and offered to issue sub-licenses in exchange for very high up-front fees and royalties.

The combination of additional costs and the fear of being sued for patent infringement caused insecurity among those who had planned to begin conducting similar testing, as well as among laboratories already performing similar genetic tests. In the United States, it has been reported that of 119 laboratories surveyed, 30% of those already offering diagnostic genetic testing for haemochromatosis stopped performing their tests after the patents and exclusive licenses were granted. Fewer institutions are carrying out genetic tests, which means less data are available to researchers seeking to better understand the disease, and fears have been expressed that high costs and royalties charged by the patent holder and licensee to laboratories are likely to trickle down to patients, who will pay more to access genetic tests for *C282Y* and *H63D*, tests that offer a means of obtaining crucial information about their health status. Patent claims on the HFE gene have also been filed in Europe.

Some laboratories continue to perform molecular diagnostic genetic tests they have developed for pre-symptomatic screening of the haemochromatosis disease. These services may very well cease should the patent issue. The EPO has not yet issued a decision on this case, but political opposition has been expressed against the type of patent right granted to the patent holder and the exclusive licensee.

Source: Cogswell et al. (1999). *American Journal of Preventive Medicine*

there is a sufficient science and technology base—which is true of relatively few developing countries. And successfully using patents in bargaining for rights with other institutions requires, for its part, an ability to negotiate effectively with institutions (multinational companies or universities, for instance) with considerable experience in parleying and resources to back that up. One possible option that we will consider later is to harness the ownership of patents by bodies such as universities (which own a substantial proportion of patents on the health biotechnology sector) as a basis for collective action.

Increasing the cost of available services

There are high-profile examples of patents on diagnostic tests resulting in the increased cost of existing services. Genetic tests for Canavan disease, familial breast cancer, Alzheimer's disease and haemochromatosis are among those that have received publicity because of the outcry by patients and clinicians that patents, combined with exclusive licensing practices, have put the price of diagnosis beyond the reach of many. Myriad Genetics charges US$ 2500 to test for *BRCA1* and

BRCA2 (for first tests in each family), and does not permit any laboratory besides its own or a few licensed laboratories in other countries to carry out the test. Haemochromatosis (see **Box 8**) is among a host of conditions for which laboratories across the United States have stopped providing genetic tests because of concerns that they are infringing the rights of patent holders, many of whom have been aggressive in sending "cease and desist" notices to offending institutions (Cho et al., 2003; Merz et al., 2002). In the latter case, laboratories perceived the cost to be excessive and stopped providing services.

As we have noted before (section 1.5.3), it is not clear that patenting DNA, as such, has posed the greatest problem in these cases, as opposed to restrictive licensing practices. Of course, licensing is only possible because of patenting; but the point is that the patenting of DNA sequences does not in every case lead to diminished access. Some of the benefit-sharing strategies discussed above may be useful in addressing the fair distribution of benefits between researchers and sources who contribute genetic material, and in a growing number of cases, substantive research support. However, given that the affected population is likely to be the principle market for the test in question, it is not clear that companies would be willing to make concessions in prices. In many cases, such as Alzheimer's disease, genetic tests are arguably not ready for widespread clinical use; however, such tests could be valuable in conducting research to further understand the disease. Research exemptions may alleviate the cost burden on researchers wanting to carry out studies using the tests for principally research purposes or in order to improve the technology.

Imposing transaction costs and inconvenience on research and development

Patents on research tools can inhibit access to services, inasmuch as they hinder research that leads to innovation in these areas. Research tools, broadly, are "any tangible or informational input into the process of discovering a drug or any other medical therapy or method of diagnosing disease". For example, recombinant DNA, polymerase chain reaction, genomics databases, micro-arrays, transgenic laboratory animals, and embryonic stem cells are examples of research tools (Walsh, Arora and Cohen, 2003). Diagnostics are particularly affected by patents on research tools because the same tools are the fundamental building blocks for making tests.

As we have seen, patents awarded for genes and DNA molecules grant a right to exclude others from using, making, selling or importing that which incorporates what is covered by the patent claims (Kluge, 2003). Researchers need to use a large number of different research tools, and in biotechnology there is evidence of the cumulative nature of scientific development such that later innovation depends heavily on prior iterative advancements. The concern is therefore that the existence of patents on research tools could slow or even block many subsequent research efforts as researchers are forced to pay high fees to a large number of research tool patent holders before even commencing their projects, or might even be denied permission for use. The fact that numerous intermediaries are involved in the very early stages of research projects could significantly increase their cost. These high costs will be incurred at a stage when the researchers do not even know if and when they will achieve any feasible result and whether that research result will be commercially viable. The fear is that the cost of basic research will increase due to the increasing number of patented basic research tools, slowing down biomedical innovation. This situation has been dubbed the "tragedy of the anticommons" (Heller and Eisenberg, 1998), and contrasts with the tragedy of the commons feared to result from leaving valuable resources in the public domain.

A recent report by the National Research Council of the United States examines, on the basis of interviews and archival data, "the changes in patenting and licensing in recent years and how these have affected innovation in pharmaceuticals and related biotech industries" (Walsh, Arora and Cohen, 2003). The authors conclude that drug discovery has *not* been significantly hampered by the increase in patents on research tools. But to this conclusion they add the following caveat:

"Restrictions on the use of patented genetic diagnostics, where we see some evidence of patents interfering with university research, are an important exception". The same report suggests that the anticommons effect is worse for small businesses, and those entering the market (Walsh, Arora and Cohen, 2003), which suggests potentially greater challenges for emerging sectors in developing countries. The other very important finding is that infringement is rampant, among academics and companies both. This means that if norms shift, then these "gentlemen's agreements" could collapse.

On the one hand, this study highlights the evidence that many institutes in the United States have developed workable solutions that allow them to carry on with research, in the face of the widespread patenting of research tools. These include infringing the patent, often by informally invoking the research exception; developing and using public tools; challenging patents in court; and inventing around the patent. On the other hand, not all of these solutions may be viable within the context of genetic diagnostics.

For one thing, it has been argued that in the case of genetic diagnostics, inventing around patents may be considerably more difficult than it is with other types of invention. There is a finite number of genes, and therefore a limited number of tools, including platform technologies, for researchers to employ in gene-based research (Nuffield, 2002). Researchers doing work in genetics could have their hands tied by patents granted on research tools, which are often product rather than method patents, to a greater extent than their counterparts in other fields. Gene patents are composition of matter patents on sequences, so making or using them in the laboratory without permission for *any* purpose risks infringement. This becomes particularly problematic for the development of tests addressing diseases affected by multiple genes, each of which is patented.

Because challenging patents in courts is not a feasible option for firms with limited capital (including the majority of those in developing countries), or for research institutions and universities, a more viable long-term solution may indeed be to clarify the criteria for DNA patentability, and to apply these criteria more strictly. This could result in fewer DNA patents being granted, but in an overall higher quality of the patents and a greater confidence on the part of inventors and researchers in the validity of granted patents, and thus in the credibility of the system.

The bottom line is that these constraints present obstacles that may be sufficiently high as to create disincentives for the pursuit of certain lines of research, and could be particularly heavy for diagnostics, a field in which the raw materials of genomics may translate most easily into useful health applications for developing countries. What's more, these disincentives will chiefly affect institutions that have relatively limited capital, such as research centres and public–private operations, which are often those groups most concerned with research in areas relevant to developing countries.

It is significant that the National Academy of Sciences report states:

> Our interviews suggested that the main reasons why projects were not undertaken reflected considerations of technological opportunity, demand, and internal resource constraints, with expected licensing fees or "tangles" of rights on tools playing a subordinate role, *salient only for those projects which were commercially less viable* (Walsh, Arora and Cohen, 2003—emphasis added).

This means that research oriented towards non-lucrative markets, including research addressing developing country health needs, is particularly vulnerable to the "tangling" effects of obstacles to accessing research tools.

Countries can learn important lessons from each other, but should be wary of looking to others for ready-made solutions. The United States patent system, for instance, has evolved over a period of

more than two hundred years, during which time the system itself has adjusted to meet the changing scientific and technological needs of the country. United States patent law formerly excluded foreign "prior art" as a deliberate measure to allow United States patent applicants to obtain a patent domestically on a copied foreign invention. This option is limited because of TRIPS. Moreover, with reference to new and emerging industries, including biotechnology and genomics, the United States has evolved a pro-patent court system and a Bayh-Dole framework, as well as more expansive interpretation of what is patentable (e.g. business methods, algorithms), and an unrigorous non-obviousness criterion, which differs from other jurisdictions such as Japan and the EU. The question of patented research tools is being taken up in several major studies begun in 2004 (Malakoff, 2004), in an effort to collect evidence to fill the void in the current debate about their impact on downstream research. This suggests that it may be of questionable benefit for developing countries to look to the United States as a model, at least in the case of biotechnological inventions, since its own system continues to be assessed and modified to accommodate challenges; however, it will be important to monitor its progress so that important lessons may be drawn for others facing similar challenges.

Developing countries with relatively advanced technological capacity need to weigh different factors, including: the impact of adopting features of a pro-patent system (such as patent protection for research tools) on domestic issues such as competitiveness within the local industry; foreign direct investment; access of poor segments of the populations to inexpensive healthcare products; the proportion of local innovation directed at domestic needs versus those directed to overseas market; as well as its impact on the supply of generics and other cheap products to dependent markets in less developed countries. China, Brazil and India are developing countries facing these decisions; they hover on the cusp between developing countries and the industrialized world, with scientific capacity that gives them the possibility of self-sufficiency and international competitiveness, but with a considerable proportion of their population living in desperate poverty. As we saw in section 2.4 above, these countries have not approached IP in the same way; it will be very important to monitor the impact of TRIPS on the ability of these countries, and others in their position, to maintain access to affordable healthcare products for their own citizens, as well as those in other countries that rely on their capacity.

A further factor to consider is the need for patents as incentives for research in genomics. In the context of drug development, where patents have been argued to be a necessity, the number of drugs making their way into the market has slowed (FDA, 2004). The perceived 'innovation deficit', in spite of much larger R&D expenditures in recent years, may be the result of changes in the technology and methodology used for doing research, and of underestimating the scientific challenges inherent in translating fundamental scientific advances into treatments for specific conditions. The 'genomics revolution' has indicated the very important part played by public initiatives in putting fundamental genetic data into the public domain, which can then be freely used by other researchers in the public and private sectors for further applied and translational research. It has also demonstrated the need to balance incentives offered by patenting, with the need to make platform technologies as accessible as possible to downstream research and potential applications. Given the complexity of the task required to move from a gene to a therapeutic product or a diagnostic tool, it would be in the interest of innovation not to place limits on the number of institutions that can be engaged in this work.

The pharmaceutical industry has been shown to rely heavily, more than most other sectors, on patents (Scherer, 2002). Making it harder to obtain patents on research tools does not preclude companies patenting biologically active substances that are one or two steps down the development chain. The pharmaceutical industry, through its involvement in projects such as the SNP Consortium, has demonstrated the interest it has in making upstream genetic information freely available as an aid to drug discovery. Patents on DNA sequences cover a range of applications, not

all of them therapeutic; research might therefore be compromised across these applications if DNA patents were made harder to get. Firms likely to be most affected by any limits on the patenting of upstream tools are biotech companies and start-ups, which are widely held to depend heavily on biotechnology patents to garner venture capital.

In the remainder of this section, we will consider the question of access from an international point of view, namely through the lens of technology transfer.

Impeding the transfer of existing tools and technologies

The UK Commission on Intellectual Property Rights, in its report on IP and development, remarks:

> In a sense, the crucial issue in respect of IP is not whether it promotes trade or foreign investment, but how it helps or hinders developing countries to gain access to technologies that are required for their development…and whether it encourages or hinders the development of technical capacity, including knowledge-based industry in that country (IPR Commission, 2002).

In section 2.1, we noted that patents are national in application; however, we also noted elsewhere that research, particularly in emerging technologies such as genomics, is increasingly global. Thus, while it may be true that patent protection has not been obtained for genetic inventions in many countries in the developing world, it does not necessarily follow that patents do not affect access to health products and services in these countries (IPR Commission, 2002).

Most genetic research is performed in industrialized countries, and is predictably directed towards the health needs of markets in these countries, where patents have been awarded for entire genes, cell lines containing particular DNA sequences, research methods, and other forms of genetic invention. But companies, scientists and universities often refrain from filing patents on genetic compounds in the developing world, in large part because the possibility of financial returns for a patented invention in developing countries is likely to be very small, and not worth the price of filing a patent application and maintaining a patent once it is issued. In the absence of patent rights, developing countries are, in theory, free to use technologies without penalty or the need to pay licensing fees. However, a crucial practical barrier to accessing genetic tools and technologies within developing countries is that most low and middle income countries do not have the research, testing or manufacturing capacities to make use of the existing tools and technologies. This is the identical challenge faced in the context of pharmaceutical research and development, a challenge acknowledged by the "paragraph 6 problem" of the Doha Declaration, discussed in section 2.1 above. Furthermore, with few exceptions, developing countries lack facilities required to adapt existing tools and technologies to their own needs or access non-patented know-how associated with the use of patented DNA sequences.

It is clear, then, that the majority of developing countries, and particularly the least developed, unable to develop tests themselves, must rely on imports from their more industrially advanced neighbours. In those cases where a genetic diagnostic tool has been invented and patented in developed countries, and where the invention is also relevant to the health needs of poorer countries, we can draw some conclusions about the impact that the DNA patent may have on access to the genetic tool in developing countries, particularly in relation to price, by analogy to the access issues faced by developing countries in the case of product patents for drugs.

Furthermore, patents could block the ability of potential supplier countries to export patented goods to other countries, particularly through controls on distribution channels. This is another reason why companies may selectively patent in countries like South Africa, which, thanks to its relatively strong manufacturing capacities, is a potential supplier to poorer countries in the region.

At present, drugs-importing countries where there is no patent protection can import supplies from generic companies, principally in India, because these exporters need not have pharmaceutical product patent protection until 2005. Post-2005, India will have to provide product (and not simply process) patent protection on new drugs, and those for which patent applications were submitted after 1994 will be patentable; the opportunity for these imports will thus shrink over time (IPR Commission, 2002). There is no direct evidence, to date, that strategic patenting is a threat to accessing genetic information; as biotechnology and genomics become increasingly globalized, it will be important to assess whether this becomes a relevant issue.

The IPR Commission report encourages governments to consider a number of strategies to provide incentives for technology transfer to low and middle income countries, including tax breaks for companies that license technology to developing countries, and commitments to ensure open access to scientific databases. Governments of more industrialized countries can therefore have an important role to play in encouraging the transfer of beneficial technologies to less developed economies, including by way of meaningful partnerships. Developing countries, in turn, could benefit from studies that assess the impact of their domestic patent regimes and patent protection on the transfer of technology for the sustainable development of local capacity in genetic technologies.

3.2.2 Some preliminary proposals

A number of proposals have been put forward for solving the problem of access to health care products. In the case of pharmaceuticals, it has been suggested that developing countries may rely upon compulsory licensing to gain access to licensed inventions, under certain conditions. While there is some evidence that compulsory licensing provides leverage for bargaining in the context of negotiating access to therapeutic products, it is less clear that it is a viable option for preventative approaches, such as genetic diagnostics. Compulsory licensing is an important option for national governments. It is, however, a defensive mechanism that kicks in after a product has been created and patented.

Addressing licensing behaviour, by encouraging the employment of humanitarian use, medical use or research use exemptions could go a considerable distance toward rectifying the problem of accessing research tools. Several commentators advocate such changes in norms, which require much greater transparency in making public the terms of licensing agreements. One author terms this "publicly-minded licensing" (Benkler, 2004). The Public Intellectual Property for Agriculture (PIPRA), is a collaboration among agricultural research universities to share their IP and retain rights to use their technologies for subsistence and specially for crop development. Groups like PIPRA are formed to give universities much more negotiating power with biotech and pharmaceutical industries. Humanitarian use exemptions, or developing country licenses for their part, would permit research, development, manufacture and distribution of end products destined for developing country markets, or poorer markets within developed countries. Research exemptions would permit the use of a patented technology for research and education, under certain specified conditions. Such arrangements suggest a change in licensing norms, rather than changes in legislation or a tinkering with the patent system.

Alternatives to patents have also been proposed, including open source approaches that more closely resemble the loose property arrangements of copyright (Maurer, 2002), and the employment of compensatory liability rules (Reichman and Lewis, 2005). The former model is based largely on the open source software movement, which operates on distributed innovation and the ingenuity of networked volunteers. The latter model of compensatory liability rules takes a well-established method and adapts it to protect know-how under specific circumstances. Liability rules embody a legal structure that permits third parties to undertake certain actions without prior permission, provided that they compensate injured parties for all or part of the harm they inflict. Liability rules understood in relation to modern

research would operate to manage sub-patentable innovation—that is, inventions that do not meet the non-obviousness (or inventive step) standard. They would not be a substitute for the "absolute" property rights of patents, but rather would complement them, furnishing a means of providing protection for useful inventions while mitigating against access concerns tied to stronger property rights. Proponents of liability rules have argued that they provide a viable framework for encouraging small-scale innovation in developing countries:

> [Q]ualified experts have long agreed that most developing countries would benefit from a special regime to protect small-scale innovation. This follows because the more limited technical capacities of producers in most of these countries are better suited to applications of inventions made elsewhere to local conditions than to developing bigger scale inventions from scratch, especially when these depend on basic research, in which most developing countries are deficient (Reichman and Lewis, 2005).

Inasmuch as this view of liability rules specifically targets sub-patentable innovation, it is a credible model for providing property protection for genetic sequences, one that is somewhere between patents and copyrights in strength. This model would require an infrastructure that would permit mediation and the enforcement of rules, and would in practice likely function by pooling tools among owners within a given field, to facilitate access to and the management of research tools. To date, liability rules have not been applied in the context of research; it is therefore difficult to evaluate their feasibility. A good way of testing compensatory liability rules could be in the context of a specific technology, for instance, the development of a malaria vaccine or diagnostic device for tuberculosis.

The open source approach that characterizes the software industry may also prove relevant. Open source products are made accessible to third parties by a licensing system that does not require payment but does require that any innovation made as a result of using the invention be placed back into the public domain. In other words, the cost of access is the enrichment of the public domain, so that no one individual can control access to genetic tools. The system works best if subsequent inventors actually acquire rights and then license out their inventions to all comers on the same conditions that were imposed on them. This is a way for genetic knowledge to flow freely into the public domain, much in the same manner as the Human Genome Project, through copyrights that do not rely upon their inherent right to exclusivity (Gold, 2003). Open source approaches to genetic information have been promoted by an initiative founded in 1994, *Cambia* (www.cambia.org), which has been called "a clearinghouse for intellectual property issues" (Finkel, 1999). Some industry representatives have been critical, arguing that open source undermines the incentive to conduct research into viable products. And open source approaches have also yet to prove themselves in the long-term, even in the software industry. The growing intersection between biotechnology and computation, as witnessed in the emergence of bioinformatics and data mining, suggests that the models and networked framework of the software industry are likely to pervade biomedical sciences to a growing extent. India, for example, has made explicit moves to develop capacity in bioinformatics, to capitalize on its native skills in the chemical sciences and in informatics.

There nevertheless remains the possibility of including DNA among those entities excluded from patentability. In light of current practice in most economically advanced countries, and the present trend towards expansive IP coverage, it is important to point out that this is a controversial option.

Several countries have at different times excluded some inventions from patent protection, often restricting patents on products and limiting protection to the processes that make them. Food stuffs, pharmaceuticals and chemicals are sectors where exclusions have typically applied. These

products are essential goods for which the benefits of free access are perceived to override the potential stimulus to innovation. In the 19th century, this approach was adopted by many countries that are now considered developed, and some maintained it until late in the 20th century. This was also the case in the East Asian countries (such as Taiwan and Korea) until relatively recently. TRIPS now forbids discrimination in the grant of patent protection in respect of different fields of technology. TRIPS does not, however, stipulate explicitly that DNA must be subject to patent protection, insofar as it is not excluded.

Countries deciding to avail themselves of this ambiguity should do so understanding (1) the widespread view of patent lawyers that DNA is primarily a chemical compound, (2) the three-decade-long history of permitting DNA patents in several countries, and (3) the TRIPS requirement to make "patents available for any inventions, whether products or processes, in all fields of technology without discrimination, subject to the normal tests of novelty, inventiveness and industrial applicability".[43] In any event, complaining members of the WTO will have the burden to prove that TRIPS obliges the protection of DNA as an "invention".

Developing countries are required to grant product patents on pharmaceuticals by 2005 and least developed countries, by 2016. However, given evidence that genomic industries operate on a model of cumulative development and of the role of DNA as a foundational tool for further research, developing countries should carefully consider the standards they apply in permitting (product, or composition of matter) patents on DNA, in terms of encouraging innovation in genomics and other areas. The status of DNA as patentable (or unpatentable) subject matter would, precisely because of the "foundational" nature of DNA, have repercussions not only on basic research involving the study of genes, but also on a host of other areas including pharmaceutical research.

Developing countries with relatively strong scientific capacity need to think carefully about following this option, given that patents for them may provide obstacles in some instances, but in others could earn them considerable rent on a major innovation patented worldwide. Developing countries with very limited research and technological capacity have little to gain from providing patents because they do not have sufficient technical skill to attract foreign companies or to incite local innovation. These countries may, on the other hand, be in a position to be more experimental and to try options such as petty patents, compensatory liability rules or other systems to encourage small-scale innovation.

Excluding DNA from patentability as a chemical compound or "composition of matter" may be judged by some accounts to be incompatible with TRIPS, though there is nothing in the Agreement obligating the grant of patents over substances existing in nature (even if isolated). For those countries wishing to circumscribe but not to completely forbid the patenting of DNA, as an alternative to denying patents on genetic materials *tout court*, the standard of non-obviousness (or inventive step) could be applied more rigorously, in which case genetic sequences are likely to fall short in most instances. As with USPTO's revised guidelines, the utility standard could likewise be a tool for diminishing the impact of research tool patents, by diminishing the number of patents issued on sequences of dubious industrial value.

For developing countries with sufficient technological capacity to develop tools to address local needs, there is limited economic research at the country level that directly links the IPR regime to domestic innovation and development, generally. But there is evidence that relates innovation in some sectors in Brazil and the Philippines to the availability of utility models, or petty patents,[44] which offer limited protection for inventions that may not meet the standards of the patent system. The intellectual property protection provided by utility models tends to be more widely used by local residents than by foreign companies, while in many countries the opposite is the case for full patents, the majority of which are owned by foreigners (Richards, 2002). This suggests that utility patents may be useful for stimulating local

innovation. In Japan, the evidence suggests that a system of weak protection based on utility models and industrial designs facilitated incremental innovation by small enterprises, and the absorption and diffusion of technology. This was associated, as in Taiwan and Korea, with an absence of patent protection for chemical and pharmaceutical products. Japan introduced protection for pharmaceuticals only in 1976. Some commentators have recommended a petty patent system for developing countries, though others have argued that the existence of utility models alongside the patent system creates confusion and economic inefficiencies, and provides opportunities for large companies to gain control of innovations representing incremental advances (Cornish, Llewelyn and Adcock, 2003). Petty patents differ from liability rules because the former are still absolute rights that forbid the use of the invention without the prior consent of the right holder. Liability rules operate on a "use now, pay later" model that presents no barriers for use, but only requires compensation at a later stage. The role of petty patents in encouraging domestic innovation should be weighed against the possible monopolization of particular fields by large companies, using petty patents (bearing in mind that diagnostic firms are typically small).

In some countries, attempts to overcome difficulties of accessing licensed technologies have led to the use of so-called "patent pools", which are agreements between patent owners to license their inventions to each other or third parties. However, to date the conditions do not seem to have materialized. In 2000, a report by the USPTO on patent pools and biotechnology patents concluded that "the use of patent pools in the biotechnology field could serve the interests of both the public and private industry, a win-win situation" (Clark et al., 2000). Among the benefits cited for this approach to licensing were: efficiency in obtaining rights to patented technology through "one stop" licensing mechanisms; the distribution of risks associated with research and development; and the elimination of "blocking" patents or "stacking" licenses, and the consequent encouragement of cooperative efforts. Most pools start from a group of companies with shared market and blocking patents, with no one player believing it has a clear advantage. However, such strategies may be defensive, and therefore not contribute to opening up access to tools but to limiting its use to those owning pivotal patents.

As we have seen, a case has been made that patent pools could be most useful for technologies particularly relevant to developing countries, because the lack of strong market incentives may enable agreements that lucrative incentives would make more difficult to engineer. It has been argued that such an approach could work for low-margin research such as that directed towards problems of the poor, because it tends to be conducted by universities or non-profit institutions, a relatively homogenous group that could be knit together around shared values and a shared goal, without the powerful distractions of powerful financial interests. PIPRA is precisely this kind of venture. Its members have publicly committed to generating "best practices" for systematically retaining rights that permit public institutions to freely undertake research oriented towards the needs of developing countries (Rai, 2004).

Patent pools, liability rules, and open source approaches to accessing genetic research tools, particularly genomics databases, should be explored as an alternative to patent approaches. Recent work suggests that genomics and biotechnology are appropriate candidates for these approaches, at least at the level of basic research.

Finally, developing countries with an interest in developing capacity in genomics might consider the value of networking. For instance, Brazil and Mexico have taken steps at the national level to establish competence in genomics and related

disciplines. For many countries in the region, a principal obstacle to these efforts is a lack of funds to afford equipment and facilities. This dearth of resources could be compensated by a "networking strategy" that relies on collaboration among institutions in various countries, and therefore maximizes resources (Ramírez, 2003). A similar approach was employed nationally across Brazil, which established a virtual network of institutions to facilitate cooperation across its vast territory. South Africa has recently launched a policy for developing biotechnology and genomics in a report entitled *Biotechnology platforms: strategic review and forecast*. The policy advocates the establishment of world-class genomics capacity, through the creation of a national facility and centres of excellence. The New Partnership for Africa's Development (NEPAD) has likewise committed to developing regional capacity in science and technology, including genomics, using networks of centres of excellence. The recent launch of the African Biosciences Facility in South Africa is a concrete achievement in this effort to make possible Africa's active participation in the advances of genomics. It may be that such networks facilitate the development of more "networked" approaches to innovation, such as those described earlier in this section.

4
Conclusions

Intellectual property has existed, in some countries, for centuries, and biotechnology patents have been granted in several jurisdictions for years, but it is only in the past decade that heated controversy has arisen around the patenting of biological entities (Eisenberg, 2002b). Various theories have been promulgated to explain this fact; what is clear is that the debate has by no means been put to rest.

The patenting of DNA presents an interesting point for consideration, because it is a topic about which there is great polarity in views, not only about its effects on research and access, but also due to more basic misgivings about whether DNA is the right sort of thing to patent. Ethical, legal and scientific concerns intermingle to create a complex milieu for discussions that range from consequentialist arguments about possible practical implications, to renewed and vigorous discussion of the meaning of "innovation". In this report, we have attempted to consider the various sides of this debate through the lens of public health.

One of the challenges with respect to DNA is that it is an upstream *tool* for basic research (e.g. PCR), a medically valuable *product* (e.g. gene therapy), as well as vital *information* about the molecular basis for disease. Some individual patents are therefore at once the basis for involved studies to develop therapeutics, and for immediate use in laboratories as research tools. That is, in some cases, DNA patents can conceivably do considerable work to encourage the development of therapeutics or diagnostics, and at the same time be needed for researchers, widely and at low cost. The Human Genome Project, which was itself a case study of innovation, employed incentives for scientific and medical, but not primarily commercial, research. There remains, as we have seen, an unresolved question about whether such an approach can equally succeed in spurring the work needed to move the fruits of this research down the pipeline, to produce benefits for public health. In other areas, evidence suggests that a proliferation of patents has not been accompanied by a proliferation of medical applications—though this tells us only that patents are not solving the problem, not that they do not matter. While much of this perceived lag is no doubt owed to technical issues and the inherent complexity of the science, it is unclear how much is related, if only indirectly, to a failure of incentive mechanisms, including patents, to generate new and useful products and services.

We have seen that one possible exception is the field of diagnostics, where genetic tests are generally considerably easier and cheaper to develop than treatments or cures. Indeed, medicine has long been practised on a diagnostic model that acknowledges the tremendous importance of identifying risks, even in the absence of therapies. Diagnostics, then, for developing countries, appear to be a far more achievable application of genomics in the short term, to fill a very important public health need. Building the skills locally to diagnose these conditions not only addresses a real and present need facing many countries with endemic disease burdens; it can lay the groundwork for developing capacity in genomic applications more generally, and contribute to what is an ongoing effort on the part of researchers worldwide to translate the wealth of genomic knowledge into beneficial applications.

Indeed, given the complexity of the work to translate the wealth of raw genomic data into practical solutions, it would be preferable to permit as many researchers as possible to take up this challenge. Tying patent protection to products further down the development pipeline links innovation with socially valuable inventions that should give evidence of real-world utility. Facilitating widespread access to gene sequences and other upstream discoveries useful as research tools could encourage a large number of researchers and institutions to undertake the much trickier work to develop end-products—particularly if those products are assured of patent protection, or other reward. Patent standards are currently being stretched to accommodate arguably sub-patentable items such as gene sequences. While these useful discoveries may merit some protection of some kind, they in most cases may not deserve the absolute protection provided by patents that exclude access.

In developed countries, where the science is more advanced, there is talk of a transition from traditional *medical genetics*, which focuses narrowly but effectively on heritable conditions, to *genomic medicine*, which integrates genetic information into everyday clinical practice. Indeed, according to proponents of genomic medicine, it is knowledge that will transform medical practice in the long-term—knowledge of how genes interact with each other and with the environment to cause disease. In the foreseeable future, then, genetic tests will play an increasing—not a diminishing—role in the diagnosis and prognosis of a range of conditions of great public health concern in all countries. But even before we have the tools to treat or cure these conditions, we can make important strides in the areas of early detection and prevention.

In this report, the aim has been to evaluate the current landscape of issues and evidence. Here, we present the major conclusions of this report, and in each case offer proposals for avenues of fruitful investigation that could usefully inform policy-making in the future.

4.1 Proposals

— Ongoing ethical, legal and social controversy regarding the patentability of human DNA

The controversy about the patenting of DNA remains unabated. This controversy is at several levels, from moral and legal claims, to consequentialist arguments about social benefit. Questions of benefit sharing also arise in relation to human genetics research, particularly regarding the obligations of inventors or researchers towards those who provide genetic samples. Many of these issues are parallel to those currently being debated within the context of biodiversity, plant genetic resources and traditional knowledge. In both cases, there is arguably a similar claim that the resource in question is both communal and "cultural", and at the same time commercially valuable, suggesting that it is both "person" and "property" to those who have been its caretakers. One particular area where WHO with other agencies might make a useful contribution is in suggesting how policy-making around ethically thorny subject matter, such as DNA, might take better account of the legitimate concerns of the public. Some possible avenues of inquiry are as follows.

- Explore possible mechanisms for soliciting public input into policy changes relating to IP, including making use of the *ordre public* clause within TRIPS. Examine how such input might contribute constructively to the development of policy, particularly in relation to issues of widespread controversy (e.g. the patenting of biological organisms, like DNA and stem cells, and what kinds of innovation are judged to be of social value).

- Explore policies that encourage entities involved in commercial aspects of research to openly negotiate with community leaders (including disease-associated advocacy groups, in the case of genetic diseases) for

equitable benefit sharing, and create standards to guide such negotiations. Moreover, carefully assess the value of certificates of origin, or similar mechanisms, for negotiating benefits for the results of international genetic research.

- Assess the relevant similarities and differences of benefit-sharing issues relating to genetic resources derived from humans, and those derived from the environment, i.e. biodiversity. Explore what these contrasts suggest for the synergistic development of policy in these areas.

- Consider strategies for increasing the transparency of funding sources that support both public and private R&D initiatives in genomics and related fields in selected developed and developing countries, in order that there might be greater accountability for publicly supported ventures. Likewise examine ways of increasing the transparency of licensing inventions arising from federal and non-profit funding, in order to better track how inventions are being used.

— Ambiguity in TRIPS regarding whether DNA may be excluded from patentability

National legislation is constrained by provisions within international agreements. TRIPS, in particular, requires that WTO Members adopt minimal standards of intellectual property protection, though countries may take advantage of certain flexibilities to protect the health and safety of their populations. In relation to DNA patents specifically, however, there is ambiguity as to whether TRIPS requires countries to grant patents on DNA sequences. DNA patents have been widely permitted in Europe and the United States, but not all countries have responded in like manner. In light of this, it would be useful to undertake the following.

- Conduct comparative studies of selected developing countries to identify ways in which they have employed flexibilities in TRIPS for the protection of health-related interests (e.g. ambiguity about some types of patentable subject matter; compulsory licences; etc.) to advance health priorities, particularly in relation to genomics.

- Compare the status of DNA as reflected in the patent law of different developing countries, and analyse how this has affected (or will in the future affect) the ability of developing countries with relatively strong research and technology bases to harness gene-based approaches to improve the health of their populations. Furthermore, evaluate how these issues intersect with the overall changes to these countries' patent systems as a result of TRIPS coming into force in these countries in 2005, with a view to providing guidance for least developed countries that must make the same transition in 2016.

- Clarify the impact of current research exemption clauses on clinical research in selected countries (both developed and developing), and particularly on genomic research. This work could help to guide developing countries in devising clear and effective methods of fostering research. In particular, issues to consider include whether the exemption should be statutory, and if so, how to define so it does not destroy reagent, instrument and other "research tool" industries aimed towards research laboratories; whether it be made explicit for non-profit and government-funded research, mandating "research use" exemptions in licensing practices; and whether it should

emerge from norms and practices (i.e. self-regulation) in technology licensing, such as through humanitarian-use licensing.

- Assess the role of petty patents/utility models in encouraging domestic innovation and weigh their use against the possible monopolization of particular fields by large companies, using petty patents. The particular value of petty patents in cumulative sectors, such as biotechnology and genomics, should also be evaluated, especially in relation to encouraging domestic innovation.

— Developing countries stand to benefit from genomics

There is a body of epidemiological data that attests to the not inconsiderable burden of debilitating genetic diseases, particularly blood disorders, in developing countries. Moreover, other conditions with a significant genetic component, including heart disease, cancer and diabetes, contribute to a growing burden of common conditions among all countries. DNA-based diagnostics, which can be applied to diagnosis of both infectious and noncommunicable diseases, are generally inexpensive to manufacture. Building on the *Genomics and World Health* report, WHO and its partners can work to build a global strategy on how innovation in genomics can better serve the health needs of the world's poor. This would include considering how developing countries at the leading edge of technological development in genomics and biotechnology, such as Brazil, China, India and South Africa, could provide leadership by sharing experiences and expertise relating to the development of endogenous research capacity, as well as the development of infrastructure and capacity for appropriately evaluating, processing and enforcing patents. Questions whose answers might usefully inform such a process include the following.

- Consider how the development of low-cost, effective gene tests for use in developing countries could form a case study for the application of a compensatory liability rules system.

- Identify platform genomic technologies, such as microarrays, that could be easily adapted for application in poor settings, as a basis for pinpointing research opportunities. For example, for infectious diseases DNA analysis could mean making links with the biodefence research establishment, particularly academic and company groups developing portable detection methods.

- Undertake studies to systematically identify genetic tests of specific importance to developing countries (particularly genetic disorders and infectious diseases), and to determine which patents exist on these tests, by whom and in which countries. These studies would also assess the current licensing agreements surrounding the use of these tests. This will fill an important lacuna of knowledge, and provide a starting point for determining concrete policy steps, where necessary.

- Study cases such as Mexico, which has adopted a national strategy for the integration of genomics into medicine, to discover the factors underlying this move, including existing capacity in molecular science and biotechnology, and to shed light on the role of patents in the innovation process in these areas.

- Assess the extent to which researchers in developing countries make use of the growing repository of publicly available genomics data, and current strategies to develop indigenous capacity in bioinformatics and data mining in low-resource settings.

- Explore mechanisms for developing countries to share experiences, and work together to strengthen the capacity of patent offices and courts to respond to the challenges of newcomer fields, like genomic

industries. In particular, develop strategies for building capacity among policy-makers in developing countries to permit them to recognize and avail themselves of the flexibilities in TRIPS.

- Explore policies in OECD countries that foster indigenous technical development, particularly in biotechnology and genomics, and assess to what extent these have been effective in generating health applications of local relevance.

- Explore patent pooling, as well as open source approaches to licensing genetic research tools, particularly genomics databases, as an alternative to proprietary approaches. In particular, assess their viability for providing incentives for the development of medical applications, such as diagnostics and therapeutics (being careful to consider relevant differences between these fields) for populations with no ability to pay.

4.2 Some final remarks

Research networks, and particularly those in the biotech sector, are increasingly complex; understanding how they affect, and are affected by, the patent system is by no means a straightforward project, particularly when one tries to assess the implications for countries that are behind the wave of technological development. The most productive way to move forward is undoubtedly for countries, to the greatest extent possible, to share their experiences and challenges with each other, and to work together to create best practices that can also usefully guide those likely to face similar challenges in the future. Many industrialized countries have valuable experiences at both the technical and policy levels, and international bodies should double their efforts to encourage supportive networks for information sharing and capacity building in these areas.

WHO can, as an international body principally concerned with public health, play an important role, as it has in the past, by focusing a health-centred lens on the debate around intellectual property and in fostering dialogue in this area. It can also facilitate the studies that are needed to fill the remaining gaps in our knowledge about the true impact of intellectual property systems on health outcomes, particularly in developing countries. Indeed, in 2003 the World Health Organization, at the request of its membership, established a Commission on Intellectual Property Rights, Innovation and Public Health to consider IP in addition to broader issues impinging on health-related R&D.

It is clear that a discussion of patents does not present a complete picture of all the issues relevant to the discussion of access. The notion of innovation itself is a complex one; to the extent that patents impact on this process, they are certainly one factor among many. Education, scientific capacity, physical infrastructure, and appropriate regulatory and safety standards are among an array of components needed to ensure a functioning innovation system.

Finally, it is important to maintain a realistic and moderate view of the impact of genetics and genomics on health outcomes. The reality is unlikely to involve dramatic shifts in the short term, or even the longer term; rather, what we have seen so far suggests an evolution of practice rather than a revolution. The work of sequencing the human genome was a landmark achievement, but only a first step along a process that will inevitably take many years to achieve its full potential. Nevertheless, it is at the beginning of the process that timely consideration can be given to the possible incentives and barriers that could mould the directions of research, and affect access to its results.

Clarifying the interplay among patents, innovation and genomics could suggest one set of strategies for encouraging the right kinds of research, and a more equitable distribution of benefits.

5
References

Abbott A (2005). Europe pares down double patents on breast-cancer gene. *Nature*, 26 January 2005, 433(7024):344.

Adewole TA, et al.(1999). Application of polymerase chain reaction to the prenatal diagnosis of sickle cell anaemia in Nigeria. *West African Journal of Medicine*, 1999, 18(3):160–165.

Ahmed S, et al. (2002). Screening extended families for genetic haemoglobin disorders in Pakistan. *New England Journal of Medicine*, 347(15):1162–1168.

Altonn H (2002). UH makes gene patent history. *Star-bulletin*, 23 December 2002 (http://starbulletin.com/2002/12/23/news/story7.html, accessed 7 March 2004).

Alwan A, Modell B (2003). Opinion: Recommendations for introducing genetics services in developing countries. *Nature Reviews: Genetics*, 2003, 4(1):61–68.

Andrews LB, Mehlman MJ, Rothstein MA, eds (2002). Chapter 5: Commercialization of genetic research: Property, patents, and conflicts of interest. In: *Genetics: Ethics, Law and Policy.* St. Paul, Mn., West Group, 2002.

Barbosa DB (2004). The New Brazilian Patent Law (http://www.nbb.com.br/public/memos5.htm, accessed 2 March 2004).

Bar-Shalom A, Cook-Deegan R (2002). Patents and innovation in cancer therapeutics: Lessons from CellPro. *The Milbank Quarterly*, 2002, 80(4)637–676.

Benkler Y (2004). Commons-based strategies and the problems of patents. *Science*, 305(5687):1110–1111.

Berg K et al. (2000) Genetic benefit sharing. *Science*, 6 October 2000:49.

Berne Declaration (2003).

Biological Procedures Online (2004). Announcement of the chicken genome sequence and genome variation maps. *Biological Procedures Online* (http://www.biologicalprocedures.com/bpo/general/news/040301/05.htm, accessed 5 March 2004).

BioSpectrum (2003). Biotech industry outlook. Biospectrum India (http://www.biospectrumindia.com/advertising/bs.asp accessed 22 February 2005).

Bosch X (2004). Myriad loses rights to breast cancer gene patent. *Lancet,* 2004, 363(9423):1780.

Boyle J (2003). The second enclosure movement and the construction of the public domain. *Law and Contemporary Problems*. Winter/Spring, 66(1&2):33–74.

Brazil Law (1996). Law No.9.279/96.

Brower V (2000). Canavan families slam scientists over test patent profits. *Biotechnology Newswatch*, 2000:1.

Brower V (2001). Tackling the most difficult diseases: Genetics and genomics open new strategies to fight vector-borne diseases.

EMBO Reports, 2001, October, 2(10):875–877.

Brown MS, Ho YK, Goldstein JL (1976). The low-density lipoprotein pathway in human fibroblasts: relation between cell surface receptor binding and endocytosis of low-density lipoprotein. *Annals of the New York Academy of Sciences*, 1976, 275:244–257.

Cahill LS (2001). Genetics, commodification, and social justice in the globalisation era. *Kennedy Institute of Ethics Journal*, 2001, 11(3)221.

Cao A et al. (2002). Screening for thalassemia: A model of success. *Obstetric and Gynecology Clinics of North America,* June 2002, 29(2):305–28 (vi–vii).

Carroll AE (1995). A review of recent decisions of the United States Court of Appeals for the Federal Circuit: Comment: Not always the best medicine: Biotechnology and the global impact of U.S. Patent Law. *The American University Law Review*, 1995, 44:2433.

Check E (2002). Canada stops Harvard's oncomouse in its tracks. *Nature,* 12 December, 420(6916):593.

China Daily (2002). New patent rules to up standards. 2 September 2002 (http://www.china.org.cn/english/MATERIAL/21876.htm, accessed 6 March 2004).

Cho MK et al. (2003). Effects of patents and licenses on the provision of clinical genetic testing services. *Journal of Molecular Diagnosis,* February 2003, 5(1)3–8.

Clark J, et al (2000). Patent pools: A solution to the problem of access in biotechnology patents? 5 December 2000:1–16 (http://www.uspto.gov/offices/pac/dapp/opla/patentpool.pdf, accessed 2 July 2004).

Clegg JB, Weatherall DJ (1999). Thalassemia and malaria: New insights into an old problem. *Proceedings of the Association of American Physicians*, 1999, July–August, 111(4):278–282.

Coghlan A (2001). Patient power. *New Scientist,* 2001, 24 February 24 (http://www.pxe.org/news/newscientist_022401.html, accessed 9 July 2004).

Cogswell ME et al. (1999). Screening for hemochromatosis: A public health perspective. *American Journal of Preventive Medicine,* February, 16(2):134:140.

Cohn A (2003). Now more common in non-Jews: Years of genetic testing virtually erase Tay-Sachs. *Jewish Bulleting News*, June 2003 (http://www.jewishsf.com/bk030613/1b.shtml, accessed 7 March 2004).

Connor S (2003). Glaxo chief: Our drugs do not work on most patients. *Independent*, 8 December 2003 (http://209.157.64.200/focus/f-news/1035880/posts, accessed 19 February 2005).

Cook-Deegan R, Chan C, A Johnson (2000). World survey on funding for genomics research. September 2000 (http://www.stanford.edu/class/siw198q/websites/genomics/entry.htm, accessed 9 March 2004).

Cooper H (2001). White House drops WTO claim against Brazilian Patent Law. *Wall Street Journal*, 26 June 2001.

Cornish WR, Llewelyn M, Adcock M (2003). *Intellectual Property Rights (IPRs) and genetics: A study into the impact and management of Intellectual Property Rights with the healthcare sector*. Cambridge, Public Health Genetics Unit, 2003.

Cox SM et al. (2003). International genetic testing. *Genetic Medicine,* 2003, May–June, 5(3):176–182.

Cukier KN (2003). Open source biotech. *Acumen Journal of Life Sciences*, 2003, I:3.

da Graça Derengowski Fonseca M, da Silveira JMFJ (2002). *Frontiers of Innovation Research and Policy* (a Workshop between the Instituto de Economia—UFRJ, Brazil and CRIC/University of Manchester), September 2002,

Rio de Janeiro, Brazil (http://les1.man.ac.uk/cric/workshops/frontiers/papers.htm, accessed 3 March 2004; paper available at http://les1.man.ac.uk/cric/workshops/frontiers/papers/fonseca.pdf, accessed 3 March 2004).

Dalton R (2004). Bioprospectors edge towards deal with developing countries. *Nature*, 26 February 2004, 427:769.

Devanand CJ, Schlich GW (2003). Is there a future for "speculative" gene patents in Europe? *Nature Reviews*, May 2003, 2:407.

Diamond v. Chakrabarty (1980), 447 U.S.

DiMasi JA, Harsen RW, Gatowski HG (2003). The price of innovation, new estimates of drug development costs. *Journal of Health Economics,* 2003, 885:1–35.

EC (1998). European Parliament and Council of European Union. Directive 98/44/EC of the European Parliament and of the Council. *Official Journal of the European Communities,* L 213/13, 30.7.98.

EC (2004). *Results of the Competitiveness Council of Ministers*. Brussels, 11th March 2004, Internal Market, Enterprise and Consumer Protection issues. Brussels, 12 March 2004 (http://europa.eu.int/rapid/pressReleasesAction.do?reference=MEMO/04/58&format=HTML&aged=0&language=EN&guiLanguage=en accessed 22 June2004).

Economic and Social Council (2002). *Capacity of the public sector to support the creation and application of knowledge, innovation and technology for development*. Report of the Secretariat. 10 May 2002 (E/C.16/2002/5).

Economist (2000). Science and technology: Fruits of co-operation. *The Economist* (London), 22 July 2000, 356(8180):79.

Eisenberg R (2001). The shifting functional balance of patents and drug regulation. *Health Affairs*, September–October 2001.

Eisenberg RS (2002a). Concerns about the patenting of genes. In: Andrews LB, Mehlman MJ, Rothstein MA, eds, *Genetics: Ethics, Law and Policy.* St. Paul, Mn., West Group, 2002:169–172.

Eisenberg RS (2002b). Why the gene patenting controversy persists. *Academic Medicine*, 2002, 77(12):1381–1387.

ETC Group (2004). From global enclosure to self enclosure: Ten years after – A critique of the CBD and the Bonn Guidelines on Access and Benefit Sharing. *Communiqué,* Issue 83, February 2004 (http://www.etcgroup.org/documents/Comm83_COP7_CBDCBonn.pdf accessed 20 March 2004).

FDA (2004). *Challenge and opportunity on the critical path to new medical products*. Washington, DC, United States Department of Health and Human Services, Food and Drug Administration, 16 March 2004.

Feng Z (2003). Rules set for study on genetic resources. *China Daily* (HK Edition), 25 November 2003.

Finkel E (1999). Australian center develops tools for the developing world. *Science,* September 1999, 285:3.

Fleishmann RD et al. (1995). Whole-genome random sequencing and assembly of *Haemophilus influenza. Science,* 28 July 1995, 269:496–512.

Gibbs RA, et al. (2004). Genome sequence of the brown Norway rat yields insights into mammalian evolution. *Nature*, 2004, 428(6982):493–521.

Gold ER (2003). Exclusive rights in life: Biotechnology, genetic manipulation, and Intellectual Property Rights. In: Jackson JF, Linskens, HF, eds, *Molecular methods of plant analysis*, *vol. 23, Genetic transformation of plants.* New York, Springer, 2003:1–22.

GRAIN (2002). *WIPO moves towards "World" patent.* Genetic Resource Action International (GRAIN), July 2002 (http://www.grain.org/publications/wipo-patent-2002-en.cfm, accessed 2 March 2004).

Guttmacher AE, Collins FS (2002). Genomic medicine—a primer. *New England Journal of Medicine*, 7 November 2002, 347(19):1512–1520.

Hall N et al. (2002). Sequence of *Plasmodium falciparum* chromosomes 1, 3–9 and 13. *Nature*, 2002, 419(6906):527–531.

Hardin G (1968). The tragedy of the commons. *Science*, 162:1243–1248.

Heller MA, Eisenberg RS (1998). Can patents deter innovation? The Anticommons in biomedical research. *Science*, 1 May 1998, 280:698–701.

Howard K (2004). University entrepreneur initiatives on the rise. *Nature Biotechnology*, 2004, 22(5):625–626.

International Human Genome Mapping Consortium (2001). A physical map of the human genome. *Nature*, 15 February 2001, 409(6822):934–41.

IPR Commission (2002). *Integrating Intellectual Property Rights and Development Policy*. London, United Kingdom, Commission on Intellectual Property Rights, 2002:127 (http://www.iprcommission.org/papers/pdfs/final_report/CIPRfullfinal.pdf, accessed 29 December 2003.

Jimenez-Sanchez G (2003). Developing a platform for genomic medicine in Mexico. *Science,* 11 April 2003, 300(5617):295–296.

Kaplan F (1998). Tay-Sachs disease carrier screening: A model for prevention of genetic disease. *Genetic Testing*, 1998, 2(4):271–292.

Khoury MJ (2003). Genetics and genomics in practice: The continuum from genetic disease to genetic information in health and disease. *Genetic Medicine,* July–August 2003, 5(4):261–268.

Kirby M (2002). *Report of the IBC on ethics, intellectual property and genomics*. Paris, International Bioethics Committee, UNESCO, January 2002 (http://portal.unesco.org/shs/en/file_download.php/0f8d8bed17083342b45db84beef431acFinalReportIP_en.pdf, accessed 4 January 2004).

Kluge E-HW (2003). Patenting human genes: When economic interests trump logic and ethic. *Health Care Analysis*, June 2003, 11(2):119–130.

Knoppers BM (1999). Status, sale and patenting of human genetic material: An international survey. *Nature Genetics*, May 1999, 22:23–26.

Lecrubier A (2002). Patents and public health. *European Molecular Biology Organization Reports*, 2002, 3(12):1120–1122.

Lewis R (2000). Clinton, Blair stoke debate on gene data: US–UK joint statement creates initial stir among commercial interests. *The Scientist*, 3 April 2000, 14(7):1.

Mabey D et al. (2004). Diagnostics for the developing world. *Nature Reviews*, March 2004, 2:231–240.

Madey v. Duke University (2002). 307 F3d 1351 (Federal Circuit Court of Appeal 2002).

Malakoff D (2004). NIH roils academe with advice on licensing DNA patents. *Science*, 2004, 303:1757–1758.

Marks D, Thorogood M et al. (2003). A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. *Atherosclerosis*, May 2003, 168(1):1–14.

Marshall E (2000). Families sue hospital, scientist for control of Canavan gene. *Science*, 2000, 290(5494):1062.

Marshall E (2004). Patient advocate named co-inventor on patent for the PXE disease gene. *Science*, 27 August 2004, 305:1226.

Merz JF et al. (2002). Diagnostic testing fails the test: The pitfalls of patents are illustrated by the case of haemochromatosis. *Nature,* 7 February 2002, 415:577–579.

Ministry of Health and Long-Term Care (2002). Genetic, testing and gene patenting: Charting new territory in healthcare. Toronto, Ontario, Ministry of Health and Long-Term Care, 2002 (http://www.health.gov.on.ca/english/public/pub/ministry_reports/geneticsrep02/report_e.pdf, accessed 29 December 2003).

Moukheiber Z (2003). Junkyard dogs. *Forbes*, 6 October 2003.

Musungu SF, Dutfield G (2003). Multilateral agreements and a TRIPS-plus world. The World Intellectual Property Organisation (WIPO), Ottawa, 2003 (TRIPS Issues Paper No. 3).

Nuffield (2002). *The ethics of patenting DNA, A discussion paper*. London, Nuffield Council on Bioethics, July 2002 (http://www.nuffieldbioethics.org/filelibrary/pdf/theethicsofpatentingdna.pdf, accessed 29 December 2003).

OECD (2004). *Patents and innovation: Trends and policy challenges*. Paris, Organisation for Economic Co-operation and Development (http://www.oecd.org/dataoecd/48/12/24508541.pdf accessed 18 February 2005).

Ogbu O (2002). African Science and Technology Day: Has Africa surrendered in the field of science and technology? *Science and Development in Africa*, 2002 (http://www.sciencenewsdev.co.ke/special-f.htm, accessed 19 December 2003).

Oxfam (2001). *WTO patent rules and access to medicines: The pressure mounts*. Oxford, June 2001 (http://www.oxfam.org.uk/what_we_do/issues/health/wto_patentrules.htm, accessed 19 February 2005).

People's Daily (2001). Chinese firms keen on patent application for WTO entry. *People's Daily*, 15 August 2001 (http://fpeng.peopledaily.com.cn/200108/15/eng20010815_77382.html, accessed 6 March 2004).

Pharmaceutical Executive (2005). January 2005:S5 (http://www.inmegen.org.mx/Portal/Pharmaceutical_Executive/Articulo_P_E.pdf, accessed 29 Maarch 2005).

Rai AK (1999). Intellectual property rights in biotechnology: Addressing new technology. *Wake Forest Law Review,* Fall 1999, 34:827–847.

Rai AK (2004). Proprietary rights and collective action: The case of biotechnology research with low commercial value. Manuscript provided by author, 2004.

Ramírez JL, Holmes D (2003). The need for genomics networking in Latin America. *SciDevNet*, 14 August 2003.

Rausch LM (2002). International patenting of human DNA sequences. *InfoBrief*. National Science Foundation, August 2002.

Read TD et al. (2000). Genome sequences of *Chlamydia trachomatis* MoPn and *Chlamydia pneumoniae* AR39. *Nucleic Acids Research,* 2000, 28:137–1406.

Reichman JH, Lewis T (2005). Using liability rules to stimulate innovation in developing countries: Application to traditional knowledge. In: Maskus KE, Reichman JH, eds, *International public goods and transfer of technology under a globalized intellectual property regime*. Cambridge University Press (forthcoming 2005).

Richards J (2002). Introduction. *Petty patent protection*. Ladas & Perry, 2002 (http://www.ladas.com/Patents/PatentPractice/PettyPatents/PettyP_c.html, accessed 3 March 2004).

Rother L (2001). Model for research rises in a Third World city. *New York Times*, 1 May 2001.

Scassa T (2003). A mouse is a mouse is a mouse: A comment on the Supreme Court of Canada's decision on the Harvard Mouse Patent. *Oxford University Commonwealth Law Journal,* 2003, Summer.

Scherer FM (2002). The economics of human gene patents. *Academic Medicine,* December 2002, 77(12 Pt 2):1348–1367.

Science and Engineering Indicators (2002a). International patenting trends in two new technology areas (http://www.nsf.gov/sbe/srs/seind02/c6/c6s5.htm#fn37, accessed 6 March 2004).

Science and Engineering Indicators (2002b). Human DNA sequence patents: Number of international patent families, by priority country and priority year (http://www.nsf.gov/sbe/srs/seind02/append/c6/at06-15.xls, accessed 6 March 2004).

Secretary's Advisory Committee on Genetic Testing (2000). *Summary of Panel Session on Human Gene Patenting and Licensing Practices and Access to Genetic Tests*, 7 June 2000, vol. 3 (http://www4.od.nih.gov/oba/sacgt/reports/patent_panel_sum.pdf accessed 18 February 2005).

Service R (2003). Genetics and medicine: Recruiting genes, proteins for a revolution in diagnostics. *Science,* 11 April 2003, 300(5617):236–239.

Service R (2004). Incyte throws in the towel on genomics, trims workforce. *Science,* 13 February 2004, 303:941.

Simpson A et al. (2000). The genome sequence of the plant pathogen *Xylella fastidiosa*. *Nature*, 13 July 2000, 406(6792):151–157.

Singh G, Agarwal P (2003). Forward and backwards on patent law. *The Hindu Business Line*, 4 October 2003 (http://www.blonet.com/2003/10/04/stories/2003100400090800.htm, accessed 18 February 2004).

Surendran A (2004). US NIH draft guidelines threaten diagnostics sector. *Nature Biotechnology*, 2004, 22(5):496.

Suter SM (2001). The allure and peril of genetics exceptionalism: Do we need special genetics legislation? *Washington University Law Quarterly,* Fall 2001, 79(3):669–748.

Terry SF, Boyd CD (2001). Researching the biology of PXE: Partnering in the process. *American Journal of Medical Genetics*, Fall 2001, 106(3):177–184.

The International HapMap Consortium (2003). The International HapMap Project. *Nature*, 2003, 426:789–96.

Thorold C (2001). Indian firms embrace biotechnology. *BBC News Online*, 6 April 2001 (http://news.bbc.co.uk/1/low/world/south_asia/1264569.stm, accessed 20 February 2004).

Thorsteinsdóttir H et al. (2003). Genomics—a global public good? *Lancet*, 2003, 361:891–2.

Trafford A (2001). California vintners put hopes in Brazil's labs. *Washington Post*, 29 December 2001:A01.

UNDP (1999). Globalization with a human face. New York, United Nations Development Programme, 1999.

UNESCO (1997). *Universal Declaration on Human Rights and the Human Genome*. UNESCO, Paris, 1997.

USPTO (2004). *Revised interim utility guidelines training materials, 2004*. United States Patent and Trademark Office (http://www.uspto.gov/web/menu/utility.pdf, accessed 8 July 2004).

Venter C et al. (2001). The sequence of the human genome. *Science,* 16 February 2001, 291(5507):1304–1351.

Verma IC et al. (2003). Genetic counselling and prenatal diagnosis in India—Experience at Sir Ganga Ram Hospital. *Indian Journal of Pediatrics*, April 2003, 70(4):293–297.

Verma P, Sharma YD (2003). Malaria genome project and its impact on disease. *Journal of Vector Borne Diseases,* March–June 2003, 40(1–2):9–15.

Walsh JP, Arora A, Cohen WM (2003). Effects of research tool patents and licensing on biomedical innovation. In: Cohen WM, A Merrill, eds, *Patents in the knowledge-based economy*. Washington, DC, The National Academies Press, 2003:285–340.

Wang Y (2001). Monsanto under fire for "pirating" Chinese soy strain. *China Daily*, 30 October 2001.

Waterston RH et al. (2002). Initial sequencing and comparative analysis of the mouse genome. *Nature*, 2002, 420(6915):520–562.

WHO (1964). *Human genetics and public health. Second report of the WHO Expert Committee on Human Genetics*. Geneva, World Health Organization (WHO Technical Report Series No. 282).

WHO (1994). *Guidelines for the control of haemoglobin disorder*. Geneva, World Health Organization (WHO/HDP/HB/GL/94.1).

WHO (1996). *Control of hereditary diseases*. Geneva, World Health Organization (WHO TSR, no. 865:1–86).

WHO (1998). *Proposed international guidelines on ethical issues in medical genetics and genetic services*. Geneva, World Health Organization (WHO/HGN/GL/ETH/98.1).

WHO (1999). *Report of a WHO/WAO meeting on prevention and care of genetic disease and birth defects in developing countries*. Geneva, World Health Organization (WHO/HGN/WAOPBD/99/1).

WHO (2000). *Report of a WHO meeting on public health approaches for the control of genetic disorders*. Geneva, World Health Organization (WHO/HGN/WG/00.1).

WHO (2002). *Genomics and World Health*. Geneva, The Advisory Committee on Health Research of the World Health Organization, 2002 (http://www3.who.int/whosis/genomics/pdf/genomics_report.pdf, accessed 12 January 2004).

Wickelgren I (2004). Heart disease: Gene suggests asthma drugs may ease cardiovascular inflammation. *Science,* 13 February 2004, 303(5660):941.

Wilson RK (1999). How the worm was won. The C. elegans genome sequencing project. *Trends in Genetics*, 1999, 15(2):51–58.

Wirth D (2001). *A harvest not yet reaped: Genomics to new drugs in Leishmania and Trypanosomes*. Boston, MSF/DND Working Group, September 2001.

WTO (2001). Ministerial Declaration. WTO/MIN(01)/DEC/2, 20 Nov 2001. Doha, Qatar (http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_e.pdf).

WTO (2003). Decision removes final patent obstacle to cheap drug imports. *WTO Press Release*, 30 August 2003 (Press/350/Rev.1).

Yoon CK (2000). Agriculture takes its turn in the genome spotlight. *New York Times*, 18 July 2000.

6
Other reading

Articles

Agarwal MB. Advances in management of sickle cell disease. *Indian Journal of Pediatrics*, August 2003, 70(8)649–654.

Akinyanju OO et al. Initiation of prenatal diagnosis of sickle-cell disorders in Africa. *Prenatal Diagnosis*, 1999, 19:299–304.

Alwan A, Modell B. *Community control of genetic and congenital disorders*. Cairo, World Health Organization, Regional Office for the Eastern Mediterranean, 1997 (EMRO Technical Publications Series 24).

Arzberger P et al. An international framework to promote access to data. *Science*, 2004, 303:1777–1778.

Attaran A, Gillespie-White L. Do patents for antiretroviral drugs constrain access to AIDS treatments in Africa? *JAMA: Journal of the American Medical Association*, 2001, 286(15):1886–1892.

Barton JH. Patents, genomics, research, and diagnostics. *Academic Medicine*, 2002, 77(12):1339–1347.

Barton JH. Research-tool patents: Issues for health in the developing World. *Bulletin of the World Health Organization*, 2002, 80(2):121.

Barton JH, Strauss J. How can the developing world protect itself from biotech patent-holders? *Nature*, 2000, 406:455.

Beck IA et al. Simple, sensitive, and specific detection of human immunodeficiency virus type 1 (HIV-1) subtype B DNA in dried blood samples for diagnosis in infants in the field. *Journal of Clinical Microbiology*, 2001, 39(1):29–33.

Beitz C. Social and cosmopolitanism liberalism. *International Affairs*, 1999, 75(3):515.

Bendekgey L, Hamlet-Cox D. Gene patents and innovation. *Academic Medicine*, 2002, 77(12):1373–1380.

Benenson Y, et al. An autonomous molecular computer for logical control of gene expression. *Nature*, 2004, 429(6990):423–429.

Black J. Regulation as facilitation: Negotiating the genetic revolution. *Modern Law Review*, 1998, 61:621–660.

Bobrow M, Thomas S. Patents in a genetic age: The present patent system risks becoming a barrier to medical progress. *Nature*, 2001, 409:763.

Bounpheng M et al. Rapid, inexpensive scanning for all possible *BRCA1* and *BRCA2* gene sequence variants in a single assay: Implications for genetic testing. *Journal of Medical Genetics*, 2003, 40(4):e33.

Boyle J. *Enclosing the genome: What the squabbles over genetic patents could teach us.* 2003 (http://www.law.duke.edu/boylesite/low/genome.pdf accessed 19 February 2005).

Broder S et al. Cures for the Third Word's problems. *EMBO Reports*, 2002, 3(9):806.

Buchanan A. Rawls's Law of Peoples: Rules for a vanished Westphalian world. *Ethics,* July 2000:697.

Burch RK et al. Divergent incentives to protect Intellectual Property: A political economy analysis of North–South welfare. *Journal of World Intellectual Property*, March 2001, 3:169–195.

Burke W et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. *JAMA: Journal of the American Medical Association*, 1997, 277(12):997–1003.

Butler D. Genetic diversity proposal fails to impress international ethics panel. *Nature*, 1995, 377:373.

Cantu JM, Figuera LE. Virtual molecular medicine in developing countries: The Mexican Initiative. *Molecular Medicine Today*, 2000, 6:190–192.

Caplan A, Merz J. Patenting gene sequences. *British Medical Journal*, 13 April 1996, 312(7036):926.

Carey NH, Crawley PE. Commercial exploitation of the human genome: What are the problems? *Human Genetic Information: Science, Law and Ethics*. Toronto, John Wiley and Sons, 1990:133–147.

Caulfield T. Globalization, conflicts of interests and clinical research: An overview of trends and issues. *Widener Law Symposium Journal,* 2001, 8:31.

Caulfield TA et al. Genetic technologies, health care policy and the patent bargain. *Clinical Genetics*, January 2003, 63(1):15–18.

Caulfield TA, Gold ER. Genetic testing, ethical concerns, and the role of Patent Law. *Clinical Genetics*, 2000, 57:370–375.

Cherniawsky K. Commercialization/Patents. In: Knoppers BM, eds, *Human DNA: Law and Policy, International and Comparative Perspectives*. Kluwer Law International, The Hague, 1997:385.

Chong SS et al. Single-tube multiplex-PCR screen for common deletional determinants of alpha-thalassemia. *Blood*, 2000, 95(1):3602.

Clavel C et al. Hybrid Capture II-based human papillomavirus detection, a sensitive test to detect in routine high-grade cervical lesions: A preliminary study on 1518 women. *British Journal of Cancer*, 1999, 80(9):1306–1311.

Cook-Deegan RM, McCormack SJ. Intellectual property: Patents, secrecy, and DNA. *Science*, 2001, 293(5528):217.

Correa CM. *Integrating public health concerns into patent legislation in developing countries*. Geneva, South Centre, October 2000 (http://www.netamericas.net/Researchpapers/Documents/Ccorrea/Ccorrea1.pdf, accessed 5 January 2004).

Correa CM. Public health and patent legislation in developing countries. *Tulane Journal of Technology and Intellectual Property,* 2001, 3:1.

Couzin J. Cancer sharpshooters rely on DNA tests for better aim. *Science*, 27 August 2004, 305:1222–1223.

Crigger BJ. The West knows best? *Hastings Center Report,* March/April 1996, 26(2)50.

Cullet P. Patent and medicines: The relationship between TRIPS and the human right to health. *International Affairs*, 2003 79(1):139.

D'Amato RF et al. Rapid diagnosis of pulmonary tuberculosis by using Roche AMPLICOR Mycobacterium tuberculosis PCR test. *Journal of Clinical Microbiology*, 1995, 33(7):1832–1834.

Daniels N. *Just Health Care*. Cambridge and New York, Cambridge University Press, 1985.

Davies K. Playing by Aussie rules (Conversation: Mervyn Jacobson). *Bio·IT World* (www.bio-itworld.com), 13 August, 2003.

Dennis C. Geneticists question fees for use of patented "junk" DNA. *Nature*, 8 May 2003, 423:105.

Dickson D. Open access to sequence data will boost hunt for breast cancer gene. *Nature*, 1995, 378:425.

Drahos P, Braithwite J. Intellectual property, corporate strategy, globalization: TRIPS in context. *Wisconsin International Law Journal*, 2002, 20:451 (Proceedings of 2002 Conference Access to Medicines in the Developing World).

Dryer O. US awards patent for tribesman's DNA. *British Medical Journal*, 1995, 311(7018):1452a.

Eisenberg RS, Nelson RR. Public vs. proprietary science: A fruitful tension? *Academic Medicine*, 2002, 77(12):1392–1399.

Eisenberg RS. Patent swords and shields. *Science*, 2003, 299:1018–1019.

Enriquez J, Martinez R. The next revolution: Who's ready? Who's not. *Perspectives in Health Magazine* (The Magazine of the Pan American Health Organization), Special Centennial Edition, 2002, 7:1 (http://www.paho.org/English/DPI/Number14_article4_5.htm, accessed 15 December 2003).

Ergenziger E, Spruill M. Basic science in US universities can infringe patents. *The Scientist*,10 March 2003, 17(5):43.

Fidle DP. Racism or realpolitik? U.S. foreign policy and the HIV/AIDS catastrophe in sub-Saharan Africa. *Journal of Gender, Race and Justice,* 2003, 7:97.

Friedman MA et al. Out-licensing: A practical approach of improvement of access to medicines in poor countries. *Lancet*, 2003, 361:341–44.

Genetic diversity proposal fails to impress international ethics panel. *Nature*, 5 October 1995.

Gitter D. International conflicts over patenting human DNA sequences in the United States and the European Union: An argument for compulsory licensing and a fair-use exemption. *New York University Law Review*, 2001, 76:1623–1691.

Gold ER. From theory to practice: Health care and the patent system. *Health Law Journal*, September 2003, Special Edition 2003: Precedent & Innovation: Health Law in the 21st Century.

Gold ER. Gene patents and medical access. *Intellectual Property Forum*, 2000, 49:20–27.

Gold ER. Making room, Integrating basic research, health policy and ethics into patent law. In: Caulfield T, Williams-Jones B, eds, *The Commercialisation of genetic research, Ethical, legal and policy issues.* New York, Kluwer Academic/Plenum Publishers, 1999:63–78.

Gold ER. Moving the gene patent debate forward: A framework for achieving compromise between industry and civil society. *Nature Biotechnology*, 2000, 18:1319–1320.

Gold ER. Owning our bodies: An examination of property law and biotechnology. *San Diego Law Review*, 1995, 32(4):1167–1247.

Gold ER. SARS genome patent: Symptom or disease? *Lancet*, 2003, 361:2002–2003.

Gold ER et al. Gene patents and the standard of care. *Canadian Medical Association Journal*, 6 August 2003, 167(3):256–57.

Gold ER, Caulfield TM. The moral tollbooth: A method that makes use of the patent system to address ethical concerns in biotechnology. *Lancet*, 2002, 350:2268–2270.

Gold ER, Gallochat A. The European directive: Past and prologue. *European Law Journal,* September 2001, 7(3):331–366.

Gold ER, Lam DK. Balancing trade in patents: Public non-commercial use and compulsory licensing. *Journal of World Intellectual Property,* 2003, 6(1):5–31.

Granda H et al. Cuban program for prevention of sickle cell disease. *Lancet*, 1991, 337:152–153.

Greco A. From bench to boardroom: Promoting Brazilian biotech (Profile: Fernando Reinach). *Science*, 2003, 300:1366–1367.

Hanson MJ. Biotechnology and commodification within health care. *Journal of Medicine and Philosophy,*1999, 24:267.

Herdegen M. Patenting human genes and other parts of the human body under EC biotechnology directive. *Bio-Science Law Review*, 2001:13.

Heredero L. Comprehensive national genetic program in a developing country—Cuba. *Birth Defects Original Article Series*, 1992, 28(3):52–57.

Hill AV. Molecular epidemiology of the thalassaemias (including haemoglobin E). *Baillieres Clinical Haematology,* January 1992, 5(1):209–38.

Hoffman SL. Research (Genomics) is crucial to attacking malaria. *Science*, November 2000, 290:5496, 1509.

Human Genetic Organisation Ethics Committee. HUGO urges genetics benefit-sharing. *Community Genetics*, 2000, 3:88–92.

Ida R. Human genome as the common heritage of mankind. *Bioethics in Asia,* 1998:59–63 (http://www.biol.tsukuba.ac.jp/~macer/asiae/biae59.html, accessed 5 January 2004).

James JS. India research opportunities, price and patent problems. *AIDS Treatment News Issue,* 1999:321.

Jia H. IP litigation in China could drive innovation. *Nature Biotechnology*, 2004, 22(4):368.

Jones JS. Biotechnology "roadmap" for South Africa unveiled. *SciDevNet*, 17 September 2004.

Kass LT, Nitabach MN. A roadmap for biotechnology patents? Federal Circuit precedent and the PTO's new examination guidelines. *American Intellectual Property Law Association Quarterly Journal,* 2002, 30:233–265.

Kent A. BC sidesteps patent claim, Transfers *BRCA* gene testing to Ontario. *Canadian Medical Association Journal*, 21 January 2003, 68:2.

Knoppers BM. Biotechnology: Sovereignty and sharing. In: Caulfield T, Williams-Jones B, eds., *The Commercialisation of genetic research, ethical, legal and policy issues.* New York, Kluwer Academic/ Plenum Publishers, 1999:1–11.

Koch WH. Technology platforms for pharmacogenomic diagnostic assays. *Nature Reviews: Drug Discovery,* 2004, 3:749–761.

Kongolo T. The African Intellectual Property Organizations: The necessity of adopting one uniform system for all Africa. *Journal of World Intellectual Property*, 2000:265–288.

Lanjouw JO. A new global patent regime for diseases: US and international legal issues. *Harvard Journal of Law & Technology*, 2002:16:85.

Lazzarini Z. Making access to pharmaceuticals a reality: Legal options under TRIPS and the case of Brazil. *Yale Human Rights & Development Law Journal*, 2003, 6:103.

Le Saux O et al. A spectrum of ABCC6 mutations is responsible for pseudoxanthoma. *American Journal of Human Genetics*, 2001, 69:749–764.

Lesko JL, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: A regulatory perspective. *Nature Reviews*, September 2004, 3:763–769.

Lichtman MA, Hunter MD, Liders GJ. Intellectual property—the dispute between research institutions and voluntary health agencies. *Nature Biotechnology*, 2004, 22(4):385–386.

Lindpaintner K. Genetics and genomics: Impact on drug discovery and development. *Annual Conference on Research in Computational Molecular Biology, Proceedings of the fifth annual international conference on Computational Biology*. Basel, GSIA, 2000:221–222.

Lock M. The Human Genome Diversity Project: A perspective from cultural anthropology. In: Knoppers BM, ed., *Human DNA: Law and Policy, International and Comparative Perspectives*. The Hague, Kluwer Law International, 1997.

Macklin R. The ethics of gene patenting. In: Thompson AK, Chadwick R, eds. *Genetic Information*. New York, Kluwer Academic/ Plenum Publishing, 1999:129–37.

Marks SP. Health and human rights: The expanding international agenda. *American Society of International Law Proceedings*, 2001, 95:64.

Marks SP. Tying Prometheus down: The International Law of Human Genetic Manipulation. *Chicago Journal of International Law*, 2002, 3:115.

Martinez PA et al. Simple and rapid detection of the newly described mutations in the HLA-H Gene. *Blood*, 1997, 89:1835–1836.

Martone M. The ethics of the economics of patenting the human genome. *Journal of Business Ethics*, 1998, 17:1679.

Maskus K. Intellectual property rights in the global economy. Institute for International Economics, 2000 (http://www.iie.com/publications/bookstore/publication.cfm?Pub_ID=99, accessed 15 January 2003).

Matthijs G, Halley D. European-wide opposition against the breast cancer gene patents. *European Journal of Human Genetics*, 2002, 10:783–784.

Mayor S. Charity makes cancer gene freely available across Europe. *British Medical Journal*, 21 February 2004, 328:423.

McCabe KW. The January 1999 Review of Article 27 of the TRIPs Agreement: Diverging views of developed and developing countries toward the patentability of biotechnology. *Journal of Intellectual Property Law*, 1998, 6(41):41–67.

McLeland L, O'Toole JH. Patent systems in less developed countries: The Cases of India and the Andean Pact countries. *Journal of Law Technology*, 1987:226–247.

McManis CR. Intellectual property, genetic resources and traditional knowledge protection: Thinking globally, acting locally. *Cardozo Journal of International and Comparative Law*, 2003, 11:547.

Merz JF. Disease gene patents: Overcoming unethical constraints on clinical laboratory medicine. *Clinical Chemistry*, 1999, 45(3)324–330.

Merz JF et al. Protecting subjects' interests in genetics research. *American Journal of Human Genetics*, 2002, 70:965–971.

Morgan S et al. Predictive genetic tests and health system costs. *Canadian Medical Association Journal,* 15 April 2003, 168(8):989–991.

Mugabe J. *Centers of Excellence in Science and Technology for Africa's sustainable development: Towards new forms of regional and sub-regional network*s. For African Ministerial Conference on Science and Technology for Development (http://www.touchtech.biz/nepad/files/documents/126.pdf, accessed 15 January 2004).

Mugabe J. *Intellectual property protection and traditional knowledge: An exploration in international policy discourse*. For World Intellectual Property Organization on behalf of African Centre for Technology Studies. African Centre for Technology Studies, Kenya,1998.

Nau JY. Une Pétition Lancée par le Prof. Mattei S'oppose aux Brevets sur les Gènes Humains. *Le Monde*, 26 May 2000.

Nelsen L. The role of university technology transfer operations in assuring access to medicines and vaccines in developing countries. *Yale Journal of Health Policy Law and Ethics*, January 2003, 3(2):301–308.

Nerozzi MN. The battle over life-saving pharmaceuticals: Are developing countries being 'TRIPped' by developed countries? *Villanova Law Review*, 2002, 47:605.

Nolff M. Compulsory patent licensing in view of the WTO Ministerial Conference Declaration on the TRIPS Agreement and Public Health. *Journal of the Patent and Trademark Office Society*, 2002, 84:133.

Nwabueze RN. Ethnopharmacology, patents and the politics of plants' genetic resources. *Cardozo Journal of International and Comparative Law*, 2003, 11:585.

Page AK. Prior agreements in international clinical trials: Ensuring the benefits of research to developing countries. *Yale Journal of Health Policy, Law, and Ethics*, 2002, 3:35.

Perkel C. Ontario defying American gene company by using new breast-cancer test. *Canadian Press*, 6 January 2003 (http://mediresource.sympatico.ca/health_news_detail.asp?channel_id=12&news_id=578, accessed 5 January 2003).

Petrou M, Modell B. Prenatal screening for haemoglobin disorders. *Prenatal Diagnosis*, 1995, 15:1275–1295.

Poste G. The case for genomic patenting. *Nature,* 1995, 387:534.

Pridan-Frank S. Human-genomics: A challenge to the rules of the game of international law. *Columbia Journal of International and Comparative Law*, 2002, 40:619.

Ragavan S. Can't we all get along?: A case for a workable patent. *Arizona State Law Journal*, 2003, 35:117.

Ragavan S. Protection of traditional knowledge. *Minnesota Intellectual Property Review*, 2001, 2:1.

Ramirez JL, Holmes D. The need for genomics networking in Latin America. *Science and Development Network* (www.SciDev.net), 14 August 2003.

Rapp RT, Rozer RP. Benefits and costs of Intellectual Property protection in developing countries. *Journal of World Trade*, 1990, 24:75–102.

Raskins S et al. DNA analysis of cystic fibrosis in Brazil by direct PCR amplification from Guthrie cards. *American Journal of Medical Genetics,* 1 July 1993, 46(6):665–659.

Rosendal GK. The politics of patent legislation in biotechnology: An international view. *Biotechnology Annual Review,* 1995, 1:453.

Roses AD. Pharmacogenetics and drug development: The path to safer and more effective drugs. *Nature Reviews*, September 2004, 5:645–656.

Russo E. Merging IT and biology. *The Scientist*, 2000, 14(23):8.

Salotra P et al. Development of a species-specific PCR assay for detection of *Leishmania donovani* in clinical samples from patients with kala-azar and post-kala-azar dermal leishmaniasis. *Journal of Clinical Microbiology*, 2001, 39(3):849–854.

Savithri HS et al. Predictive testing for familial adenomatous polyposis in a rural South Indian community. *Clinical Genetics*, 2000, 58(1):57–60.

Service RS. Gene and protein patents get ready to go head to head. *Science*, 7 December 2001, 294(5549): 2082.

Shattuck-Eidens D et al. *BRCA1* sequence analysis in women at high risk for susceptibility mutations. Risk factor analysis and implications for genetic testing. *JAMA: Journal of the American Medical Association*, 1997, 278(15):1242–1250.

Sheremeta L, Gold ER. Creating a patent clearinghouse in Canada: A solution to problems of equity and access. *Health Law Review*, 2003, 11(3):17–19.

Spectar JM. Patent necessity: Intellectual property dilemmas in the biotech dominant treatment equity for developing countries. *Houston Journal of International Law,* 2001, 24:227.

Streit C et al. CFTR gene: Molecular analysis in patients from South Brazil. *Molecular Genetics and Metabolism*, April 2003, 78(4):259–264.

Streit C et al. CFTR gene: Molecular analysis in patients from South–Brazil. *Molecular Genetics and Metabolism*, 2003, 78:259.

Taubes G. Scientists attacked for patenting Pacific tribe. *Science*, 17 November 1995, 270(5239).

Taylor AL. Globalization and biotechnology: Unesco and an international strategy to advance human rights and public health. *American Journal of Law & Medicine*, 1999:479.

Thomas SM et al. Ownership of the human genome. *Nature,* 1996, 380:387–388.

Thomas SM et al. Public-sector patents on human DNA. *Nature*, 1997, 388:709.

Verma IC. Burden of genetic disorders in India. Symposium: Genetics for Pediatricians-I. *Indian Journal of Pediatrics,* 2000, 67(12):893–98.

Wadman M. Ethical terms set for breast cancer test. *Nature*, 27 November 1997, 390:324.

Warner JP, Barron LH, Brock DJ. A new polymerase chain reaction (PCR) assay for the trinucleotide repeat that is unstable and expanded on Huntington's disease chromosomes. *Molecular and Cellular Probes*, 1993, 7(3):235–9.

Warner S. Diagnostics + therapy = theranostics. *The Scientist*, 30 August 2004, 18(16):38.

Weinshilboum R, Wang L. Pharmacogenomics: Bench to bedside. *Nature Reviews: Drug Discovery*, 2004, 3(9):739–748.

Wheeler C, Berkley S. Initial lessons from public-private partnerships in drug and vaccine development. *Bulletin of the World Health Organization*, 2001, 79:728.

Williamson AR. Gene patents: Are they socially acceptable monopolies or an unnecessary hindrance to research. *Drug Discovery Today,* November 2001, 6(21):1092–1093.

Willison DJ, Macleod SM. Patenting of genetic material: Are the benefits to society being realised? *Canadian Medical Association Journal*, 6 August 2002, 167(3):259–262.

Winnick E. DNA sequencing industry sets its sights on the future. *The Scientist*, 27 September 2004, 18(18):44.

Wolfson JR. Social and ethical issues in nanotechnology: Lessons from biotechnology and other high technologies. *Biotechnology Law Report*, 2003, 22:376.

Books

Boyle J. *Shamans, software & spleens: Law and the construction of the information society*. Cambridge, Massachusetts and London, Harvard University Press, 1996.

Cain B. *Legal aspects of gene technology*. London, Thompson, 2003.

Gold ER. *Body parts: Property rights and the ownership of human biological materials.* Washington, D.C., Georgetown University Press, 1996.

Greider G. *One world, ready or not: The manic logic of global capitalism*. New York, Simon and Shuster, 1997.

Knoppers BM, ed. *Human DNA: Law and policy, international and comparative perspectives*. New York, Kluwer, 1997.

Laurie G. *Genetic privacy: A challenge to medico-legal norms*. Cambridge, Cambridge University Press, 2002.

Mason S, Megone C, eds. *European neonatal research: Consent, ethics committees and law*. Aldershot, Ashgate, 2001.

Radin M. *Contested commodities*. Cambridge, Harvard University Press, 1996.

Silver LM. *Remaking Eden.* New York, Avon Books, 1997.

Proceedings and symposiums

Fidler DP. Introduction to written symposium on Public Health and International Law. *Chicago Journal of International Law*, 2002:3.

Fifth Meeting of the Secretary's Committee on Genetic Testing, Volume III. United States, Secretary's Advisory Committee on Genetic Testing (SACGT), 7 June 2000 (http://www4.od.nih.gov/oba/sacgt/sacgtmtg.htm, accessed 9 March 2004).

Nelkin D. A Brief history of the political work of genetics. Symposium: Legal & Ethical Issues in Genetic Research or Indigenous Populations. *Jurimetrics*, 2002, 42:121.

Pai GS et al. Challenges in human genetics in India in the new millennium. Symposium: Genetics for Pediatricians-I. *Indian Journal of Pediatrics*, 2000, 67(11):809–811.

Report of a WHO meeting on collaboration in medical genetics. Geneva, World Health Organization, 2002 (WHO/HGN/WG/02.2).

Scidev. Africa's Scientific Revival Day now recognized. *Scidev Workshop*, Uganda, 29 September to 3 October 2002 (http://www.sciencenewsdev.co.ke/special-f.htm, accessed 15 January 2004).

Sheremeta L, Gold ER. *Creating a patent clearinghouse in Canada: A solution to problems of equity and access?* poster presentation, GELS Winter Symposium 2003, 6–8 February 2003, Montreal, Quebec.

Verma IC. Burden of genetic disorders in India. Symposium: Genetics for Pediatricians-I. *Indian Journal of Pediatrics*, 2000, 67(12):893–98.

Verma IC et al. Genetic counseling and prenatal diagnosis in India—Experience at Sir Ganga Ram Hospital. *Indian Journal of Pediatrics*, 2003, 70:293–97.

World Health Assembly Resolution WHA56.27. *Intellectual property rights, innovation and public health*. Fifty-sixth World Health Assembly, 28 May 2003 (http://www.who.int/gb/ebwha/pdf_files/WHA56/ea56r27.pdf accessed February 2005).

Reports

American College of Obstetricians and Gynaecologists

Screening for Canavan Disease, fact sheet number 212. American College of Obstetricians and Gynaecologists, November 1998 (http://www.tay-sachs.org/medical.php accessed 5 January 2004).

British Society for Human Genetics (BSHG)

Statement on patenting and clinical genetics. United Kingdom, British Society for Human Genetics, 1 February 1998.

Canada Department of Justice

Gold ER, Caulfield TA. *Human genetic inventions, patenting and human rights*. Ottawa, Department of Justice, Government of Canada, 2003.

Canadian Cancer Society

The patenting of BRCA1 and 2 genes facts sheet. Canada, The Canadian Cancer Society (http://www.cancer.ca/ccs/internet/standard/0,3182,3172_31282995_32777862_langId-en,00.html, accessed 30 December 2003).

Patenting of genes and gene sequences. Canada, The Canadian Cancer Society, 17 June 2003 (http://www.cancer.ca/ccs/internet/standard/0,3182,3172_61901275__langId-en,00.html, accessed 15 December 2003).

Center for Advanced Studies at the University of Buenos Aires

Carlos M Correa. *Intellectual property rights and the use of compulsory licenses: Options for developing countries* [Working Paper]. Buenos Aires, Center for Advanced Studies at the University of Buenos Aires, A, 1999.

Center for International Environmental Law

Downes D. *The 1999 WTO review of life patenting under TRIPS* [Revised discussion paper]. Washington, D.C, Center for International Environmental Law, September 1998:1.

Centre for Law and Genetics

Nicol D, Nielsen J. Patents and medical biotechnology: An empirical analysis of the issues facing the Australian industry. Tasmania, Australia, Centre for Law and Genetics, 2003 (Occasional Paper No. 6).

Centre for Management of Intellectual Property in Health Research and Development

Mahoney RT ed. *Handbook of best practices for management of intellectual property in health research and development*. Oxford, UK, Centre for Management of Intellectual Property in Health Research and Development, November 2003.

Conference of the Parties to the Convention on Biological Diversity

Sixth Meeting of the Conference of the Parties to the Convention on Biological Diversity, Decision VI/24, Access and benefit-sharing as related to genetic resources. The Hague, April 2002 (http://www.biodiv.org/welcome.aspx, accessed 5 January 2004).

Econexus and GeneWatch UK

Patenting genes—Stifling research and jeopardising healthcare. United Kingdom, Econexus and GeneWatch UK, 1 April 2001 (http://www.genewatch.org/Publications/Patenting/Patents.pdf, accessed 3 January 2004).

Economic and Social Research Council

ESRC Genomics Scenarios Project: 3. *Key drivers of genomics: forecasts for 2015*. Economic and Social Research Council, January 2002.

Global Forum for Health Research

The 10/90 Report on Health Research. Geneva, Global Forum for Health Research, 2000.

International Association for the Protection of Intellectual Property

Patentability requirements and scope of protection of Expressed Sequence Tags (ESTs), Single Nucleotide Polymorphisms (SNPs) and entire genome. Sorrento, International Association for the Protection of Intellectual Property, 14 April 2000 (http://www.aippi.org/reports/resolutions/res-q150-e-exco-2000.htm, accessed 5 January 2004).

International Intellectual Property Institute

Patent protection and access to HIV/AIDS pharmaceuticals in sub-Saharan Africa. Washington DC, International Intellectual Property Institute, 2000 (http://www.iipi.org/activities/Research/HIV%20AIDS%20Report.pdf accessed 21 January 2004).

Medical Research Council of South Africa

Guidelines on ethics for medical research: Reproductive biology and genetic research. Tygerberg, The Medical Research Council of South Africa, 1 April 2002 (http://www.sahealthinfo.org/ethics/ethicsbook2.pdf, accessed 15 December 2003).

National Institute for Health Care Management Research and Educational Foundation

Changing patterns of pharmaceutical innovation. Washington, DC, The National Institute for Health Care Management Research and Educational Foundation, May 2002.

National Research Council

Patents in the knowledge-based economy. National Research Council, USA, 2003 (http://books.nap.edu/books/0309086361/html/297.html#pagetop accessed 21 January 2003).

Organisation for Economic Development and Cooperation

Genetic inventions, intellectual property rights and licensing practices: Evidence and policies. Paris, Organisation for Economic Development and Cooperation (OECD), 2002:50.

Royal Society

Needham R et al. *Keeping science open: The effects of intellectual property policy on the conduct of science.* London, The Royal Society, April 2003.

United Nations Commission on Human Rights

Motoc A. *Specific human rights issues. Universal Declaration on the Human Genome and Human Rights.* Geneva, UN Commission on Human Rights, 2002 (doc.E/CN.4/sub.2/2002/37).

United Nations Educational Social and Cultural Organization

Report of the IBC on ethics, intellectual property and genomics. UNESCO, International Bioethics Committee (IBC), 10 January 2002.

United States Federal Trade Commission

To promote innovation: The proper balance of competition and patent law and policy. Washington, DC, Federal Trade Commission, October 2003.

University of Toronto Joint Center for Bioethics

Top 10 biotechnologies for improving health in developing countries. Toronto, Program in Applied Ethics and Biotechnology and Canadian Program on Genomics and Global Health, University of Toronto Joint Center for Bioethics, 2003 (http://www.utoronto.ca/jcb/pdf/top10biotechnologies.pdf, accessed 30 December 2004).

World Bank

Fink C. *How stronger patent protection in India might affect the behavior or transnational pharmaceutical industries*. Development Research Group, World Bank, 2000 (http://econ.worldbank.org/docs/1106.pdf, accessed 15 January 2004).

Yang G, Maskus KE. *Intellectual property rights, licensing, and innovation.* World Bank, 2003 (Policy Research Working Paper 2973).

World Health Organization

Berg K, Boulyjenkov V, Christen Y. *Genetic approaches to noncommunicable diseases*. Geneva, World Health Organization and Fondation IPSEN, Springer-Verlag, 1996:1–155.

Fifty facts from the World Health report 1998, Global health situation and trends 1955–2025. Geneva, World Health Organization, 1998 (http://www.who.int/whr2001/2001/archives/1998/pdf/factse.pdf, accessed 30 December 2003).

Genomics and World Health: Report of the Advisory Committee on Health Research. Geneva, World Health Organization, 2002 (EB112/4).

Guidelines for control of haemoglobin disorders. Geneva, World Health Organization, 1994 (WHO/HDP/HB/GL/94.1).

Human genetic technologies: implications for preventative care. Geneva, World Health Organization, 2001 (WHO/HGN/Rep/02.1).

Report of a WHO meeting on collaboration in medical genetics. Geneva, World Health Organization, 2002 (WHO/HGN/WG/02.2).

The molecular genetic epidemiology of cystic fibrosis. Geneva, World Health Organization, 2004 (WHO/HGN/CF/WG/04.02).

World Health Report 1999: Making a difference, Part I. Geneva, World Health Organization, 1999 (http://www.who.int/whr2001/2001/archives/1999/en/pdf/whr99.pdf, accessed 29 December 2003).

Patent office publications

India Patents Office. *Exclusive Market Rights* (http://www.patentoffice.nic.in/ipr/patent/emr.htm, accessed 26 February 2004)

United States Patent and Trademark Office, Utility Examination Guidelines. 66:4 *Federal Register*, 5 January 2001, 1092.

Case Law

Canada

Schmeiser v. *Monsanto Canada Inc.* [2002] 21 C.P.R. (4th) 1 affirming 12 C.P.R. (4th) 204 (FCA).

Harvard College v. Canada (Commissioner of Patents), (2002) SCC 76.

United States of America

Chou v. *Univ. of Chicago*, 254 F.3d 1347, 1363 (Fed. Cir. 2001).

Greenberg v. Miami Children's Hospital Research Institute, Inc 16 Fla.L. Weekly Fed D 417.

Legislation

Agreement on Trade-Related Aspects of Intellectual Property Rights, being Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization, 33 I.L.R. 1197 (1993).

Brazil. Patent Law 9.279 of 1997.

China. Patent Law 1985, amended in 1992 and in 2003.

Convention on Biological Diversity, Rio de Janeiro, 5 June 1992 (http://www.biodiv.org/doc/legal/cbd-en.pdf, accessed 5 January 2004).

France. *Projet de loi relatif à la protection des inventions biotechnologiques*. France: Sénat. Session ordinaire de 2001–2002; 2001 Nov 6. No 55. Art. 11. (www.senat.fr/leg/pjl01-055.html, accessed 6 January 2004).

Genomic Research and Diagnostic Accessibility Act of 2002, H.R. 3967, 107th Cong., 2nd Sess. (2002).

India. Patents Act 1970.

International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA), FAO, November 2001 (ftp://ext-ftp.fao.org/ag/cgrfa/it/ITPGRe.pdf, accessed 5 January 2004).

United Nations Convention on the Law of the Sea. Montego Bay, 1982 (http://www.un.org/Depts/los/convention_agreements/texts/unclos/closindx.htm, accessed 5 January 2004).

Statements

European Group on Ethics in Science and New Technologies

Opinion No. 16, Ethical aspects of patenting inventions involving human stem cells. Brussels, European Group on Ethics in Science and New Technologies, 7 May 2002 (http://europa.eu.int/comm/european_group_ethics/avis3_en.htm, accessed 14 January 2004).

European Council

Council agreement relating to Community patents. Luxembourg, European Council, 15 December 1989 (89/695/EEC) (http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=en&numdoc=41989A0695(01)&model=guichett, accessed 25 January 2004).

Government of India

Ethical policies on the human genome, genetic research and services. New Delhi, Department of Biotechnology—Government of India, June 2001 (http://dbtindia.nic.in/publication/publicmain.html, accessed 13 January 2004).

Human Genome Organisation

Statement on benefit sharing. HUGO, 2000 (http://www.gene.ucl.ac.uk/hugo/benefit.html, accessed 5 January 2004).

Statement on patenting DNA sequences. HUGO, April 2000 (http://www.hugo-international.org/hugo/patent2000.html, accessed 12 January 2004).

Statement on patenting issues related to early release of raw sequence data. HUGO, 1997 (http://www.gene.ucl.ac.uk/hugo/ip1997.htm, accessed 13 January 2004).

Indigenous Peoples Council on Biocolonialism

A resolution to oppose the human genome diversity project and condemning unethical genetic research on indigenous peoples. Wadsworth, Indigenous People Council on Biocolonialism (IPCB), 15 January 1998 (http://www.ipcb.org/resolutions/htmls/model_resolution_hgdp.html, accessed 13 January 2004).

The "Heart of the Peoples" Declaration. Fort Belknap Reservation, Indigenous Peoples Council on Biocolonialism (IPCB), 7 August 1997 (http://www.ipcb.org/resolutions/htmls/dec_heartopeoples.html, accessed 13 January 2004).

International Federation of Gynecology and Obstetrics

Recommendations on ethical issues in obstetrics and gynaecology-patenting human genes. FIGO Committee on the Study of Ethical Aspects of Human Reproduction. *International Digest of Health Legislation,* 1997, 48:447.

United Nations

UN Agreement governing the activities of States on the Moon and other celestial bodies. New York, 18 December 1979.

7
Notes

[1] In 2004, the World Health Assembly officially adopted the following definition of "genomics": the study of genes and their functions, and related techniques (WHA 2004, a57.16). See the Glossary for definitions of terms used in this report.

[2] This is not to say that it accepts all of the conclusions of these reports. Rather, in terms of its aims and the subject matter with which it is concerned, the present report can be said to find its place at the intersection of these three documents.

[3] In this report, when we refer to *developing countries*, we refer broadly to countries, primarily in sub-Saharan Africa, Latin America and Asia, with a weak industrial base, and where a considerable proportion of the population lives near subsistence level. We acknowledge the shortcoming of this terminology, in light of the great diversity among countries in this category—diversity in health needs, economic development and scientific capacity. Where possible, we will try to point out where these factors make a difference in terms of the impact of DNA patents.

[4] As Clegg and Weatherall's review points out, there is a hypothesized relationship, with growing empirical support, between the haemoglobinopathies and protection against malaria, which provides clues about why these conditions are prevalent in malaria endemic areas.

[5] See, for instance, the USA Department of Energy Office of Science's human genome project information website, for a list of available genetic tests: http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetest.shtml#testsavailable (accessed 8 March 2004).

[6] Civil law does not take prior cases to be precedent in the same way as the common law system. While judges do refer to previous cases, commentary plays a much more important role in the civil law. So, while precedent is important for common law system, doctrine is important for civilians.

[7] This being said, neither the United States Constitution (Article I, Section 8) nor the United States Code (Title 35, Part II, Chapter 10, Section 101) distinguishes inventions from discoveries. The latter document states that: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title." Courts have consistently interpreted Article 101 as excluding natural phenomena, such as principles, powers and products of nature. *O'Reilly v. Morse* [56 U.S. (15 How.) 62 (1853)] rejected Samuel Morse's claim seeking a patent on electromagnetism. Though he was the first to harness it in inventing the telegraph, the court argued that he had not invented electromagnetism, which is a force of nature and thus not patentable subject matter.

[8] More specifically, they cover purified or isolated genes, the protein coded for by a gene, cells engineered to express the gene or protein to detect or treat disease (Andrews, Mehlman and Rothstein, 2002).

[9] For example, the British Society of Human Genetics, the American College of Medical Geneticists, the Human Genetics Society of Australasia.

[10] The patent holder may also opt not to use the patented invention in countries where local laws do not impose a working obligation. "Exclusive" licenses do not always confer rights for all uses. Sometimes an invention is exclusively licensed to multiple groups under different conditions.

[11] An agreement on a "common political approach" regarding the Community Patent, reached at the Competitiveness Council of Ministers in Brussels on 3 March 2003, brought this one step closer to realization. However, at their meeting in March 2004, the Ministers failed to reach agreement on the proposed Regulation, primarily due to a lack of consensus on how to treat infringements of patents that could arise due to mistranslations. See Results of the Competitiveness Council of Ministers (EC, 2004).

[12] See USPTO website on Trilateral Studies, http://www.uspto.gov/web/tws/sr-3.htm (accessed 29 September 2004).

[13] All WTO Member States are eligible to import pharmaceuticals made under compulsory licences abroad, but 23 developed countries have already stated that they will not use this provision. All other members are eligible if they notify the Council for TRIPS of their intention to use the system as an importer.

[14] TRIPS, as noted earlier, sets minimum standards for countries; it offers relatively little direction on how to implement these norms. Anything above these minimum standards falls within a zone of "flexibility" (see South Centre, http://www.southcentre.org/info/southbulletin/bulletin63/bulletin63-09.htm, accessed 14 May 2004). In bilateral negotiations, pressure has been brought to bear on developing countries to extend stronger IP protection than what is required in TRIPS, i.e. so-called TRIPS-plus provisions.

[15] See, for example, http://www.bio.org/ip/primer/patentsay.asp, accessed 1 April 2004.

[16] In 2000, Myriad Genetics claimed to have invested the equivalent of about 150 person-years of effort and tens of millions of dollars into the discoveries of these genes, and the development of a highly automated and accurate clinical test. The company has argued that this investment would not have been possible without the potential for patent protection on these discoveries. See Secretary's Advisory Committee on Genetic Testing (Vol. III), 7 June 2000. It is not clear whether such figures would apply today, several years after the initial identification and sequencing of *BRCA1* and *BRCA2*.

[17] See *Cutting-edge technology for low-cost diagnosis*. Sustainable Sciences Institute (www.ssilink.org/immunosensorhistory.html, accessed 14 May 2004).

[18] Law No. 9.279 increases the patent term to 20 years for all products and processes, and removes prior prohibitions on the granting of patents for chemical products and processes for the production of pharmaceuticals and foods. Law No. 9.279 has an important affect on Brazil's ability to manufacture generics. Brazil can no longer freely produce generic versions of pharmaceuticals that are patented overseas. The generics industry can, however, continue to produce generics based on products patented overseas before 1996. In addition Brazil has the option of issuing compulsory licences (see Glossary, Appendix 1) to produce generics under certain conditions.

[19] Oxfam and the Consumer Project on Technology defended Brazil's position and contended that the complaint threatened the most successful AIDS treatment programme in the developing world. In June 2001, a compromise was reached, where the United States agreed to drop the complaint and Brazil agreed to give United States officials advance notice before invoking the provision.

[20] Article 18, item III, states that living beings, in whole or in part, are not considered patentable. Article 10, item IX, states that natural living beings, in whole or in part, and biological material encountered in nature or isolated including the genome or germplasm of any natural living being, are not considered as inventions. The Brazilian Group states that if sequences of DNA are interpreted as chemical products they may be patentable.

[21] Ibid.

[22] For instance, New Zealand's Ministry of Health, in a report to the Cabinet Policy Committee, concluded that Brazilian patent law considers genetic material, even in a purified and isolated state, as a discovery and therefore not patentable; and in a paper presented for the *Frontiers of Innovation Research and Policy*, Maria da Graça Derengowski Fonseca and José Maria F.J. da Silveira state that Brazilian legislators have decided to allow patenting for genetically modified organisms *only (*Fonseca & Silviera, 2002). Ladas & Perry LLP also state that the patent law makes it clear that transgenic microorganisms are patentable. But they do not specify whether genes and DNA sequences are excluded from patenting.

[23] See the Beijing Genomics Institute website (http://www.genomics.org.cn/bgi/english/1.htm, accessed 5 March 2004).

[24] See *China Daily*, 2002.

[25] Ibid.

[26] See Chinese firms keen on patent application for WTO entry, *People's Daily* (2001).

[27] Ibid.

[28] Counting patent families can only provide a rough guide of a nation's technological activity relative to other countries, because differing national patent laws and customs can result in higher levels of patenting in some countries than in others. Because a patent generally offers protection only in the country in which it is issued, and because it can be very expensive to apply for patent protection in multiple countries, organizations are assumed to seek patent protection abroad only for those inventions they believe will have significant commercial value. Comparing *international patent families* (inventions for which patent protection has been sought in more than one country) makes international comparisons more accurate and provides a more precise measure of technological activity. A *priority application* refers to the first application filed anywhere in the world and it is generally assumed that the country in which the priority application was filed is the country in which the invention was developed.

[29] See *Science and engineering indicators,* 2002a.

[30] See Appendix table 6-15, Human DNA sequence patents: Number of international patent families, by priority country and priority year. *Science and Engineering Indicators*, 2002b.

[31] See Achievements, Human Genetics and Genome Analysis (http://dbtindia.nic.in/programmemes/progmain.html, accessed 26 February 2004).

[32] See Biotech Desk. *Biotechnology in India – Initiatives by the Government* (http://www.biotechdesk.com/market4.php, accessed 24 February 2004).

[33] Ibid.

[34] See Patents Office India. *Exclusive Market Rights* (http://www.patentoffice.nic.in/ipr/patent/emr.htm, accessed 26 February 2004).

[35] Ibid.

[36] See Gene Campaign. *International Trade Policy* (http://www.genecampaign.org/about_us/impact_efforts.html, accessed 24 February 2004).

[37] Although, as with Chinese and Indian programmes, there are aspects mainly aimed at export markets.

[38] The human genome, itself, is not currently patentable. Some have claimed that the human genome is therefore safeguarded from the charge of commodification, because it is only specific sequences that are subject to patents. But this protection is currently de facto, and is not the basis of any principled distinction; there is nothing within the current system that prohibits the eventual allowance of large-scale patenting of portions of the genome, or the genome in its entirety. Moreover, since the genome just simply is composed of DNA sequences, a principled objection to the patenting of the genome would seem to impose similar constraints on the patenting of its components.

[39] Groups such as the Action Group on Erosion, Technology and Concentration (ETC Group), however, have raised concerns that such guidelines establish national sovereignty over genetic resources, thus *reducing* the rights of indigenous peoples and rural communities and their decision-making capacity. According to the ETC Group, a national level approach to benefit sharing undermines customary systems of resource exchange (for example seed exchange between indigenous farmers). In response they call for the reformulation of the Bonn guidelines to encourage governments to establish non-proprietary systems of benefit sharing, and for the CBD to facilitate the establishment of a global biodiversity fund to support the conservation and development of biodiversity in a manner independent of IP rights (ETC, 2004).

[40] In 1984, John Moore filed a lawsuit against the University of California. While he was undergoing treatment for leukemia, his physician developed a medically useful cell-line against cancer, on the basis of which a patent was later obtained and commercial profits earned on the subsequently developed therapies. The California Supreme Court, in 1990, stated that donors do not have "property rights" in the tissue earned from their bodies, and that in fact such a position would hinder research and access to raw materials (*Moore v. Regents of the University of California*, 793 P.2d 479 [Cal. 1990])

[41] In one respect, this represents a more technical basis for arguing for the special status of DNA. One version, as stated above, rests on DNA's essential difference from other natural products, even those molecules that are similarly situated in the human body. What this argument seems to suppose, like the more technical argument, is that DNA is fundamentally valuable, in a "moral" sense, because it has a kind of "informational content" that separates it from other kinds of chemicals. It is a molecule that encodes instructions for every aspect of a cell's function, and for yet-unknown aspects of a person's behaviour and identity. It is therefore the so-called informational value of DNA that lends it its special-ness.

[42] See USPTO's announcement of its new guidelines for assessing utility of genetic inventions (http://www.uspto.gov/web/offices/com/speeches/01-01.htm, accessed 8 March 2004).

[43] See WTO (http://www.wto.org/english/tratop_e/trips_e/intel2_e.htm, accessed May 12, 2004).

[44] Countries where there are significant differences in standards of invention between full patents and petty patents tend to grant more petty patents. According to WIPO statistics, in 1999, for example, China received 44 369 applications for utility model patents, Korea received 30 650, Germany received 23 584 and Taiwan received 17 954.

Appendix 1
Glossary of terms

Benefit sharing	the fair and equitable sharing of the benefits arising from the use of genetic resources
Biopiracy	the appropriation of the knowledge and genetic resources of farming and indigenous communities by individuals or institutions seeking exclusive monopoly control (usually patents or plant breeders' rights) over these resources and knowledge
Compulsory licensing	a state-granted licence to a third party, not requiring approval from the patent holder, allowing the licensee to exploit the patented invention
DNA	(deoxyribonucleic acid); the biochemical substance that makes up genetic material; a double-stranded molecule comprising two linear chains made from four bases (A, C, G and T), together forming a double helix
EST	(expressed sequence tag); a short section of complementary DNA sequence, where location and nucleotide sequences are known. ESTs have applications in the discovery of new human genes, mapping of the human genome, and identification of coding regions in genomic sequences
Gene	an ordered sequence of *nucleotides* located in a particular position on a particular chromosome that encodes a specific functional product, i.e. a protein or RNA molecule
Genetic patent	(or DNA patent); a patent issued by any national patent office, which claims subject matter relating to specific sequences of DNA, including isolated genes, modified genes, etc., or any use or application of such
Genetic testing	DNA analysis to determine the carrier status of an individual; to diagnose a present disease in the individual; or to determine the individual's genetic predisposition to developing a particular condition in the future

International patent family	a *patent family* consists of all the patent documents associated with a single invention that are published in one country. An *international patent family* consists of all the patent documents relating to an invention for which patent protection has been sought in more than one country. Counting patent families can only provide a rough guide of a nation's technological activity relative to other countries, because differing national patent laws and customs can result in higher levels of patenting in some countries than in others. The comparison of international patent families (based on the assumption that organizations seek patent protection abroad only for those inventions they believe will have significant commercial value) makes international comparisons more accurate and provides a more precise measure of relative technological activity
Licence	the exclusive or non-exclusive transfer (*not* assignment) of patent rights to a third party, permitting the third party, under negotiated conditions, to make, use or sell the patented invention
Patent	a legal document providing an exclusive right to the owner for the manufacture, use or sale of the invention claimed therein
Patent claim	the text within a patent that specifies all the elements, features and critical aspects of the invention
Patent scope	the interpretation that is given to the patent claim, which determines the boundaries or limitations of legal protection over the invention
Penetrance	the probability that a genetic trait will be expressed. A genetic variant may have "complete" or "incomplete" penetrance. The latter refers to cases where having the particular genetic variant leads to a less than 100% likelihood of manifesting the condition
Research exemption	(or research exception); a doctrine that enables the unlicensed use of a patented invention in pure research, which is usually interpreted as non-commercial in its aim
Research tool(s)	the full range of resources that scientists use in the laboratory, e.g. cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry libraries, drugs and drug targets, clones and cloning tools, laboratory equipment and machines, databases and computer software
RNA	(ribonucleic acid); a single-stranded nucleic acid molecule comprising a linear chain made from four bases (A, C, G and U). There are three types of RNA: messenger (mRNA), transfer (tRNA) and ribosomal (rRNA)
SNP	(single nucleotide polymorphism); DNA sequence variation that occurs when a single *nucleotide* (A, T, C or G) in the *genome* sequence is altered

TRIPS-plus	intellectual property systems that go beyond the minimum standard required by TRIPS, i.e. systems that provide stronger intellectual property protection to inventors than what is explicitly required under TRIPS
Utility model	(or petty patent); like a patent, grants a registered exclusive right to the inventor to manufacture, sell or use an invention; the standards required for protection (inventive step, novelty, industrial application) and the level of protection offered are generally lower than with patents; however, the application process is usually cheaper and quicker because utility models may be granted without prior examination to establish that above conditions have been met

Appendix 2
Methodology

In November 2003, the Human Genetics Programme commissioned the writing of a background paper on the "impact of DNA patents on access to genetic technologies and services for the control and management of non-communicable diseases in low to middle income countries", by McGill University's Centre for Intellectual Property Policy, Montreal, Canada.

This background document formed the basis for a three-round electronic review process, initiated in January 2004. Twenty-two individuals were selected as Scientific Review Panellists, on the basis of recommendations, demonstrated expertise, and their record of publications in the area of genetics or intellectual property rights. This work sought to explore and to highlight the crucial issues relating to intellectual property (particularly patents) through the lens of public health, rather than to produce official policy; the Scientific Review Panel therefore comprises chiefly academics, rather than policy-makers. Each of these individuals formally agreed to participate in the review process, and submitted a Declaration of Interests form. Table 1 presents a complete list of the members of the Panel.

The goal of the review process was to obtain critical feedback from academics, representing a balanced distribution across regions, and between sexes, on the document. During the first round of the review process, extensive feedback was received from several reviewers, which led to a dramatic re-shaping of the document. In general, the first round of comments reflected a desire for a more detailed exploration of the ethical issues relating to the patenting of DNA sequences, and concrete linkages between the issues addressed and the specific needs of developing countries. The aim of the review was not to achieve consensus at all costs, or to privilege particular viewpoints; rather, it was, as much as possible, to present the important issues, including points of ongoing disagreement. The report was re-drafted in line with the comments received during the first round, and was sent back to the reviewers. The second round of comments were, in general, more specific—for example, pointing to technical matters, and to the need to clarify various arguments, as well as suggestions for the inclusion of a glossary and list of acronyms—rather than proposing the re-framing or substantial alteration to the report. Changes were again made by the editors on the basis of this feedback, and a third version of the document was sent out electronically for final review, including to several WHO staff. This third and last wave of comments comprised largely minor proposals for clarification of terms, and alternative language for some portions of text. These comments were incorporated, and the final report underwent professional editing and publication.

Table 1
Scientific Review Panel

Name	Institutional affiliation
Shaikha Al-Arrayed	Gulf Genetic Center, Ign Al Nafees Hospital, Kingdom of Bahrain
Amir Attaran	Centre for International Development & Kennedy School of Government, Harvard University, United States of America
John Barton	Law School, Stanford University, United States of America
Kare Berg	Institute of Medical Genetics, University of Oslo, Norway
José Maria Cantu	Genetics Division, Centro de Investigacion Biomédica de Occidente, Mexico
Jean-Jacques Cassiman	Center for Human Genetics, Campus Gasthuisberg, Belgium
Mildred Cho	Center for Biomedical Ethics, Stanford University, United States of America
Carlos Correa	University of Buenos Aires, Argentina
Abdallah Daar	Joint Centre for Bioethics, University of Toronto, Canada
Prabuddha Ganguli	"Vision-IPR", India
Cathy Garner	Centre for the Management of IP in Health R&D, United Kingdom
E. Richard Gold	Centre for Intellectual Property Policy, McGill University, Canada
Vladimir Ivanov	Research Institute for Medical Genetics, Russian Federation
Patricia Kameri-Mbote	International Environmental Law Research Centre, Kenya
Darryl Macer	Eubios Ethics Institute, Japan
Patricia Aguilar-Martinez	Laboratoire d'Hématologie, Hôpital Saint Eloi, France
Sisule Musungu	South Centre, Switzerland
Victor Penchaszadeh	Mailman School of Public Health, Columbia University, United States of America
Sandy Thomas	Nuffield Council on Bioethics, United Kingdom
Lap-Chee Tsui	University of Hong Kong, China
Ishwar Verma	Department of Medical Genetics, Sir Ganga Ram Hospital, India
Huanming Yang	Beijing Genomics Institute, Chinese Academy of Sciences, China