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International Divergence in Gene Patenting

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Abstract

This review explores the recent divergence in international patent law relating to genes and associated subject matter. This divergence stems primarily from decisions of the highest courts in the United States and Australia on the eligibility of patent claims relating to the *BRCA* gene sequences. Patent offices, courts, and policy makers have struggled for many years to clearly articulate the bounds of patent claims on isolated and synthetic DNA and related products and processes, including methods for their use in genetic diagnostics. This review provides context to the current divergence by mapping key events in the gene patent journey from the early 1980s onward in five key jurisdictions: the United States, the member states of the European Patent Convention, Australia, Canada, and China. Early approaches to gene patenting had some commonalities across jurisdictions, which makes exploration of the recent divergence all the more interesting.

There is insufficient empirical evidence to date to confidently predict the consequences of this recent divergence. However, it could potentially have a significant effect on local industry and on consumer access.

1. INTRODUCTION

Anyone involved in genomics or human genetics has more than likely had dealings with patents, whether through involvement in commercializing their research results, concerns about infringement of other people's intellectual property, or broad-ranging philosophical discussions. Most biomedical researchers have never really liked the concept of patenting genes, and have been puzzled about how this could ever have become mainstream patent practice (31, 81). From our perspectives as long-term patent watchers, we observed a collective sigh of relief when the US Supreme Court decided in *Association for Molecular Pathology v. Myriad Genetics, Inc.* (9, hereafter *AMP*) that isolated naturally occurring *BRCA* gene sequences were not patentable subject matter. A harmonized approach was ostensibly maintained between the United States and Australia when the Australian High Court followed suit in *D'Arcy v. Myriad Genetics, Inc.* (35, hereafter *D'Arcy*). Yet what has arisen as a result of these and related decisions is a high level of uncertainty about what types of gene-related subject matter are eligible for patenting in the United States and Australia, and an increasing level of inconsistency in the patent eligibility of genes and related subject matter across countries. Worldwide, this is causing consternation across the biotechnology industry in both agriculture and biomedicine, because of the uncertainty it creates for investment in product development. One consequence is that the industry has been prompted to explore a range of alternative strategies, from creative claims drafting (3) and greater reliance on trade secrecy (32) to lobbying for legislative reform (41).

Although patent applications are generally filed in more than one country, there is no such thing as a global patent. Rather, each country or region examines each patent application in accordance with its own laws. Once granted, the patent provides its holder with the temporary right (a minimum of 20 years) to exclude others from using the patented invention. The patent holder can decide whether to retain their patent rights, sell or license them exclusively to another party, or broadly disseminate them through nonexclusive licenses. It is also within their rights to do nothing other than to keep their patent as a defensive buffer against more aggressive rights holders, or to allow free use.

The scope of the exclusionary patent right depends on each jurisdiction's laws and what is claimed in the patent. There is inevitably some international diversity in the boundaries of patent claims depending on national rules of interpretation and on how standard patent requirements are applied. These requirements include the technical patent criteria of novelty, inventive step/nonobviousness, and utility/industrial application, as well as conditions relating to the sufficiency of description of the invention. There will inevitably be greater levels of confusion when whole areas of technology are excluded from patenting in some countries but allowed in others. This is the current situation with regard to gene patenting, and the topic of this review.

Before we go further, we should explain what we mean by gene patent. Typically, the term encompasses two types of patent claims. The first type of claim is directed to products such as isolated nucleotide sequences. For example, one of the claims that was challenged in *AMP* read, "[a]n isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2" (120, claim 1). The word isolated was defined in the definitions section of the patent specification to mean "a nucleic acid sequence…which has been removed from its

naturally occurring environment" (120). This definition is typical for these kinds of claims. The second typical type of claim is directed to processes, such as methods of using or interrogating nucleotide sequences. For example, other claims challenged in *AMP* were directed to detecting mutations by comparing a patient's sequence with a reference sequence (119, claim 1). It is important to note, though, that there are wide variations in these two types of claims, including claims to human-made cDNA, primers, testing kits, isolated sequences in vectors, methods of screening potential drugs, and methods to amplify genomic regions, many of which were also included in the *BRCA* patents.

In exploring the current international divergence in gene patenting, we have chosen to focus on the United States and Europe, given that they are the powerhouses of genomics and human genetics. To give broader context, we also consider Australia and Canada, primarily because some of the interesting legal and policy developments in gene patenting have occurred in these two jurisdictions. We also include China. Although a late entrant into the patent system, and lacking significant legal developments in the specific context of gene patents, China is destined to join the United States and Europe as a home for the leading research teams in genomics and human genetics (if it hasn't already).

We separate this analysis into four parts. First, we explore more fully the current global patent system and provide a historical overlay to patent law. We then turn to a more specific analysis of the history of gene patenting, through the lens of significant turning points across three decades: the 1980s, 1990s, and 2000s. What we see across these decades is an increasing convergence in gene patenting internationally. The next and most significant part of the review analyzes legal developments post-2010, with particular focus on divergence in approaches to patent eligibility between jurisdictions. Finally, we interrogate the current international divergence in gene patenting and ask whether it really matters.

2. UNDERSTANDING THE GLOBAL PATENT SYSTEM

For well over a century, international instruments have made it easier to file patent applications in multiple countries (103, 104). However, the push to globally harmonize the laws that determine patentability started in earnest only around 25 years ago, when intellectual property was linked to trade negotiations (59). One of the requirements for membership in the World Trade Organization is joining the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which was agreed to in 1994. TRIPS specifies common minimum standards for intellectual property protection in domestic legislation of member states but does not, pointedly, fully harmonize substantive patent law (142).

Countries did not start with a blank slate post-TRIPS. All but a few of the developing and least developed countries already had patent laws, some of which were long-standing. Indeed, the first English patent legislation, the Statute of Monopolies, came into force in 1624. This statute laid the foundation for patent laws across the British Commonwealth. Even in the United States, which separated from the British Commonwealth soon after colonization, the legal system has remained steeped in English legal tradition. The Statute of Monopolies used the language of "manner of new manufacture" to describe the subject matter for which the letters patent should be made available.

Australia has still retained the so-called manner of manufacture test as the touchstone of patentability in the most recent iteration of its patent legislation, the 1990 Patents Act (Act No. 83, sched. 1, § 18). In the United States, the current Patent Act refers to "processes, machines, manufactures or compositions of matter" (35 U.S.C. § 101). The US Supreme Court has determined that laws of nature, natural phenomena, and abstract ideas do not meet this requirement (36, p. 309; 117). Likewise, the Canadian Patent Act of 1985 defines an invention as "any new and useful

art, process, machine, manufacture or composition of matter, or any new and useful improvement in any art, process, machine, manufacture or composition of matter" (R.S.C. 1985, c. P-4, § 2). In all three countries, it is left to the courts and patent offices to determine what types of subject matter fall inside and outside these broad concepts. When faced with patent applications in new areas of technology, patent offices make their determinations based on analogies with like cases. If, however, a court reaches a different conclusion, the patent office must modify its practice. Thus, when the US Supreme Court and the Australian High Court determined that isolated naturally occurring gene sequences were not patent eligible, patent offices in both countries had to adapt (9, 35). In doing so, each undertook extensive consultations before setting the new examination parameters (14, 41, 127).

In contrast to the United States, Canada, and Australia, the United Kingdom abandoned its traditional approach to patent law in the 1970s when it joined with European partners in adopting the European Patent Convention (EPC) (30). The foundations for European patent law were different from the British tradition. Continental Europe began establishing national patent acts in the mid-nineteenth century, and a European patent system came into being in 1973 with the adoption of the EPC. On the basis of a single application and examination procedure, an invention can be protected in up to 38 European countries, comprising the contracting states that ratified the EPC. The term European patent, however, is misleading from two perspectives. First, there is no single patent that is valid for the whole of Europe: The application and granting procedures are uniform, but the patent is then broken into a bundle of national patents, each of which is exploited and enforced under national law. Second, the EPC does not form part of the architecture of the European Union (EU). That is, a European patent has little to do with the EU apart from the fact that all EU member states have adopted the EPC.

In principle, a European patent can be granted for any invention that fulfills the standard patent criteria. Even though the EPC lacks a formal definition of the term invention, it is generally recognized that a product or process that has a technical character and provides a technical contribution to the state of the art is patentable subject matter (49, rules 42, 43, and 47). However, certain subject matter is specifically excluded: discoveries; scientific theories and mathematical methods; aesthetic creations; schemes, rules, and methods for performing mental acts, playing games, or doing business; and programs for computers as such (so-called noninventions) (30, art. 52). There are further exclusions for inventions the commercial exploitation of which would be contrary to *ordre public* or morality, plant or animal varieties or essentially biological processes for the production of plants or animals, and methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body (so-called nonpatentable inventions).

China enacted its first patent statute much later than other jurisdictions. The Patent Law of the People's Republic of China was enacted in 1984 to protect "inventions, utility models and appearance designs" (art. 2). With regard to inventions, it adopts a similar approach to the EPC, excluding a specific list of subject matter. Relevant exclusions include scientific discoveries, rules and methods for intellectual activities, methods for the diagnosis or treatment of diseases, animal or plant varieties, and substances obtained by means of nuclear transformation (art. 24). Additionally, patents cannot be granted for inventions that violate the law or social ethics or harm public interests, or for inventions created in reliance on illegally obtained genetic resources (art. 5).

Varying degrees of divergence in patent laws are thus long-standing in the global patent system. The stated aim of TRIPS was to set consistent minimum patent standards in national patent laws to facilitate free trade, which would spur innovation (101). The history of innovation is replete with debates over the justifications for patent protection (80) and the patent eligibility of many of the most significant technological developments, including steam engines (122), light bulbs

(116), sewing machines (93), airplanes (20), and the telephone (19). Many of the issues that were raised in relation to these technological upheavals are reminiscent of the gene patent debates. The ongoing dilemma is that too much patent protection could stifle innovation, but too little could deter commercial development of these transformative technologies, particularly where the path to the market is filled with risk.

The path for new pharmaceuticals from drug discovery to the pharmacy shelves is widely recognized as long and tortuous. The path for diagnostic genetic tests to reach the clinic, though less complex, is also becoming increasingly difficult, as genetic test providers are having to register their tests as in vitro devices in many countries. Whether gene patents serve as an appropriate mechanism to facilitate the development of these new technologies has been hotly contested for many years. One challenge is that genes clearly have different attributes from steam engines and flying machines. Not least, they already exist in the natural world in various forms, they have both informational and chemical qualities, and they have important uses as research tools as well as in the development of drugs and diagnostics. Patenting of genes thus raises a host of issues for the research community, industry, and the public that go beyond facilitating product development.

Despite these concerns, gene patenting has been a common practice, which has only recently started to unravel. How was it that this situation arose, and how was it allowed to continue for so long in so many countries? The next section of this review explores the historical circumstances surrounding this gene patenting saga.

3. INTERNATIONAL CONVERGENCES IN GENE PATENTING

3.1. The 1980s and Beyond: University Patenting

Across the industrialized world, the prolonged recession of the 1970s focused attention on innovation as a way to reinvigorate the economy, particularly in the United States (110). This concern led the US Congress to make two significant changes that affected the patent system. In 1980, it enacted the Bayh–Dole Act (35 U.S.C. § 200–212), which gave universities the right to patent faculty inventions financed by the government (33, 106). Furthermore, in 1982, the United States established the Court of Appeals for the Federal Circuit to hear patent appeals from national trial courts and the Patent and Trademark Office [28 U.S.C. § 1295; 39]. Both measures had a profound effect on biotechnology.

Prior to Bayh–Dole, the US government retained rights to the fruits of sponsored research, sometimes patenting and licensing advances on a nonexclusive basis and sometimes leaving them in the public domain. Neither approach led to strong commercialization, and Congress had reason to think universities could handle transfer technology better and involve faculty in commercialization more effectively (40, 47). Shortly before Bayh–Dole went into effect, Stanley Cohen and Herbert Boyer received a patent on recombinant DNA insertion technology (28, 118). Their patent was broadly licensed, earned millions of dollars for Stanford University and the University of California, stimulated research in both academia and industry, and led to the founding of Genentech (33, 55, 121). A great success, Genentech spawned many other successful university spin-offs, many of which produced significant advances in both fundamental science and commercial applications. Interestingly, though, equivalent patents were not pursued in other jurisdictions, and some doubt that the US patent would have withstood legal challenge (6).

Bayh–Dole had a broader effect of changing university patent practices. Technology transfer offices, interested in maximizing returns, started to push the boundaries of patent eligibility. A series of judicial decisions gave them good reason to expect success. In 1980, the US Supreme Court decided in *Diamond v. Chakrabarty* that living organisms—in this case, a bacterium into

which previously existing plasmids that degraded oil had been inserted—were patentable, holding that "Congress intended statutory subject matter to 'include anything under the sun that is made by man'" (36, p. 309). In 1981, *Diamond v. Diehr* extended protection to computer technology (37). Federal Circuit decisions like *State Street Bank & Trust Co. v. Signature Financial Group, Inc.* increased patent scope to include anything that produces "a useful, concrete and tangible result" (124, p. 1373). University-led patent applications in biotechnology and bioinformatics were among the many beneficiaries of this broader approach to patent eligibility.

This shift in government policy in the 1980s to encourage university patenting was not so overt in other countries, though it was implicit in the actions of the major funding agencies. The legislative framework of many EU countries allows universities or their individual academics to patent research results. In 2000, the Lisbon strategy created a 10-year economic development plan for the EU and indirectly provided the legal foundation for academic centers to protect and exploit the outcome of (EU-funded) university research (131). In Australia in 2001, the major funding bodies, universities, and government agencies formally agreed to a set of intellectual property principles reflecting the same arrangements (16). An updated set of principles was formally adopted by the major funding bodies in 2013 (15). Canada did not have, and continues not to have, an explicit policy on university patenting and licensing. Like Australia, the major funding bodies have left patent decisions to the universities and other research institutes. Each university and institute, through its employment arrangements with its research staff, decides whether the institution or the researcher has first right to own patents. The Chinese government likewise supports university ownership of inventions arising from government-funded research (67).

Government support for university patenting was important because it provided one key trigger for the formation of a private biotechnology industry around preproduct development research (48). Patent landscape analyses have shown that a sizable portion of the gene patents filed in the 1980s and 1990s originated in the public sector, even though many of them were subsequently assigned to private firms (33, 76).

3.2. The 1990s and Beyond: The Human Genome Project, the Expressed Sequence Tag Patent Problem, and the Biotechnology Directive

In 1990, the Human Genome Project was established with the goals of mapping and sequencing the entire human genome. Craig Venter, then at the National Institutes of Health (NIH), developed the technique of using short fragments of cDNA, known as expressed sequence tags (ESTs), to accelerate the process (33). ESTs are valuable as probes for the genes from which they were derived (4), and this was therefore an important development in the mapping and sequencing effort. By 1992, the large number of NIH EST applications led to serious questions about patenting Human Genome Project research (43, 86).

Although the NIH later abandoned its EST patent applications, companies such as Incyte Genomics and Human Genome Sciences continued to push the boundaries of patent eligibility, filing large numbers of applications for genes and gene fragments. Eisenberg (45, pp. 1383–84) aptly described these types of claims as "patenting genes as research tools" and "patenting genes as trivial advances." In marked contrast, the NIH and other participants in the Human Genome Project agreed to rapidly release raw sequence data into the public domain in accordance with what became known as the Bermuda Principles (140). Patents were, however, still available for products and processes using this sequence data (133).

In the United States, the utility requirement was considered an option for addressing the EST patent problem. In an early decision on utility in 1966, the Supreme Court held in *Brenner v. Manson* (22) that research uses were insufficient to meet the utility requirement (35 U.S.C. §

101). It was not until 2001, however, that the US Patent and Trademark Office finally decided how to apply *Brenner v. Manson* to gene patents, stating in their Utility Guidelines that the utility recited in the patent specification must be credible, substantial, and specific (64). The guidelines were finalized two years after the release of proposed guidelines in 1999 (62), which were the first signal of a change in policy direction by the Patent and Trademark Office relating to utility. Policy changes relating to the written description requirement followed the same course, with a new set of examination guidelines finalized in 2001 (63). Together, these developments have been described as a "notable success" on the part of the Patent and Trademark Office and the scientific community "in working together to determine how best to apply the standards of patent law to new types of discoveries in genomics" (29, p. 99).

In 2005, the Federal Circuit ruled on the utility of ESTs in the case of *In re Fisher* (72). The case related to five EST patent claims in maize, claiming they could be used for multiple purposes, including as molecular markers, to measure mRNA levels in tissue samples, to provide sources for primers, to identify polymorphisms, to isolate promoters, to control protein expression, and to locate genetic molecules in other plants. The Federal Circuit found these uses insubstantial, holding that they are "nothing more than a 'laundry list' of research plans" and were not specific to any particular EST (72, p. 1370). The court also decided that because the ESTs had no qualifying utility, the application did not enable use and thus failed to meet the disclosure requirement [35 U.S.C. § 112(a)]. Recent cases interpreting the industrial applicability requirement for gene-related claims in Europe indicate close alignment with this approach to assessing the utility requirement in the United States (38, chap. 4). Australia, too, has adopted the language of specific, substantial, and credible utility (Patents Act 1990, Act No. 83, § 7A).

In parallel, policy makers in the EU started to consider what was increasingly perceived as a bigger gene patent problem. Germany had been issuing patents for living matter since the 1960s (61, 129). The European Patent Office (EPO) had also started routinely granting patents for subcellular fragments, including DNA sequences, genes, plasmids, and vectors, provided they met the conditions of novelty, inventive step, and industrial applicability. The lenient EPO granting policy was first formally challenged when a patent was granted for a DNA fragment encoding human H2-preprorelaxin. The Opposition Division of the EPO concluded, in a 1995 decision relating to the gene sequence coding for human relaxin, that the claimed invention was not an exception to patentability because it was not contrary to *ordre public* or morality, nor was it a discovery (50, p. 2).

In a direct bid to resolve confusion caused by this and other decisions, and to harmonize member states' legislation on this point, a directive on the legal protection of biotechnological inventions (the Biotechnology Directive) was adopted by the European Parliament in 1998. Discussions on this issue had started in the mid-1980s in response to what were perceived as more receptive policies in the United States and Japan. However, these discussions stalled over contentious questions around the patentability of genetically modified higher organisms and other subject matter considered by some to be contrary to *ordre public* and morality (61, 130). The EU restarted discussions in the mid-1990s. Arguably, the successful conclusion of these discussions represented a subtle victory for the EU in steering the granting policy of the EPO indirectly, having no authority to do so directly. The directive was incorporated into the EPC in 1999, thus providing the EPO with more detailed guidelines with regard to the patenting of biotechnological inventions, and genes in particular. The final directive met with strong opposition by some member states of the EPC. Indeed, the Netherlands brought a case for annulment to the European Court of Justice in 1998 (77). However, the court did not accept any of the arguments in favor of annulment.

The Biotechnology Directive stipulates that inventions that are new, involve an inventive step, and are susceptible of industrial application are patentable even if they concern a product consisting of or containing biological material or a process by means of which biological material is

produced, processed, or used [54, art. 3(1)]. With regard to human beings, the directive states that neither the human body at the various stages of its formation and development nor the simple discovery of one of its elements, including the sequence or partial sequence of a gene, can constitute a patentable invention [54, art. 5(1)]. However, 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 [54, art. 5(2)]. In the relaxin case, the EPO board of appeal was given the opportunity to reconsider the patentability of the relaxin gene following the implementation of the directive, concluding that there was nothing in the new provisions to affect the patentability of the invention (50, pp. 10–11).

Crucially, the directive requires that the industrial application of a sequence or partial sequence of a gene must be disclosed in the patent application [54, art. 5(3)]. However, no further guidance was provided at the time the directive came into force on how to interpret this requirement (132, 134). It was generally understood—but not explicitly mentioned—that industrial applicability referred to function.

3.3. The 2000s: A Myriad of Gene Patents

By the turn of the century, there were serious concerns about the risk that patenting of fundamental research could take a toll on firms downstream, which had to pay royalties to utilize basic building blocks of science. One of the features of the industry is that innovation is cumulative: Many small steps must be taken on the road to product development, and many pathways intersect and overlap. Where each step or pathway is protected by a patent, the pace of innovation could be slowed, particularly when broad patent rights are granted to early innovators (44; 112, pp. 32–33). Innovation is likely to be inhibited if these broad research platforms are not made widely available to follow-on researchers (68).

In 1998, Heller & Eisenberg (68) raised theoretical concerns about the potential impact of gene and related patents on innovation in a famous article on the anticommons in biomedical research. They posited that "a proliferation of intellectual property rights upstream may be stifling life-saving innovations further downstream in the course of research and product development" (68, p. 698; see also 115). A controversial study by Jensen & Murray (76) lent support to this concern, concluding that nearly 20 percent of all human genes had been claimed in patents granted in the United States, with some genes featuring in up to 20 separate patents (see also 137). More than 75 percent of these gene patents had only one patent owner, but the remainder had fragmented ownership (76). By contrast, other empirical studies reported that those industry participants who needed to in-license patents were able to do so (24, 46, 99, 139). Nonexclusive licensing of foundational research tools, including gene sequences, was also reported as common.

Gene patents could also have a profound effect on consumer access to health care (26, 91, 113). During the 1990s, research groups began focusing on identifying specific disease-related genes and developing diagnostic tests. For example, two genes were identified as having links to breast cancer susceptibility (*BRCA1* and *BRCA2*). Myriad Genetics, through its own in-house research and a series of patent licensing deals, came into possession of highly contentious patents relating to the *BRCA* genes that were ultimately the subject of the *AMP* and *D'Arcy* cases. These actions provided Myriad with exclusivity in relation to *BRCA* testing (87). In 2004, Myriad sold its *BRCA* patents to the University of Utah Research Foundation but continued to hold exclusive licenses to the patents (141). Myriad chose to actively enforce its patent rights against laboratories offering *BRCA* tests in a number of countries (102). As a consequence, Myriad became the poster child for the anti-gene-patent movement. As Gold & Carbone (60, p. S43) pointed out,

> What [Myriad] failed to realize was that it had entered into a storm about the patenting of biotechnology, the ways in which to regulate genetic testing, the role of private companies in determining which health services are on offer within public health systems, and how to provide access to genetic testing. Those miscalculations would thwart Myriad's success outside the United States.

Despite initial attempts, Myriad failed to gain traction in countries other than the United States (23, 60). Myriad did, however, enjoy many years of success as the exclusive provider of *BRCA* tests in the United States (23, 60). In 2009–2010, the Secretary's Advisory Committee on Genetics, Health, and Society undertook a study on gene patents and licensing practices and their impact on patient access to genetic diagnostic tests and concluded that pursuit of exclusivity threatened to undermine the potential of genetic technology, and that few mechanisms existed under US patent law to mitigate these effects (113, pp. 89–90). For example, the United States lacks the compulsory licensing regimes and statutory research exemptions found in other jurisdictions. The committee further concluded that patent incentives are arguably not essential for genetic diagnostic tests that cost US$8,000–10,000 to reach market; instead, the existence of such patents threatens to hinder the delivery of testing services (113, p. 90).

Beyond Myriad, it had been suggested that a broader patent thicket might emerge in the diagnostic sector, resulting in an undersupply of diagnostic testing services or the development of suboptimal diagnostic tools. An empirical study by Huys et al. (69) in the early 2000s analyzed the patent landscape surrounding genetic diagnostic testing for the 22 inherited disorders most frequently tested for in Europe, in order to assess (*a*) the nature, extent, and scope of patents in genetic diagnostics in Europe and the United States; (*b*) patent ownership; and (*c*) the impact of the patents on access to health care in view of the best practices in the field. The results showed significantly fewer claims on genes per se than was initially suggested by others. By contrast, numerous method claims were identified, and it was these that tended to have the greatest blocking effect. The study also noted that many claims were of unclear scope, giving rise to legal uncertainty. A follow-up study showed that, by the end of 2014, most of the problematic blocking patents identified in the earlier study were not in force outside Europe, the United States, and Canada, because they were never filed, never granted, or not renewed on the required yearly basis, or had already expired (84). That is, the risk of problematic patents blocking diagnostic access appeared to be an issue primarily for European and North American countries to worry about.

From the legal perspective, there were several significant decisions relating to the *BRCA* patents in Europe. The EPO issued five *BRCA* patents over a period of five years: three relating to *BRCA1* and two relating to *BRCA2*. Soon after the first *BRCA1* patent was granted, opposition proceedings were launched with respect to all five patents (opposition proceedings can be initiated before the EPO up to nine months after the grant of a European patent). In the *BRCA* oppositions, arguments relating to the eligibility of human genes as patentable subject matter were summarily rejected based on the provisions of the Biotechnology Directive. Arguments based on lack of novelty (focusing on the questionable validity of one specific priority document) were more successful (51–53). The outcome was that the scope of Myriad's *BRCA1* and *BRCA2* patents was drastically reduced in Europe (88).

Myriad was left with patents covering the detection of an individual Ashkenazi mutation in the *BRCA1* gene (patent EP705902), methods for detecting frameshift mutations in the *BRCA1* gene (patent EP699754), probes and cloning vectors and host cells relating to the *BRCA1* gene (patent EP705903), and methods for detecting mutations in the *BRCA2* gene (patent EP785216). The patents no longer covered the *BRCA1* gene sequence as such and were maintained only in a selection of countries in Europe. The decade-long challenge to the Myriad patents left no lasting legacy in European patent law, with the Biotechnology Directive remaining at its cornerstone for

biotechnology-related inventions. A 2016 report by the Expert Group on the Development and Implications of Patent Law in the Field of Biotechnology and Genetic Engineering concluded that, while several issues were "not necessarily…resolved entirely and faultlessly satisfactory by the Biotech Directive," the "overwhelming majority of Experts were not in favor of reopening" it (21, p. 6).

The attempt by Myriad to enforce its *BRCA* patents in Canada could have had a more profound effect. Myriad first attempted to enter the Canadian market in the early 2000s by starting negotiations with several provincial governments responsible for the delivery of health services, including genetic services (23, 60). Rather than take the time to work through the process, Myriad threatened legal action. The provinces fought back, developing a common legal front in early 2002. As a result of the strength of the resistance to its tactics by the provinces, Myriad backed down and no longer asserted its patents in Canada. There was thus no action taken, before either the patent office or the courts, to ascertain the validity and scope of gene patents in the country. Myriad managed to obtain contracts for overflow work in several provinces, however, providing it with a steady stream of revenue, albeit relying more on the quality of its services than its patents. For several years, no other firm attempted to assert a gene patent against a Canadian public health provider. This changed in 2006 when a Canadian licensee of a pending patent for *JAK2* warned provincial health providers that it held the Canadian rights to test for the gene. After another concerted effort, this time led by the federal rather than provincial government, the French patent holder assured access to the test by public health providers throughout Canada (105).

In Australia, although Myriad never attempted to enforce its patents in its own right, a complex licensing arrangement with the Melbourne-based company Genetic Technologies in 2002 led to the reasonable apprehension that patent enforcement actions relating to the *BRCA* tests were inevitable (96). A policy response to these palpable concerns was swift. In 2003, the Australian Law Reform Commission was given a reference from the federal government to inquire into the impact of gene patenting on human health, the final report of which was completed in 2004 (13). The Australia Senate, the upper house of the Australian Parliament, also undertook two inquiries in 2010 (17) and 2011 (18). The major reform recommendations included the introduction of an experimental use exception to infringement, modification of the inventive step requirement, introduction of a clear utility requirement, and significant changes to the disclosure requirements so that they aligned more closely with the requirements in other jurisdictions. These changes were implemented in 2012 by amendments to the Patents Act 1990 through the Intellectual Property Laws Amendment (Raising the Bar) Act. A specific proposal to exclude gene sequences from patenting was rejected in all three reports.

In the United States, despite the aggressive enforcement of the *BRCA* patents, no court challenges emerged during the decade 2000–2009. In the meantime, though, the courts started to find ways to narrow gene patent claims, particularly through the disclosure and nonobviousness (inventive step) requirements. *In re Wands* (74) was an early case concerning an assay for detecting hepatitis B using high-affinity monoclonal antibodies. The court there emphasized that the disclosure must enable others to make the patented invention without "undue experimentation"—in this case, by showing how to produce the necessary antibodies (74, p. 737). Relying on *Wands*, in *Amgen, Inc. v. Chugai Pharmaceutical Co.* (7, p. 1212), the Federal Circuit invalidated a broad claim covering "all possible DNA sequences that will encode any polypeptide having an amino acid sequence 'sufficiently duplicative' of EPO [erythropoietin] to possess the property of increasing production of red blood cells" because it required undue experimentation to find operative sequences.

More controversially, the Federal Circuit began to curb gene-related patents by emphasizing the requirement that the patent contain "a written description of the invention" (35 U.S.C. § 112).

For example, in *Regents of the University of California v. Eli Lilly & Co.* (108, pp. 1567–69), the court invalidated a patent on recombinant plasmids and microorganisms that produce human insulin on the ground that the human DNA sequence was not "described," even though the invention was fully enabled through a description of the analogous rat sequence. This interpretation of written description was seen as contentious, because of the perception that it could "profoundly limit the scope of protection available for new gene inventions" (94, p. 615).

In 2007 in *KSR v. Teleflex* (78; 35 U.S.C. § 103), the Supreme Court substantially raised the height of nonobviousness by requiring courts to consider the substantial background knowledge possessed by those skilled in the pertinent art. Because the decision invigorated the nonobviousness inquiry, it dramatically reduced the scope for patenting genes. Whereas it was previously thought that patents could be obtained on genes coding for known proteins (71), *In re Kubin* (73) upheld the rejection of a patent on isolating and sequencing the polypeptide NAIL, reasoning that skilled biotechnologists could sequence it based on known information about the protein. Assuming a higher level of skills in the art may, however, have a paradoxical effect on enablement and written description cases. Like nonobviousness, fulfilling these requirements depends on the abilities of ordinary artisans. Recognizing higher levels of skill will mean that less information will be regarded as necessary to fully disclose the invention.

Thus, up to 2010, the subject matter requirement had not been applied by the patent offices, courts, or legislatures to deal with the perceived gene patent problem. From the perspective of the courts, this reflects the fact that, aside from the European *BRCA* oppositions, they were not given the opportunity to deliberate on such matters. This changed in 2010.

4. DIVERGENCE IN PATENT ELIGIBILITY

From the US perspective, even with the efforts made by the courts to narrow claims, the Supreme Court became concerned that "sometimes too much patent protection can impede rather than 'promote the Progress of Science and useful Arts'" (79, per Justice Breyer, quoting the US Constitution, dissenting from the denial of certiorari). In a series of cases, the Supreme Court put new emphasis on the sentences following *Chakrabarty*'s statement that everything under the sun is protectable: "Laws of nature, physical phenomena, and abstract ideas have been held not patentable" subject matter in that they must be freely available to everyone (36, p. 309).

Two of these cases, *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* (89) and *AMP* (14), directly affect biotechnology. *Mayo* was a process patent case, involving a prognostic test that used the blood level of a thiopurine drug's metabolite to determine whether the dose was within a stated therapeutic window. Calling the correlation between metabolite levels and toxicity a law of nature, the Supreme Court held the method unpatentable.

AMP's challenge to the *BRCA* patents involved both product and process claims. Even before the Supreme Court judges reached their decision in *Mayo*, both the trial judge (10) and the Federal Circuit judges (11) in the *AMP* case invalidated diagnostic method claims correlating *BRCA* sequence mutations with early-onset breast cancer. Following the decision in *Mayo*, the Supreme Court ruled that the Federal Circuit should reconsider its decision in *AMP* in light of *Mayo*. Not unexpectedly, the Federal Circuit judges did not change their view that the method claims were invalid, because this part of their decision already aligned with *Mayo* (12). However, the key issue was that the majority of the Federal Circuit (Judges Lourie and Moore) had decided that the product claims to isolated nucleotide sequences were patent eligible (11). Judges Lourie and Moore did not change their views on this issue post-*Mayo* (12). Given that the method claims were already invalidated, *AMP* only challenged the validity of the product claims in the Supreme Court.

The Supreme Court then went on to find that the product claims to *BRCA* isolated sequences are unpatentable phenomena of nature. Curiously, despite the court's stated concerns that the unimpeded flow of information encoded in DNA molecules is required to spur invention (9, p. 590), it upheld the corresponding cDNA sequence claims, reasoning that cDNA is human made. Synthesizing the teachings of these cases, the US Patent and Trademark Office now imposes a two-step test to determine patent eligibility. The first step asks whether the claim is directed to a law of nature, natural phenomenon, or abstract idea or, for products, is markedly different from nature. The second step asks whether the claim adds significantly more—an "inventive concept" that is not "well-understood, routine, conventional activity previously engaged in by researchers in the field" (89, p. 73; 128, § 2016). The Patent and Trademark Office released a new guidance note in January 2019, providing further clarification on the application of the two-step test (65).

Limiting patents on diagnostics and genetic sequences has had a largely positive impact on patient access to diagnostic testing in the United States. However, the effect on research is mixed. Although DNA sequencing information that was previously disclosed in patents is now available to researchers, Myriad continued to retain trade secrecy in its variant sequence database, which was created during the time that Myriad exercised its patent monopoly, giving it a significant ongoing commercial advantage (32, 109). Aside from Myriad, the combination of *AMP* and *Mayo* is of significance for other commercial developers. For example, in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.* (8), the inventors had found paternally inherited cell-free fetal DNA circulating in maternal plasma and developed a method for using it to determine fetal characteristics. The test developed out of this discovery, known as noninvasive prenatal testing, was an important innovation. Yet the Federal Circuit found it unpatentable: Cell-free fetal DNA, although previously unknown, is a phenomenon of nature; its correlation with phenotypic characteristics is a law of nature; and the techniques used to analyze it were routine. The result has significant implications for new platform technologies or medical tests that rely on a natural phenomenon and use known, routine techniques.

But a new approach is on the horizon in the United States. After the Supreme Court refused to review *Ariosa* (114), the Federal Circuit issued several decisions that emphasized how the claim characterizes the invention. In *Vanda Pharmaceuticals, Inc. v. West-Ward Pharmaceuticals International Ltd.* (136), the patentee used genomic information to determine the dose of iloperidone to administer to a schizophrenic patient. The court distinguished *Mayo*, reasoning that this claim was directed not to a natural relationship but rather to a novel method for treating a disease. Whether the Supreme Court will agree with this approach, which relies heavily on how a claim is drafted, remains to be seen. There are also substantial open questions on what constitutes a marked difference from nature or an inventive concept. Furthermore, the commercial significance of patents issued under these restraints is unclear. These uncertainties have led the life sciences industry to lobby for a legislative expansion of protection and a return to a regime that relies on other standards of patentability to maintain judicial limits on patent scope (127).

In Australia, in *D'Arcy* (35), the High Court invalidated what were essentially the same sequence claims in Myriad's Australian *BRCA1* patent as those invalidated in the United States in *AMP*. The essence of the court's decision was that the isolated sequences as claimed did not fall within the concept of manner of manufacture. Prior to *D'Arcy*, the leading case on manner of manufacture was *National Research Development Corporation v. Commissioner of Patents* (95, hereafter *NRDC*). There, the High Court emphasized that the manner of manufacture test does not qualify for precise formulation; rather, the relevant question is, "Is this a proper subject of letters patent according to the principles which have been developed for the application of § 6 of the *Statute of Monopolies*?" (95, p. 269). In *NRDC*, the High Court held that the requirement was satisfied because the subject matter at issue was (*a*) an artificially created state of affairs that (*b*) had

economic utility (95, pp. 278–79). In *D'Arcy*, the court reconsidered what had, over time, become established as the two-limb *NRDC* test. While the joint decision of the majority of High Court judges recognized that, in many instances, the two-limb test will be sufficient, they added that in some circumstances it is necessary to look to a range of other factors. These circumstances arise when there is "a new class of claim [involving] a significant new application or extension of the concept of 'manner of manufacture'" (35, para. 28), in which case it is necessary to examine the consequences of extending the patent monopoly, including whether it would result in a chilling effect on activities beyond the scope of the granted patent. Here, the court was concerned that the patent could be infringed without the infringer being aware of it and that the claimed class of isolated nucleic acids was very large (35, para. 93).

One significant difference between the Australian and US decisions is that the High Court in *D'Arcy* appeared unwilling to draw the same distinction between the invalidity of isolated sequence claims and the validity of cDNA claims. The court emphasized that it is the existence of that information that is essential and "that characteristic also attaches to cDNA" (35, para. 89). Subsequent to *D'Arcy*, the Australian Patent Office issued a new examination practice note in December 2015 (14). The note makes it clear that the *D'Arcy* exclusion extends to isolated naturally occurring sequences, and synthetically made sequences that merely replicate the genetic information of a naturally occurring organism may also be excluded (97).

The method claims in Myriad's patent were not challenged in the *D'Arcy* litigation, and as a consequence the High Court did not have any opportunity to rule on their validity. In light of the findings in the study by Huys et al. (69) that method claims tended to have the greatest blocking effect, this omission is unfortunate. There is, however, a case currently before the Australian courts relating to method claims. The claims at issue in *Meat and Livestock Australia Ltd. v. Cargill, Inc.* (90, hereafter *Cargill*) relate to a method for identifying bovine traits from nucleic acid samples using single-nucleotide polymorphisms (SNPs) in the management of cattle breeding (90, para. 147). It is, of course, irrelevant that *Cargill* is not a human gene patent case, since the legal principles remain the same. Justice Beach, the trial judge, distinguished *D'Arcy* on a number of grounds, primarily because the claims were to methods rather than sequences per se. The argument that the methods were simply the practical application of a naturally occurring phenomenon was rejected (90, para. 455). Rather, Justice Beach accepted that taking a sample and analyzing it to identify SNPs associated with particular traits of interest gave rise to an artificially created state of affairs, thus satisfying the *NRDC* requirement. He rejected the applicability of *Mayo* in Australia on the basis that it was not helpful to his decision (90, para. 492). Although the decision is being appealed, it illustrates that, even where countries have similar requirements for patent eligibility, there can still be significant divergence in the way these requirements are interpreted and applied (41).

In light of changes in two sister common-law jurisdictions—the United States and Australia—Canadian experts were uncertain whether the Canadian Intellectual Property Office's decision to grant gene patents would be upheld by the courts. To resolve this uncertainty, the Children's Hospital of Eastern Ontario launched an action in 2014 to invalidate or circumscribe the scope of both method and product patents covering long QT syndrome, a genetic illness that predisposes children to sudden cardiac arrest. The long QT patent claims were drafted at approximately the same time as the Myriad patents and thus read in a similar fashion. Again, the patent holder was the University of Utah, although once the litigation began, the university transferred all rights to its licensee, Transgenomic. After prolonged discussion, the hospital proposed a novel solution: a license that would allow any public health provider to provide a genetic test related to the patented genes without payment and without accounting. The license neither acknowledged the validity nor accepted the invalidity of the patents. Instead, it made the patents irrelevant to the public health care system through which all genetic health services were delivered in Canada. More generally,

the license serves as a model for other agreements that could be negotiated between the public sector and patent holders.

Until recently, no European court had decided whether claims to isolated nucleotides or methods of detecting mutations are patentable subject matter. Thus, the 2016 decision of the Bundesgerichtshof (the apex patent court in Germany) in *Receptor Tyrosine Kinase* (107) is of lasting importance. The patent claimed mutant forms of the gene FMS-like tyrosine kinase 3 (*FLT3*). Somewhat curiously, these claims did not include the word isolated. Additionally, the patent claimed methods for detecting the mutations as well as associated testing kits and proteins. Certain mutations in *FLT3* are useful for predicting the severity of acute myeloid leukemia. In light of the Australian and US decisions, one might be surprised that the court found all the claims patentable. Regarding the claims to mutant forms of *FLT3*, the court held that isolation is inherent in the claims, and since isolation is a technical process (as specified in the Biotechnology Directive), the claims are therefore patentable (56, p. 227). The court found all the other claims valid for the same reason as the composition of matter claims—that is, they all included isolation or another technical process (56, p. 227). The court also specified that, in Europe in general and Germany in particular, there is no need to identify an "inventive surplus" or inventive concept akin to what the US Supreme Court stated is necessary in *Mayo* (56, pp. 226–27).

The Bundesgerichtshof did, however, offer a ray of light for those wanting to offer the test without obtaining authorization. The defendants had offered *FLT3* tests to German patients by collecting samples in Germany and arranging for a Czech laboratory to analyze the samples and send the test reports back to Germany, as the patent was never obtained in the Czech Republic (57, p. 233). The court held that this arrangement did not infringe the German patent, stating that the only way it could was if the "products" (the test reports) sent to Germany were patentable themselves (57, p. 234). However, since the test reports consisted only of information about the presence or absence of a mutation, and the reporting of information is specifically excluded from patent protection, no infringement occurred (57, pp. 234–36).

Shortly after the German *FLT3* case, a UK court decided *Illumina, Inc. v. Premaitha Health Plc* (70), concerning patents for noninvasive prenatal testing, one of which was the equivalent of the US patent invalidated in *Ariosa*. As in *Ariosa*, the defendants argued that the claims for noninvasive prenatal testing disclosed only the unpatentable discovery of fetal nucleic acids that are paternally inherited and detectable in the blood of pregnant women. The court, however, disagreed, holding that the claims were patentable because they included creating samples for analysis from mothers and involved detecting nucleic acids—both of which do not exist in the natural world and are technical in nature (70, para. 189).

In China, there have been no significant legal cases examining the patent eligibility of any type of gene patent claims. Guidelines issued by the State Intellectual Property Office of the People's Republic of China in 2010 make it clear that isolated gene sequences, whether from microorganisms, plants, animals, or humans, or prepared by other means, are seen in essence as chemical substances (83; 123, pp. 129–42). While finding genes or DNA fragments in nature is seen as a mere scientific discovery, once they are isolated or extracted from nature for the first time, they can be patented, provided that their base sequences have not been described in the existing literature, they can be accurately characterized, and they have industrial application. As such, the current Chinese position appears to be akin to that in Europe. However, the exclusion of methods for the diagnosis or treatment of diseases in the Patent Law of the People's Republic of China [art. 25(3)] appears to be broader than the EPC equivalent, which is limited to methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body [30, art. 53(c)]. This suggests that genetic screening and diagnostic methods could

fall within the scope of the Chinese exclusion, although other gene technology methods would remain patentable.

There is nothing to suggest that China may take a different approach to patenting genes in light of the US decision in *AMP* and related cases. Rather, in 2016, the Supreme People's Court of China relaxed the standards for the scope of patent claims for biological sequences in a retrial case on proteins involving the Patent Reexamination Board of the State Intellectual Property Office, Novozymes, and Jiangsu Boli Bioproducts (82). This may reflect an ambition in China to provide broader protection in the field of gene patents, because prior to this decision the scope of protection for gene patents in China appeared to be narrow compared with that of Europe and the United States (82).

5. WHERE NOW?

This analysis of the law shows that the United States and Australia have diverged from the rest of the world on whether gene patents constitute patentable subject matter. The difference in legal analysis is interesting to lawyers, but for many people, the more important question is the extent to which the cases matter for the development of new gene-based technologies or for access to genetic tests.

Immediately after *AMP* in the United States, competitors started offering *BRCA* tests previously covered by Myriad's patents at a cheaper price (111, p. 212; 138). *BRCA1* and *BRCA2* also started to be routinely included in commercial cancer gene panel tests (42, p. 2244). More broadly, the Supreme Court decisions in *AMP* and *Mayo* have had implications for the validity of a large body of other sequence and method patents. A series of other cases have already resulted in similar patents being found invalid (see, e.g., 8, 27). Unfortunately, though, no study has examined how many other test markets in the United States are now subject to increased competition as a result of the *AMP* and *Mayo* decisions. We do know that many gene patents expired before the decisions and that the number of granted US gene patents has been in decline since 1999 (2, 66). Other markets for genetic testing are likely to be even less affected, even those that have not been exposed to equivalents of *AMP* and *Mayo* (84). An Australian study found that the *D'Arcy* decision has had no discernible effect on markets for genetic testing (100). Prior to *D'Arcy*, Australia, like many other nations (58), witnessed few patent enforcement actions against providers of genetic tests (98). This suggests that even if *AMP*- or *Mayo*-type cases were decided in countries other than the United States, it is unlikely they would result in significantly increased patient access to genetic testing.

Has *AMP* or *Mayo* affected the development of new gene-based tests in the United States? It is possible that patents on isolated sequences and methods of diagnosis using conventional techniques are needed for the development of new tests. The argument here is that if such patents are not available, innovators will not be able to recoup the expenses associated with developing and proving tests because, once the tests have launched, competitors will copy them and offer them at a lower price. No study has, however, assessed whether these patents are necessary or whether other patent claims (e.g., to cDNA or methods using unconventional methods) will suffice. The studies by the Secretary's Advisory Committee on Genetics, Health, and Society in the United States found that patents were not necessary to develop 10 first-generation genetic tests (e.g., *BRCA* and *GJB2*) (113). The tests developed today are, however, much more complicated, often involving advanced types of sequencing, tens if not hundreds of loci, and/or a variety of details from patients' medical histories. The increased complexity of modern tests also raises the prospect that translational research on diagnostics is more resource intensive and has a greater need for patent protection to attract investment.

Would the developers of noninvasive prenatal testing have trodden the more-than-10-year path to market without broad patent protection? In this particular example, there is evidence that at least one of the early developers commercially launched its test without having secured prior patent rights (5, p. 526), perhaps suggesting a positive answer to this question. However, the fierce patent rivalry among other developers points to a more negative response (5).

Although we do not know whether the patent protection afforded before *Mayo* and *AMP* in the United States is necessary for the development of tests in that jurisdiction, we can garner some insight from patent filings. One study found that 87% of personalized medicine patents examined after *Mayo* received subject matter rejections, compared with 17% of the same class of patents examined before *Mayo* (25). This finding raises a concern that innovators may be continuing to seek patents for their inventions but failing to obtain them, or at least having significant difficulty obtaining them. Whether the statistics illustrate a chilling effect in the translation of new tests, though, remains to be proven. It is possible that patentees are settling for narrower protection and complementing their patent protection with other forms of competitive advantage (e.g., first to market). Deeper analysis of differences in the patent filing strategies of test developers in Europe and the United States may shed some further light on this issue.

Empirical research suggests that the Supreme Court's decision in *AMP* is not significantly affecting the number of applications for gene patents in the United States, mainly because applications for these types of claims were already in decline (2, 66). However, a common corollary of court decisions that change legal practice is that the change unexpectedly spills out into other areas. A study on *AMP* found that, as of the fifth anniversary of the decision, the US Patent and Trademark Office had cited the case when rejecting claims in nearly 7,000 applications and that 85% of these rejections were to subject matter beyond isolated DNA (1). *AMP* was thought by many people to be a narrow decision, applying only to isolated DNA, but this study shows that it has wider effects.

6. CONCLUSION

The global patent system is challenged whenever there is significant technological disruption, and it can take many years for courts, legislatures, and policy makers to find appropriate solutions. The gene patent challenge (if one exists) has been with us for some 40 years, yet there is still no common global solution. Rather, there is now a greater divergence than ever before. Recognizing that approaches to the subject matter eligibility inquiry are nuanced and that decisions about validity go well beyond subject matter eligibility alone, what follows is a summary account of this divergence:

- In the United States, isolated naturally occurring nucleotide sequences are not eligible, and methods of using them are not eligible if they are conventional and routine. By contrast, cDNA sequences remain eligible.
- In Australia, isolated naturally occurring nucleotide sequences and equivalent cDNA sequences are not eligible, but methods of using them remain eligible.
- In Canada, these issues remain undecided legally, although the willingness of patentees to compromise could be seen as an indication that they saw the validity of their patents as tenuous.
- In Europe, isolated naturally occurring nucleotide sequences, equivalent cDNA sequences, and methods of using them remain eligible.
- In China, the eligibility of isolated and cDNA sequences remains undecided, though diagnostic methods may not be eligible.

Such divergence could have a profound effect on local industry and on consumer access. In the United States, the *AMP* decision had the immediate effect of opening up the market for *BRCA* testing. The impact on the local biotechnology industry remains uncertain, though if the fervor of the lobbying is anything to go by, the industry is clearly concerned. A similar intensity of debate has not been observed in Australia; there have been no significant changes in the market for *BRCA* testing and no zealous calls for law reform. This probably reflects the low level of pre-*D'Arcy* gene patent enforcement activity (100). In Canada, pressing concerns have been solved by negotiation. Whether innovators headquartered outside the United States now have a comparative advantage because they can obtain broad, local patent rights is yet to be determined.

Arguably, postgrant solutions may have been more effective in addressing the gene patent problem. The United States lacks a statutory experimental use exception to patent infringement, and there is limited scope for reliance on a common-law exception following the Federal Circuit decision in *Madey v. Duke University* (85, p. 1362). The United States also lacks statutory provision for compulsory licensing of patents for failure to adequately work the underlying inventions. By contrast, statutory provisions for exemption from infringement for experimental use and for compulsory licensing are found in the legislation of EPC member states (75, 126, 130, 134), China [Patent Law of the People's Republic of China, art. 48–58 and 69(4)] and Australia (Patents Act 1990, Act No. 83, §§ 119C, 132B–36M, and 163–70), albeit in varied circumstances. Across Europe, for example, there is considerable variability in the operation of these provisions (135). Canada, while lacking a statutory experimental use exception, has a broader common-law exception than the United States (92, 125). However, it has only limited provision for compulsory licensing in its Patent Act of 1985, solely for international humanitarian purposes to address public health problems (§ 21). Had the US patent statute included provisions akin to those in some of the other jurisdictions we have considered in this review, some of the fuss about gene patents could perhaps have been avoided. We are not alone in thinking that it is timely for these postgrant options to be reconsidered (34). Relying primarily on the blunt tool of patent eligibility has its risks. As the authors of the recent study on the impact of *AMP* on patent prosecution, referred to above, state, the "results are a reminder of how an ostensibly crisp legal decision can have unexpected impacts well beyond what was in mind when the change was made" (1, p. 1149).

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