DNA patents and diagnostics: not a pretty picture

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Restrictive licensing practices on DNA patents are stymieing clinical access and research on genetic diagnostic testing. Diagnostic companies, university tech transfer offices and their respective associations need to pay more attention.

Four decades after the US Supreme Court first held that an artificially created bacterium had the potential to be patented in the United States[1], biotech patents continue to generate controversy—particularly human gene patents used in diagnostic testing. The persistence of the debate can be attributed to particular business models for genetic testing and university licensing that, despite public pronouncements to the contrary, have failed to acknowledge and appropriately address the real social and economic concerns raised by clinical geneticists, health care professionals, patient groups, politicians and academics. Their failure has led both policymakers and the courts to express increasing concern about broad patent rights over human genes that affect diagnostic testing.

Myriad Genetics has been the poster child for controversial DNA patent licensing.

The most recent flare-up in the ongoing DNA patent and genetic testing debate is the decision of the US District Court for the Southern District of New York in *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*[2]. On 29 March, US Federal District Court Judge Robert Sweet ruled that isolated DNA is not patentable in the United States, and also that Myriad Genetics' (Salt Lake City, UT, USA) method claims relevant to testing for *BRCA1* and *BRCA2* genes are invalid. Essentially, the District Court held that neither isolated DNA nor cDNA is sufficiently different from DNA as it occurs within host cells to be considered an invention. As for the diagnostic tests, the court held that they simply involved drawing a mental correlation between facts, something that does not fall within the scope of what is patentable.

A week earlier, the US Court of Appeals for the Federal Circuit held in *Ariad Pharmaceuticals, Inc. et al. v. Eli Lilly and Company*[3] that a researcher must do more than identify that a class of compounds has a certain effect: he or she must actually describe what those compounds are. This effectively eliminated the award of patents over basic research, requiring, instead, that the inventor "actually perform the difficult work of 'invention'—that is, conceive of the complete and final invention with all its claimed limitations—and disclose the fruits of that effort to the public."

One month before that, on 10 February, the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS; Bethesda, MD, USA) at the US Department of Health and Human Services[4], after a careful study of current knowledge on the effects of patenting genes on research and accessibility to genetic tests, found that there is no convincing evidence that patents either facilitate or accelerate the development and accessibility of such tests. What's more, the committee

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found that there was some, albeit limited, evidence that patents had a negative effect on clinical research and on the accessibility of genetic tests to patients. In addition, most gene patents relevant to diagnostics are held by universities on the basis of research funded by public money. In this context, the committee recommended that universities be more cautious in patenting and licensing human genes, that there be more transparency and accountability for university licensing practices and that an existing exception protecting medical practitioners from patent infringement when they undertake surgery or treat a patient's body be extended to include the provision of genetic diagnostic testing.

What all three developments have in common is that they reflect growing disenchantment with the patenting and licensing practices of universities and industry. These concerns have existed for over a decade without resolution[5,6]. The maturity of microarray technology that allows for multi-allele genotyping and now the prospect of full-genome sequencing deepen these concerns[7]. A legacy of exclusively licensed gene patents casts a shadow of patent infringement liability over the future of multi-allele testing and full-genome analysis.

In an attempt to better understand why concerns about DNA patenting persist and what role universities play as patentees and often exclusive licensors, this article outlines university technology transfer practices and business models that have given rise to the concerns. After outlining the practices that have given rise to concerns about the patenting of human genes for diagnostic genetic tests, we review past efforts attempting to address concerns. We then lay out the obstacles to addressing these concerns going forward, including a lack of recognition that diagnostics is a highly unusual market—and that the problem is not so much a legal question or necessarily about what gets patented, so much as how patents are licensed and enforced by both universities and industry. The ability to change these restrictive licensing practices, will, in turn, depend on several factors: first, a sharper definition of what constitutes research that needs to be protected in licensing provisions; second, more coherent university policies that promote broad dissemination, along with incentives for industry compliance with best practices; third, greater recognition of problems and the proposal of constructive solutions by key players; fourth, transparent reporting of DNA patents and diagnostic testing license agreements; and fifth, secure funding for technology transfer offices. Although legislative change may ultimately be necessary to facilitate these changes in practice, many problems can be addressed without statutory change.

A legacy of short-sighted tech transfer and business practices

Currently, universities frequently file patents on early-stage inventions[9], and license patents exclusively half the time[10–13]. A study by Mowery *et al.*[10] notes the following: "A relatively high fraction of all inventions that are licensed—as high as 90% for UC [University of California] licenses and no less than 58.8% for Stanford licenses of 'all technologies' during this period—is licensed on a relatively exclusive basis, and these shares are similar for biomedical inventions." Many of those licenses will endure for many years, including licenses on university patents relevant to DNA diagnostics.

Universities and academic medical centers that provide diagnostic testing services face private genetic testing companies that enforce patents against university genetic testing services and national reference laboratories[5]—in contrast to the situation for therapeutics, where universities are often the plaintiffs. The story often begins with publicly funded academic or nonprofit research that is either patented and licensed exclusively to a private company or forms the basis for a spin-off company that attracts further investment and develops an invention that is patented. Whether exclusive licensees or spin-offs, these companies then develop genetic testing services based on a business model that relies not only on patenting sequences and mutations—not objectionable in itself—but also on preventing other institutions, including universities from offering those genetic tests.

The case of Myriad patents over *BRCA1*, *BRCA2* and methods for diagnostic testing[14], as well as Athena Diagnostics' exclusive licenses for clinical testing from Duke University (Durham, NC, USA) over three method patents related to diagnostic testing for Alzheimer's disease[15,16], exemplify these practices and business models.

Furthermore, other neurological and metabolic conditions, as well as other entities' screening for Canavan disease, hemochromatosis and other single-gene conditions, has also generated fierce debate. In the case of Canavan testing, litigation resulted from licensing restrictions that inhibited freedom of action among those seeking to get genetic tests.

In the case of Myriad, initial research took place at the University of Utah—with public funding from the US National Institutes of Health (NIH; Bethesda, MD, USA). The researchers then spun off Myriad, which attracted investment from Eli Lilly (Indianapolis, IN, USA) and succeeded in patenting *BRCA1* and a diagnostic test for breast cancer (patents that were ultimately jointly assigned to the University of Utah, Myriad and the NIH). Rather than licensing out the test to clinical geneticists and laboratories around the world, Myriad required initial testing in each family to be performed at its laboratories in Salt Lake City. In the United States, the company sent out cease-and-desist letters to laboratories—both academic and commercial—already performing tests when the patent was issued.

Threatened patent enforcement resulted in a backlash around the world from public laboratories, clinicians, molecular geneticists and some patient groups—against both the patenting of human genes and what they viewed as Myriad's strong-arm tactics. These groups feared that by closing down public laboratories, Myriad would thwart research identifying weaknesses in Myriad's test or distinguishing the effects of different mutations in the genes on disease severity or progression, and prevent the integration of breast and ovarian cancer genetic tests into genetic health services. Although some of these fears were clearly exaggerated, Myriad's aggressive initial patent enforcement affected practice in the clinical genetics community and stirred long-standing resentment. Furthermore, in countries with public health care systems, health administrators objected to Myriad's business model because it removed their ability to deploy genetic tests to their citizens in the manner that they viewed as most efficient[14].

Myriad always permitted what it considered to be basic research on *BRCA1* and *BRCA2*, and also engaged in research collaborations. In fact, until 2004—after which Myriad ceased to do so for unknown reasons—the company contributed data to public databases. To illustrate Myriad's openness to others performing basic research using *BRCA1* and *BRCA2*, the company's president, Greg Critchfield, has identified 7,000 papers published by independent authors that mention *BRCA1* or *BRCA2* (http://docs.justia.com/cases/federal/district-courts/new-york/nysdce/1:2009cv04515/345544/158/0.pdf). This indicates that, with the exception of clinical testing at the University of Pennsylvania in 1998, Myriad did not pursue those who conducted research. Myriad also defined the University of Pennsylvania's testing as 'commercial', as later defined under the terms of a 1999 Memorandum of Understanding with the US National Cancer Institute (NCI: Bethesda, MD, USA). Myriad has been successful in arranging for payment agreements with insurers and other payers. However, as a result of Myriad's enforcement actions coupled with broad patent claims, its fairly narrow conception of what constituted acceptable research and its failure to clearly state that it would not pursue those conducting such research, university and private laboratories ceased to offer the test publicly

in the United States. Outside the United States, resistance to Myriad's model—particularly from health care administrators and government departments—caused the company to lose most of its market. Furthermore, Myriad's relationship with scientists and policymakers around the world was seriously damaged[14].

Although the biotech industry tried to portray Myriad as an outlier, a series of detailed case studies conducted by some of us (J.C., S.C., M.A. and R.C.-D.) and others[15,18–24] at Duke University's Center for Genome Ethics Law and Policy reveal that, in fact, Myriad's business model is not unique. As these studies show, diagnostic companies such as Athena Diagnostics (Worcester, MA) and PGxHealth (New Haven, CT) have adopted similar or even more aggressive business models and have shut out university laboratories from offering genetic testing for diseases such as long-QT syndrome and Alzheimer's disease. In the case of Alzheimer's disease, genes and method patents for diagnostic testing were initially patented by Duke University (and other academic institutions) and licensed exclusively to Athena Diagnostics. Athena Diagnostics then used its patents aggressively to prevent others from carrying out the test.

These case studies strongly suggest both that universities are often not managing research and patents in a way that promotes dissemination and that companies deploy their patents or exclusive licenses to remove genetic testing laboratories at academic health centers and low-margin national reference laboratories from the market. This is demonstrably a viable business model, or at least it has proven to be until recently—but is it good national policy, and does it add value to the national health system? As clinicians and laboratory directors react to cease-and-desist letters by withdrawing from those activities, clinical research and genetic testing are impeded. GeneDx (Gaithersburg, MD) and university laboratories ceased testing for the life-threatening long-QT syndrome after patent enforcement in 2002, for example, but no commercial test entered the market until 2004 (ref. 9); neither the University of Utah (which held the patents) nor the NIH (which could have been petitioned to march in, given that 'health and safety' needs were not being met) took action. Certain tests may not be offered if the patent holder or exclusive licensee does not provide them; second-opinion and verification testing may be unavailable; and tests are costly to public and private payers, sometimes prohibitively so for those lacking insurance[25,26]. Although negative effects on price and access to genetic testing are not uniform, consistent or pervasive, one cannot read the case studies as a whole without realizing there are real problems—and also that there are relatively easy solutions modeled on nonexclusive licensing, as used for Huntington's disease and cystic fibrosis testing. Gene patents over diagnostics are not just like all other patents, and the diagnostic market is not just like markets for therapeutics and instruments. Holders of gene patents need to take care in licensing them for diagnostic use.

Hurdles to resolution of concerns

The past decade saw a plethora of policy reports about DNA patents, such as those from the Nuffield Council on Bioethics[17], the US National Academy of Sciences[27], the Ontario Ministry of Health[28] and the Australian Law Reform Commission[29]. Academic articles examined the concerns, the extent to which concerns were founded and the roles of industry, universities and legislative reform in addressing these concerns[5,6,26,30–38]. Some countries also made statutory changes to their patent and health laws. France expanded compulsory licensing laws[39], and Belgium did the same, also carving out a diagnostic-use exemption from patent-infringement liability[40]. The US Patent and Trademark Office (USPTO; Washington, DC) developed guidelines on 'utility' and 'written description' specifically for examining gene patent applications[41].

In addition to evidence that gene patents covering diagnostics do not necessarily impede research, there is very little evidence of patent litigation in the field.

Recognizing that many of the concerns could be addressed through better licensing practices, many institutions also developed licensing guidelines, some aimed at universities and others at industry. These include the NIH's *Best Practices for the Licensing of Genomic Inventions*[42], the Organisation for Economic Cooperation and Development's (OECD; Paris) *Guidelines for Licensing of Genetic Inventions*[43] and *In the Public Interest: Nine Points to Consider in Licensing University Technology*[44], a document crafted by 12 institutions and subsequently endorsed by the Board of Trustees of the Association of University Technology Managers (AUTM; Deerfield, IL, USA). Since then, ~50 other institutions and organizations have also endorsed the guidelines. In November 2009, as part of AUTM's Global Health Initiative to promote licensing practices that facilitate access to essential medicines in developing countries, AUTM also endorsed a document entitled *University Principles on Global Access to Medicines*[45]. Most recently, the SACGHS recommended the implementation of an exception to patent-infringement liability for research use and diagnostic testing[4]. All of these reports and recommendations focus on broad dissemination through nonexclusive licensing of gene-based inventions, particularly for publicly funded research. They reserve exclusive licensing for situations in which it is needed to induce investment in private-sector development to bring a product or service to fruition—which, as will later be discussed, is rarely the case for genetic diagnostics.

Despite the plethora of policy reports, academic articles, guidelines and legislative changes, concerns about DNA patents persist. We must therefore turn our attention to factors that impede changing the system.

A question of law or of practice. The first response to concerns is often a call to change patent law[39,46,47]. As recent research indicates, however, the central problem does not lie with patents over human genes themselves so long as the law incorporates the appropriate checks and balances. The recent suit challenging Myriad's patents on *BRCA* genes notwithstanding[2], the following discussion indicates that there is little evidence on which to conclude that limiting the ability to patent genes is the only way to solve the problems in the system.

A recent study by Huys *et al.*[48] from Belgium suggests that relatively few claims in gene patents block competing laboratories from providing genetic tests. This study of 145 active patent documents (267 independent claims) related to genetic diagnostic testing of 22 inherited diseases (including method claims, gene claims, oligo claims and kit claims) that the European Patent Office (Munich, Germany) and the USPTO issued. It concluded that clinicians could easily get around 36% of claims and could, with work, circumvent another 49% of claims. Only 15% of claims would be difficult or impossible to circumvent. Of the gene claims studied, only 3% were found to be blocking. However, as discussed below, blocking claims were more prevalent among method claims.

In addition to evidence that gene patents covering diagnostics do not necessarily impede research, there is very little evidence of patent litigation in the field. A recent study[8] on trends in human gene patent litigation notes that there is rarely any litigation over diagnostic tests arising from gene patents. This study identified only 31 examples of litigation over human genes in the United States from 1987 to 2008. Although the low frequency of litigation

could hypothetically support the conclusion that patents successfully exclude others (that is, threatened patent enforcement stops potentially infringing activities), an examination of patent claims suggests that most patents over human genes and related diagnostic tests find themselves in a relatively weak legal position. This weak legal position is further reinforced by the dissent in *Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.*[49], which concluded that a natural correlation between two substances in the body was an unpatentable product of nature (the majority decided not to address the issue); by the United States District Court decision in *Association for Molecular Pathology et al. v. the United States Patent and Trademark Office et al.*; and by the general trajectory of recent decisions on assessing damages, the lack of automatic injunctive relief (*eBay Inc v. MercExchange, L.L.C.*[50]), as well as by the increasing ambit for finding an invention to be obvious under patent law. The recent US Supreme Court decision *In re Bilski*[51] only exasperates the uncertainty over method claims on DNA diagnostics. In fact, an eventual appeal from the District Court decision in *Association for Molecular Pathology et al. v. the United States Patent and Trademark Office et al.* may be required to determine whether these type of claims are valid.

Adding to the trend in legal thinking is the Federal Circuit's decision in *Ariad*, relating to claims based on DNA patents, where the court writes: "Much university research relates to basic research, including research into scientific principles and mechanisms of action…, and universities may not have the resources or inclination to work out the practical implications of all such research [i.e., finding and identifying compounds able to affect the mechanism discovered]. That is no failure of the law's interpretation, but its intention. Patents are not awarded for academic theories, no matter how groundbreaking or necessary to the later patentable inventions of others."

That research hypotheses do not qualify for patent protection possibly results in some loss of incentive, although Ariad presents no evidence of any discernable impact on the pace of innovation or the number of patents obtained by universities. But claims to research plans also impose costs on downstream research, discouraging later invention." Taken together, these studies and cases indicate that gene patents *per se* have closed off far less of the research landscape than is often supposed, and where expansive claims have been granted, many are vulnerable to challenge.

Method claims in patents related to diagnostic testing, however, bear special mention. Although many pharmaceutical patents claim products as chemical entities, universities and biotech firms also tend to patent ways of using knowledge, including method patents that affect genetic tests. In fact, Huys *et al.*[48] conclude that 30% of method claims relating to genetic testing are difficult, if not impossible, to circumvent. Such claims tend to be broad, often to the point of vagueness, and many cover all conceivable ways to conduct genetic tests on a gene or for a clinical condition. In the 15 of 22 conditions that Huys *et al.*[48] found had at least one blocking claim, most such claims were to methods. In the diagnostic realm, blocking patents thus appear to be common, present in 68% of the clinical conditions studied. Changes in jurisprudence could reduce the number of truly blocking patents in genetic diagnostics.

Recent and pending court decisions suggest that some fraction of broad claims in US patents on DNA sequences and methods pertinent to genetic diagnostics would be judged invalid if challenged. Although dealing with a patent claim in the information technology field, the recent US Court of Appeals for the Federal Circuit decision in *In re Bilski* narrowed criteria for patents on methods to inventions that entail a transformative step or involvement of a particular machine. Depending on how the Federal Circuit deals with the US Supreme Court in *Bilski*—perhaps in an appeal in the Myriad case—it could signal that broad method claims in DNA diagnostics might be held invalid because the link between a mutation and a probability of contracting a disease may be considered unpatentable. As it stands, many broad method claims pertinent to DNA diagnostics suffer under a cloud of uncertainty and may turn out to be invalid, thus dramatically increasing freedom to operate without fear of patent-infringement liability. Other recent US court decisions have moved in the same direction, increasing the stringency of criteria for nonobviousness[52,53] and written description[3].

Taken as a group, these decisions suggest that some of the potential obstacles to innovation that patents cause in diagnostics may not be as high, nor the amount of intellectual territory enclosed and enforced as expansive, as some had feared. A clear research exemption, a simplified method for challenging patents (for example, opposition proceedings or *inter partes* re-examination requests) and improved examination procedures to avoid overly broad patent claims could help quell concerns over blocked research and overly broad patents[54]. Overall, the problem does not lie wholly in patent law but rather concerns how decisions are made about what is patented (methods versus products) and how patents are managed and used. With one or a few successful challenges to broad patents enforced for diagnostic purposes, the business models of enforcing monopolies on genetic testing for specific conditions would probably give way to more cross-licensing, more competition and faster innovation in testing methods.

A need for changes in patent licensing practices at universities. As patent law evolves, it is increasingly apparent that the exclusive licensing strategies of universities and the business models of a few companies doing DNA diagnostics are as much, or even more, of an impediment to DNA diagnostics as any problems with the law. Meanwhile, no evidence suggests that exclusive licensing is as important in the field of diagnostic testing as in therapeutics in creating products that would not otherwise exist. The exclusive licenses over erythropoietin, growth hormone, interferon and other therapeutic proteins are of commercial significance, as illustrated by the fact that eleven legal cases that presume the validity of gene patents have been decided by the US Court of Appeals for the Federal Circuit[8]. The same cannot be said for diagnostic testing: no exclusive license in this field has been deemed to be of such importance for anyone to take to court. In fact, most cases involving diagnostic testing are settled after initial notification letters or cease and desist letters are sent out. A handful have led to litigation, but settled early. The Federal District Court's ruling of 29 March in *Association for Molecular Pathology et al. v. the United States Trademark and Patent Office* is the first diagnostic case to go before a judge for a decision. Furthermore, barriers to entering the market with a new genetic test, at least for the first-generation genetic tests that search for mutations in one or a few genes, are far lower than for therapeutics. This is because for universities and national reference laboratories that already offer other genetic tests, the cost of 'setting up' a new genetic test based on data in scientific publications is comparable to the cost of patenting the underlying inventions since they are already laboratories approved by US regulators.

Supporting this proposition is the fact that exclusive licensing does not appear to have been necessary to get a test to market in any of the cases[15,18–24] studied for SACGHS. In the study of 10 clinical conditions considered by SACGHS, three cases did not involve patent rights (i.e., there were no patents or patents were not licensed or enforced) or patents were nonexclusively licensed to multiple providers.

These were cystic fibrosis, hereditary colorectal cancer and Tay-Sachs disease. Such patenting and licensing practices comply with current guidelines. In six cases, however, exclusive licensing led to patent enforcement that

reduced availability of genetic tests already being offered: *HFE* (hemochromatosis), *APOE,* Alzheimer's disease and genes associated with Canavan disease, long-QT syndrome, hearing loss and spinocerebellar ataxias. Because tests were already available, exclusive licensing in these cases deviates from the norms that technology licensing offices generally claim to be following. In some cases, but not all, this led, at least transiently, to genetic testing by a single provider, and that exclusive license holder then eliminated other testing services that had beaten it to market. In all cases except hemochromatosis, exclusive licenses from universities were involved. Although the exclusive licensee may ultimately have developed a better test, in no case was the exclusive licensee the first to market. The tenth clinical condition studied by the SACGHS, hearing impairment, is subject to a hybrid of exclusive and nonexclusive licensing, and entails many genes and different means of testing. This case does have some examples of controversial patent enforcement action, but tests are generally widely available from several vendors.

Patent incentives may induce investment in genetic diagnostics, but in none of the case studies did this lead to new availability of a test that was not already available, at least in part. This is in stark contrast with the role of patents in therapeutics and scientific-instrument development, where the benefits attributable to private R&D and new products are much clearer. The SACGHS case studies thus reinforce the benefits of licensing nonexclusively for genetic diagnostics, unless an unusual situation arises in which exclusivity is needed to get a product to market for the first time. The cases also highlight deviations from the NIH *Best Practices*[43], OECD *Guidelines*[43] and the AUTM-endorsed *Nine Points*[44]. Exclusive licensing practices consistently reduce availability, at least as measured by the number of available laboratories offering a test, and thus reduce competition in genetic diagnostics, but with little evidence of a public benefit from services not otherwise available.

Instead of recognizing this reality, some universities continue to seek broad patents regardless of subject matter and then license exclusively, enabling business models that impede competition in genetic testing. Although the real risk of being successfully sued for patent infringement in DNA diagnostics may be low, a 2003 survey[33] and recent case studies[14,15,18–24] indicate that laboratory directors change their testing practices and clinicians avoid research areas in reaction to cease-and-desist letters. Diagnostics are generally low-margin sources of revenue, and when faced with a threat of patent enforcement, most laboratories simply stop offering a genetic test, or at least no longer advertise a test's availability publicly (in all the case studies, we learned of 'research' testing as an 'escape valve' for patients who could not get or could not afford commercial genetic tests). Although part of the problem is that licenses executed over the past decade do not embody the principles of the NIH, OECD or AUTM guidelines and yet remain in force, the reality is that only a minority of universities have endorsed the consensus *Nine Points*[44]—with no repercussions for those who do not or those who sign and then violate the norms. Shortsighted licensing practices persist.

Potential solutions

Changes that could remedy problems with the current strategy of the licensing system include the following: first, a clear definition of research that should be exempt from patent-infringement liability; second, universities' leadership in promoting the alignment of tech transfer licensing practices with the univeristies' broader goal of dissemination; third, coupling of the latter with incentives to promote industry compliance and leadership by AUTM and the Biotechnology Industry Organization (BIO; Washington, DC) in recognizing problems and proposing constructive solutions; fourth, adequate funding for tech transfer offices to learn about and implement changing practices; and finally, greater transparency in reporting patent holdings and licensing agreement terms. A more detailed discussion of each of these follows.

Defining what qualifies as research. Although most industries tolerate a broad range of research activities and most researchers ignore patents when deciding whether to do research[55], such blithe ignorance is not an obvious option in human genetic diagnostics, where threatened enforcement is common, laboratory directors and clinicians tend to respond to threatened enforcement by ceasing the activities under threat and workaround in the case of method patents are not always available[48]. Norms over what research is to be tolerated are unsettled, despite the existence of research exceptions[56] in many national laws (including an exemption in the United States for research into products that may eventually lead to the filing of an application with the US Food and Drug Administration (Rockville, MD)[57]).

One prominent example of disputed norms is the controversy between Myriad and the University of Pennsylvania Genetic Diagnostic Laboratory (GDL; Philadelphia, PA). Although Myriad states that it is generally supportive of research, it nevertheless sent GDL a cease-and-desist letter because it did not consider GDL's activities to be research. To Myriad, GDL's provision of testing services to researchers was commercial, not a research service[14]. GDL took the position, however, that its activities, which supported others' research, fell within the norm of tolerated research use, and much of the contested testing was part of clinical trials funded by the NCI, which is clearly clinical research. Much debate ensued, leaving many researchers with the (wrong) impression that Myriad would not tolerate any form of research.

In an attempt to establish a clear norm over the question of which activities should be considered 'research', Myriad entered into a Memorandum of Understanding with the NCI to provide at-cost or below-cost testing to the NCI and any researcher working under an NCI-funded project. Myriad also similarly offered to provide NIH researchers with at-cost testing, given that the NIH was a co-owner of some of the relevant patents. Importantly, the agreement with the NCI defined the type of research Myriad would tolerate as being "part of the grant supported research of an Investigator, and not in performance of a technical service for the grant supported research of another (as a core facility, for example)." Furthermore, testing services had to be paid for out of grant funds and not by a patient or by insurance. Under this definition, GDL was not conducting research. This agreement was acceptable to both parties (Myriad and the NCI), and given the 'at-cost' provisions and the known efficiency of Myriad in testing, perhaps it is a salutary precedent. It is worth noting, however, that the NCI did not seek to delegate its government use rights under the Bayh-Dole Act 35 U.S.C. § 200-212 ("Bayh-Dole Act") or Stevenson-Wydler Act 15 U.S.C. 3701 (which pertain because Myriad's patents include inventors covered by both laws).

The restricted nature of the Myriad-NCI Memorandum of Understanding limits its value as a precedent. It covered only the provision of services by Myriad; it did not address the general question of which research practices a patent holder should tolerate in the diagnostics field. Some of the conflict surrounding patents and genetics laboratories could be avoided by adopting a clearer definition of 'research' for the purposes of incorporating licensing terms that lower the threat of patent-infringement liability. The scope of government use rights under the Bayh-Dole and Stevenson-Wylder Acts is another legal gray zone. In any case, the definition of research should not be left to the individual negotiation between one company and one NIH institute. The NIH could take on a key role in developing this norm by convening a meeting of interested parties to develop

the principles by which individual actors can determine how to apply the norm.

University leadership. Implementation of licensing guidelines and best practices is difficult when interests and goals are not aligned. Participants at a workshop held at Duke University in April 2009 addressed the role of universities in DNA patents and diagnostic testing and noted that those at the front line of implementing these guidelines, tech transfer offices, face many hurdles to implementation. Many university administrators view patents as a means to secure revenues (to subsequently reinvest in research) and believe that exclusive licenses generate the most revenues. Although the evidence[58] is quite clear that most tech transfer offices either break even or lose money and that many of the most lucrative university patents have entailed nonexclusive licensing, this view persists. Compounding this problem, universities expect tech transfer offices to generate sufficient revenues to be sustainable. Despite usually being unrealistic, such expectations can lead these offices toward licensing strategies that promote short-term income over dissemination and broad availability.

If there is to be a change of behavior, it must come from two sources: first, university administrators must align tech transfer strategy with the university mission of broad knowledge dissemination; and second, universities should provide more push-back when threatened patent enforcement gets in the way of research and impedes the university's central mission. Regarding the first point, university presidents and senior management must take seriously the university mission to disseminate knowledge and technology. They must consider technology transfer as one component of their strategy to enable the wider world to access, enjoy and use university-generated knowledge. To achieve change, they need to change the way they fund tech transfer offices so that the latter have the freedom to explore alternatives to the way they currently license out technology. They also need to develop clear goals for dissemination and ensure that they impose measures of success for their technology licensing offices that correspond to those goals. Expecting technology licensing officers to forgo exclusive licenses when companies seek them is unrealistic unless the officers are rewarded for decisions that acknowledge the broad social benefit of avoiding patent thickets in genetic diagnostics. Recognition must also be given to the fact that these offices do not negotiate licenses in a vacuum: they negotiate largely with industry partners. If diagnostic companies are unwilling to accept nonexclusive licenses, broad research exemptions or other terms that universities propose to support research, tech transfer offices have little room to maneuver. Currently, there is no incentive—whether external or through the threatened use of government march-in rights under the Bayh-Dole Act—to curb industry behavior even when it is problematic. Tech transfer departments with limited funding, limited staff and unreasonable expectations to be sustainable cannot be expected to resist intransigence by licensees.

Universities need also to take a lead in encouraging their researchers, clinicians and laboratory directors to push back when threatened with patent enforcement. University administrators need to educate themselves and their staff about the freedom to operate for purposes of research and improving diagnostic testing—that is, the scope of activities allowed that do not infringe on a valid patent. University administrators, researchers, clinicians and laboratory directors can act together by sharing cease and desist letters or other patent enforcement actions to determine whether the activities are, in fact, infringing. They can share expertise about the validity of patent claims that threaten research or clinical testing. Although individual laboratories may lack the resources to conduct these analyses, other institutions may have the requisite resources (for example, the American Society of Human Genetics, the American College of Medical Genetics, the College of American Pathologists and academic units such as the science policy research units at the University of Sussex in Brighton, UK, and the University of Leuven, Belgium).

> Implementation of licensing guidelines and best practices is difficult when interests and goals are not aligned.

Leadership from AUTM and BIO. The development of a 'gene patent supermarket' by Denver firm MPEG-LA is a promising step toward enabling nonexclusive licensing, increasing simplicity and consistency in licensing terms, and reducing transaction costs[59]. Unfortunately, instead of proposing such constructive solutions, BIO and AUTM have chosen not to acknowledge the real problems that exist in the unusual market for genetic diagnostics and have been quick and vociferous in their opposition to the recommendations of the SACGHS[60,61]. It is impossible to judge the full extent of the problems, but it is certainly poor policy to deny that they exist at all. Moreover, BIO and AUTM have expended time and resources opposing SACGHS recommendations while failing to enforce the established norms laid out by the NIH and the OECD, as well as the AUTM-endorsed *Nine Points*, among their respective constituencies. Companies and universities that violate those norms have faced no action, or even recognition that they have deviated. Indeed, there has been no public statement from either BIO or AUTM that members have been responsible for some of the problems uncovered in licensing practices for genetic diagnostics. It is reasonable to disagree with the SACGHS recommendations, but it is not reasonable to read the SACGHS report and the case studies prepared for it and conclude that the system is working well across the board. BIO and AUTM should recognize the very real problems that have been uncovered, exhort compliance with established norms and—even more importantly if such norms are to be meaningful—criticize deviations from them, rather than following the politically expedient tactic of focusing their fire on SACGHS recommendations intended to prevent these problems.

The two most controversial SACGHS recommendations are, first, a proposed exemption from infringement liability for research use, and second, a similar exemption for diagnostic use. As previously noted, university licensing offices opposing a research exemption puts them at odds with their own stated principles, as licensing to ensure freedom to do research appears in every document proposing norms for licensing. Opposition to a diagnostic-use exemption is more understandable because it may be that there are unusual situations in which exclusivity is needed to get a product or service to market, and such situations simply have not been captured in the cases studied to date. Nevertheless, it is quite clear that in many if not most cases of genetic diagnostics, the main use of exclusive licenses from universities has been to reduce competition and reduce the number of laboratories offering tests, without apparent benefits of introducing tests that were not already available. Rather, tests would demonstrably have been available even without the participation of the companies involved.

The SACGHS may have judged that tech transfer offices are failing to respect existing norms, and in the absence of any credible compliance measures, the simplest legal solution is to address the problem through exemption from infringement liability. If AUTM and BIO want to preserve the option of exclusive licensing when needed to get genetic tests to market, then compliance with guidelines needs to be credible. Criticizing deviations when

they come to light, with the long-term goal of increasing compliance with stated norms, would go a long way toward reducing the need for a diagnostic-use exemption. Moreover, enforcing nonexclusive licensing norms can preserve revenue streams, as seen in the cystic fibrosis and Huntington's models, whereas a diagnostic-use exemption would eliminate those revenues because the patents would be unenforceable for diagnostic uses.

One could object that it is neither the function nor the responsibility of either BIO or AUTM to criticize their members. BIO is an industry lobby group that sees itself as "the champion of biotechnology and the advocate for its member organizations," whereas AUTM is an association of individuals working in tech transfer that seeks "to support and advance academic technology transfer globally." Developing and enforcing patenting and licensing policies fall within neither mandate. This argument is, however, disingenuous, given that both AUTM and BIO claim to be working to ensure that tech transfer serves the public good. It is just as important to reduce practices that fall short as to promote practices that achieve the goals of their respective constituencies. Both organizations have endorsed the *Nine Points* guidelines and actively promote technology transfer "in a manner that is beneficial to the public interest" (http://bio.org/ip/techtransfer/) while "improving quality of life, building social and economic well-being, and enhancing research programs" (http://betterworldproject.org/tech_transfer.cfm). Having voluntarily taken these positions, both organizations should be held accountable for them.

Increasing transparency to permit 'system learning'. To promote change, university-industry relationships need to be more transparent; indeed, the current opaqueness over existing university-industry interactions is a major hurdle to improving the intellectual property system for DNA diagnostics[11]. For example, license agreements between universities and start-up and private companies are unavailable, even in general terms. The only exceptions are universities or companies that voluntarily make such information public.

Participants at the workshop on the role of universities in DNA patents and diagnostic testing held at Duke in April 2009 noted that most licensing information is not publicly available, even for inventions arising from public funding. In some cases, but only some, it is possible to reconstruct licensing terms from company annual reports or from press announcements. There is often no way for researchers and institutions to know what practices a license covers, whether there remains scope for others to practice an invention, which regions it covers and whether it applies to any specific fields of use or contains special restrictions. The lack of information makes it difficult to substantiate claims that licensing practices are changing or comply with best practices. As a study[11] on university licensing practices notes, simply stating whether a license is exclusive or nonexclusive misses important nuances. Not only would more transparency help researchers better understand the scope and ownership of intellectual property rights, it would also allow policymakers, academics and tech transfer offices to determine in what cases exclusive licensing is justified, as opposed to enforcing a blanket norm of nonexclusive licensing.

Although under provisions[62] of the Bayh-Dole Act, all recipients of federal grants must report on activities involving the disposition of certain intellectual property rights that result from federally funded research, the information is incomplete and cannot be obtained because of strictures on access to the data. A clause of the legislation was intended to protect proprietary data from public access through the Freedom of Information Act 35 U.S.C. § 202(c)(5). The way the implementing regulations were written, however, went well beyond this, and gave licensees veto power over nongovernment disclosure of information. Tech transfer offices file reports with the interagency Edison (iEdison) database when they license inventions supported by most government funders. The reporting requirements do not require the disclosure of the licensing terms, and what is reported to iEdison is not publicly available. Indeed, access to iEdison is highly restricted; the database is unavailable for study or use outside government, and even government officials wanting to study technology transfer have been denied access unless they get permission from all licensees, a nearly impossible hurdle to overcome.

> Data on patenting and licensing practices are languishing in a government database that is not mined for valuable insights.

Making licensing terms of publicly funded inventions more transparent would require a rewrite of the implementing regulations to change interpretation of the Bayh-Dole Act's confidentiality clause. The confidentiality provision in the Bayh-Dole Act was intended to protect agencies from being forced to disclose proprietary data, but its implementing regulation is so broad that, in effect, it restricts the government's ability to use data without permission of the relevant licensee. Current nondisclosure practices lead to data being unavailable for research aimed at improving knowledge about patenting and licensing practices. Many studies could be undertaken on aggregated reported data, and there are many precedents for using census data, health statistics and other very private information in government databases. The original rationale for the Bayh-Dole Act was that government-owned inventions were languishing for want of effective patent incentives to grantees and contractors; the current problem is that data on patenting and licensing practices are languishing in a government database that is not mined for valuable insights.

On the industry side, there is a somewhat higher standard for disclosure by public companies to protect shareholders. As of 2003, the Securities and Exchange Commission (SEC) requires disclosure of material agreements, including license agreements, as part of SEC filings. Section 401(a) of the Sarbanes-Oxley Act of 2002 (Public Company Accounting Reform and Investor Protection Act of 2002, Pub. L. No. 107-204, 116 Stat. 745) requires the SEC to adopt rules to require each annual and quarterly financial report filed with the commission to disclose "all material off-balance sheet transactions, arrangements, obligations (including contingent obligations), and other relationships of the issuer with unconsolidated entities or other persons, that may have a material current or future effect on financial condition, changes in financial condition, results of operations, liquidity, capital expenditures, capital resources, or significant components of revenues or expenses." In many cases, however, these disclosures are of little assistance in understanding the licensing landscape. The reporting pertains only when a license underpins a genetic test that is a large enough portion of a publicly traded company's business that it needs to be disclosed to investors. Even then, which patents have been licensed under what terms may be disclosed vaguely. Many biotech start-up companies are not publicly traded and are not subject to SEC disclosure requirements. By the time a biotech company goes public, its prospectus may contain some, but only limited, information about licensing agreements. In the usual case of a public company acquiring technology by buying another company, disclosure of the original license may not be required.

Universities argue that if they are forced to disclose the terms of prior licensing agreements, it will undermine their negotiating position with new potential licensees. If, however, public companies must disclose the contents of their license agreements to protect the interests of those funding them (namely, shareholders) as

a matter of public policy, then it is not clear why a university should not be required to disclose the contents of its license agreements to protect those who fund it (namely, the public). The question of human resources needed to ensure transparency is very real and needs to be taken into account, but the principle of public disclosure should be entrenched within public institutions, particularly when the licensed inventions arise from publicly funded research and when data are being collected and reported already. Government and nonprofit research dollars should come with public accountability.

Secure funding of tech transfer offices. As noted above, some tech transfer offices are expected to be self-sustaining and suffer from a serious lack of resources. This situation has several consequences. First, the agreements that these offices pursue will not necessarily aim to promote dissemination but instead will focus first on securing revenues. Second, tech transfer offices lack resources to train managers on implementing guidelines and the particular challenges that different technologies raise. The DNA diagnostic market is complex and rapidly evolving. For example, technology licensing officers need to know that the development of genetic testing after the discovery of the gene requires far less investment than the development of therapeutics, suggesting that exclusive licenses are usually not as necessary[11]. Without a more nuanced and informed understanding of how optimal patenting, dissemination and licensing decisions vary across different types of technologies and uses, these offices cannot fulfill their mandate: transferring technology.

Conclusions

To address the ongoing failure to achieve the goals of the multiple guidelines, policies and even legislation aimed at ensuring continued research on and access to clinical genetic tests, practices within universities and their industry partners must conform to existing guidelines. Although some changes to patent law—such as clearer research exemptions and an opposition proceeding—could be of use, fundamentally the problem is one of strategy about what to patent (products versus methods), how broadly to make claims to early-stage gene-based inventions and how to deploy those patents (broadly versus exclusively). Patents will be properly deployed only when university constituencies unite in promoting broad dissemination, when technology transfer offices are given the necessary financial support and incentives and when universities and industry have transparent and publicly accountable practices for licensing of DNA diagnostic technologies. Industry groups such as BIO and university technology transfer organizations such as AUTM have a crucial and constructive role to play in resolving this predicament. Progress toward addressing the problems in genetic diagnostics can begin with less caustic and unhelpful rhetoric and more focus on engagement with their constituencies on seriously implementing guidelines, as well as with federal advisory bodies such as the SACGHS. By acknowledging and engaging with the distinctive problems that patenting and licensing practices raise for DNA diagnostics, both the universities licensing out technology and the companies licensing it in can bring about real improvement without the need for legislation.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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