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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/ITPGRRe.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 in-

vention. 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 fol-

lowing 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.