



Roundtable on Genetic Diagnostic Testing

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Observations from studies of patenting and licensing practices that affect DNA-based clinical testing

Online Supplement

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Online Supplement: Observations from the SACGHS case studies and other research

This section of my statement is in written form only, and is not part of the written statement submitted to USPTO formally. It is an extended written statement modified slightly from the version made available on the day of the Roundtable (January 10, 2013).

Licensing is as important as patenting

I noted above that we regard the licensing of *CFTR* as a successful model that enabled many different diagnostic approaches to be pursued to test for cystic fibrosis, while also preserving exclusivity for development of gene therapy and possible drugs, as well as humanitarian licensing to enable the *CFTR* protein to be a target for drug discovery for diarrheal diseases.

In many other cases, there were patented genes, but we found very little controversy over how those patents constrained clinical genetic testing. Genes related to Tay-Sachs disease, colorectal cancer, and other conditions have been patented [1-3]. Where patents are either not enforced against diagnostic use (Tay-Sachs) of course there is no conflict. When they are licensed in ways that do not defend a service monopoly (e.g., colorectal cancer, Huntington's disease, cystic fibrosis, hemochromatosis after an initial blip), the patents seem to have generated modest revenues for the owners while not impeding widespread genetic testing using different technical approaches and business models.

Our case studies included several instances in which controversy arose in early efforts to implement genetic testing, but practices then shifted to models that provoked less controversy. Efforts to constrain testing for Canavan disease led to litigation (although not over the gene patents themselves)[1]. This was resolved through a confidential out-of-court settlement whose terms are not known in detail, but we do know that many different laboratories can test for the relevant gene and controversy has died down.

Testing for hemochromatosis and long-QT syndrome were controversial when they were under a service monopoly business model. Controversy in these cases dissipated for different reasons. Hemochromatosis testing shifted to accommodate some nonexclusive licensing, as well as testing "kits" that any laboratory can use (and patent royalties are bundled into the kit price)[4]. In the case of long-QT and other inherited conditions that risk sudden death from cardiac channel defects, PGxHealth's monopoly was broken when GeneDx secured countervailing exclusive rights to a different set of genes relevant to the same phenotype (i.e. cluster of diseases with similar clinical features). Cardiac channel defect testing thus became a duopoly, with quite different pricing practices.

Diagnostic tests are quite different from therapeutics

Until *Mayo v Prometheus* and *AMP v Myriad*, "gene patent" case law was about therapeutics, not diagnostics. Chris Holman has documented how relatively sparse the case law has been, compared to the level of public debate about "gene patents" [5, 6]. The eleven "gene patent" cases that had reached the Court of Appeals (CAFC) before his analysis was

published were not about the patent-eligibility of genes. *AMP v Myriad* is really the first direct approach to that question. That is, the litigation over gene patents underlying therapeutic proteins was over who got the rights, not whether they should be granted at all. *AMP v Myriad* changed that, and in the different context of diagnostics rather than genes encoding therapeutic proteins.

One feature in the debate that has often gotten lost is why the distinction between diagnostics and therapeutics matters for purposes of patent law, and how it plays out in the real world. A patent on a gene that becomes part of a long and complex manufacturing process for a drug (where the trail of human invention is obvious) is quite different from a diagnostic test whose usefulness is completely dependent on accurately capturing the genetic information in a person's cells (whether from a cheek swab, a blood sample, or a tumor biopsy), which is the purpose of most genetic testing.

Very smart and knowledgeable experts disagree intensely over whether the differences in how patents play out in diagnostics versus therapeutics should matter, and if so, whether "patentable subject matter" is the right framework for deciding. *Mayo v Prometheus* established some case law, and *AMP v Myriad* will be decided this summer.

Any process that determines a DNA sequence (for diagnostics, prognostics or other purposes) will, by definition, entail isolating a DNA molecule in order to determine its sequence. There are many ways to "isolate" such a molecule, and some careful scholars conclude that whole-genome sequencing would not infringe [7-9]. I disagree, and read the claims to cover any molecule that is not in its normal cellular context, which is just as true of a whole-genome analysis in a Pacific BioSciences SMRT® sequencer or Oxford Nanopore GridION® or MinION® instrument as other methods that start from selectively amplified DNA. I may be wrong, and of course my opinion does not matter. What matters is how courts, not academics, will interpret patent claims.

The main point is that the answer matters to those making investment decisions and to those who might be engaging in activities, including research, that entail risk of infringement liability. Yet we have no case law to guide such decisions. The corollary point is that the USPTO is granting patent rights that include ambiguous language. This is always a problem for patent claims; it cannot be solved for gene patents any more easily than for other domains of invention, but the uncertainty is particularly prominent in genomics. To the degree ambiguity can be reduced, the system will be the better for it.

Patents are not always necessary to develop tests for Mendelian conditions

Two observations arise from the various ways that gene patents were used in our case studies. First, patents were not always needed to get products onto the market, or to get them there first. In no case that we are aware of was the patent-holder first to get a genetic test to market, and indeed, patents have mainly been used to "clear the market" of competitors already offering a service. Nine labs exited the market for Alzheimer's genetic testing and *BRCA* testing [10]. The enforcement letters emanated from Athena (Alzheimer's) and Myriad (*BRCA*). Myriad's enforcement letters planted the seed for the lawsuit filed in 2009. Four or five laboratories offered testing for Canavan's,

hemochromatosis, Duchenne/Becker muscular dystrophy, spinocerebellar ataxias, and myotonic dystrophy before abandoning such testing under threat of patent enforcement [10]. All those laboratories made the initial investment to develop a test, and by definition had the wherewithal to do so without patent incentives. The argument that the information created by Myriad was the basis for competitors' tests is weak, because it is clear that both *BRCA1/2* would have been discovered fairly quickly without Myriad.

Quashing competition is of course an expected feature of patents, indeed the very purpose, but these cases do show that the barriers to entry for introducing a new genetic test can be fairly low. In two cases, the initial mutations were discovered by companies (Myriad for *BRCA1/2* and Mercator for *HFE* [hemochromatosis]), but in most cases, it is quite clear that the patent incentive had little or nothing to do with the technical ability to introduce a new test, and the test flowed from research, most of it publicly funded (in our studies and others, between 2/3 and 3/4 of patents relevant to diagnostics are held by academic research institutions, and thus mainly based on government or nonprofit research funding) [11, 12]. In the two cases where a company won the race, it is clear the disease-associated gene would have been found soon by others studying families with the disease.

In the case of long-QT testing, patent enforcement proved problematic when there was no test on the market at all for a while, because the patent-holder (at the time, DNA Sciences) did not get a test onto the market for over a year after sending notification and enforcement letters [13].

We also found genetic tests available for many genes that are unpatented (several hearing loss genes, some genes for cardiac defects, spinocerebellar ataxia, Alzheimer's disease), or patented but never licensed (Tay-Sachs) [1-3, 14]. This shows some tests can be developed without patent incentives, but does not show patents are never useful.

Patent benefits do exist

Having said the patents were not necessary historically to get Mendelian genetic tests onto the market, it does not follow that they were not useful or that they were detrimental. Patents were used by some players to develop tests more quickly than would have occurred otherwise. We cannot judge whether the rewards were commensurate with Mercator's (hemochromatosis) or Myriad's (breast/ovarian cancer) discoveries, but the prospect of patents did change the game and induce private R&D.

It is also imprudent to conclude that patent incentives are not relevant to the future of diagnostics based on this history. As biomarkers, multi-gene tests, and other methods are being introduced, the development process is getting expensive and lengthy. Patent incentives may encourage private investment in developing products and services in ways that our case studies did not examine. Indeed, in my opinion, patents probably are supporting private R&D in diagnostics even now, despite the uncertainties about scope and strength of coverage for gene patents. That is partly because patents are not the only business tool, and also because *gene* patents are not the only—indeed often not even the most important—kind of patent useful in developing a new diagnostic product or service.

Patents on combinations of elements, methods, algorithms, or other inventions can protect DNA-based products and services from copying. Gene patents have clearly been important for Athena and Myriad, but it is worth noting that many other companies that do not have big portfolios of “gene patents” are developing DNA-based tests. Foundation Medicine, Ambry, GeneDx, Genomic Health, Agendia, NewGene and dozens of other companies are developing DNA-based tests. Their business models may depend on patents, but different kinds of patents that are not challenged in *Mayo v Prometheus* or *AMP v Myriad*. Indeed, their freedom to operate may be improved if the risk of infringement liability from claims on naturally occurring DNA sequences is reduced.

Another reason to suppose that patents (of various kinds) may be more important for diagnostics in the future is the Food and Drug Administration (FDA). FDA is signaling that it will regulate at least some DNA-based tests, which will require clinical studies as part of pre-market approval. And payers and insurers are moving toward paying for services based on evidence of clinical utility, which again entails funding studies to generate the data used to decide about coverage and payment. Patents are one approach—although just one of many ways—to induce the necessary private investment to produce the requisite data. (Others include data exclusivity, first-mover advantages, and prospect of higher quality or speed of testing.) The alternative to private investment is a system that relies solely on government and nonprofit research to produce new products and services. Clearly this can also work, but it does not so directly “add the fuel of interest to the fire of genius.”

Perhaps it is too obvious to state, but it is quite clear that Athena’s and Myriad’s stockholders, and those holding patent rights in other patent-dependent companies in genetic diagnostics, have created lucrative revenue streams as a consequence of their patent rights. For the past few years, the revenues have generated profits, and that is the very purpose of inducing private R&D investment. The question of whether this is a fair reward, commensurate with investment and risk, and whether it serves to enhance social benefit is mired in irresolvable political disagreement, but one clear benefit is spawning new profitable lines of human activity.

Price effects do exist, but patents are only one factor in pricing

Among the harms attributed to patents, price is often mentioned first. One of the most surprising findings from our case studies was that *BRCA* testing, for which the only commercial testing service in the United States is Myriad, was slightly less expensive *per unit cost* than testing for colorectal cancer. Interpreting this finding has been quite different in the eyes of different beholders. On one hand, the comparison does suggest that patent rights are not the primary driver of price for at least some sequence-based tests; it is quite plausible, however, that the reason for a weak price effect is historical rather than economic. *BRCA* testing more or less set the pace for similar tests that came to market later, and competing services chose not to compete primarily on price when introducing colorectal cancer testing in a medical market where price signals are notoriously confused, complex, and sometimes ineffectual. Price is an indicator of only one form of competition. In a market that is price-sensitive, competition will lower prices, but many medical services are notoriously insensitive to price. Price can be a factor, however, in genetic testing.

When GeneDx entered the market for long-QT testing, it set a price roughly half that of the former sole provider, PGxHealth, for a similar test aimed at the same clinical population [13]. So some price premiums associated with patent-conferred monopolies were detectable even in our limited set of case studies.

Some claims are vulnerable under 102, 103, and 112, not just 101

Deciding what can be patented is one way to narrow the scope of patents, and seems to be the tack taken by the Supreme Court in two recent cases (*Mayo v Prometheus* and *AMP v Myriad*). It is clear, however, that diagnostic patent challenges could be mounted against some of the same patents on different grounds. Claims 5 and 6 of Myriad's composition of matter patent on *BRCA1* (US 5,747,282), if literally interpreted, are clearly vulnerable to invalidation based on novelty, enablement, and written description [15] (see also statement from Thomas Kepler).

Both Athena and Myriad established sole provider standing for some of their tests because of very broad patent rights. The main line of attack on patent breadth has been via patentable subject matter, with *Mayo v Prometheus* addressing method claims and the only remaining point of dispute in *AMP v Myriad* being composition of matter claims on DNA molecules with sequences found in nature. But even without the challenges on patentable subject matter, the USPTO has been granting claims that appear vulnerable under sections 102, 103, and 112 of the patent statute (novelty, nonobviousness, enablement and written description).

The accompanying statement from Thomas Kepler reviews an example of problematic patent claims on short DNA fragments. We noted in a 2010 paper that claims 5 and 6 in Myriad's US patent 5,747,282 face substantial vulnerability on grounds of novelty. Claim 5 reads: "an isolated DNA having at least 15 nucleotides of the DNA of claim 1," where claim 1 specifies any nucleotide sequence that encodes the *BRCA1* protein.

These claims thus cover any DNA molecule that encodes a 5-amino-acid stretch of *BRCA1* protein sequence. On its face, this means any nucleotide sequence that would encode any 5-amino-acid sequence found anywhere in the *BRCA1* protein. Such short fragments are among the few claims that would be infringed by most diagnostic methods (claims 1 and 2 would not be infringed, because no one makes molecules of full-length in hybridization probes or polymerase chain reaction (PCR) amplicon-based diagnostic tests).¹ But any method of genetic diagnosis would entail making a molecule that meets the description of claims 5 and 6, as a DNA molecule would by definition be isolated or its sequence could not be determined. The definition of "isolated" is vague in the definition section of the patent, and "isolate" is used in many different senses in the specification. These claims are at best ambiguous, and on their face would seem to claim molecules that should not be claimed. If

¹ There is a separate, specific claim to PCR (claim 16) that would cover the way Myriad itself does its test, and how most tests for comparable genes (such as for other cancers) are done today. Claim 16 was not challenged in *AMP v Myriad*.

challenged, they may be found invalid, but they have been granted and presumed valid for over a decade, and they matter for DNA diagnostics.

Claims 5 and 6 were scored as “subordinate” claims by the examiner, per the file wrapper, but in that case they should be narrower than the independent claim. Yet these are wildly broader than the claims 1 and 2 to which they refer. Either their plain English meaning is wrong, or their scope has to be read as much narrower than the claim states.

It is ironic that senior examiner James Martinell rejected 15-mer claims similar to these in 1992 in the infamous NIH EST patent applications from J. Craig Venter. But the examiners for Myriad’s ‘282 patent, Bruce R. Campbell and Abdur Razzaque, several years later allowed these claims, perhaps reasoning that it would be understood that the relevant molecules would actually arise in *BRCA1* by implication. The problem is that the claims language reads on an immense number of molecules, and should not be granted with such ambiguity.

The claims language can be easily reduced to an approximate bioinformatic algorithm, and that is what Thomas Kepler did. Bioinformatic analysis suggested that searches even in the USPTO’s database alone (without resort to GenBank) would have found prior art more than a year before the application that became the ‘282 patent was filed (see Tom Kepler’s analysis). Certainly these claims could not be successfully enforced against sequences from entirely different parts of the genome outside *BRCA1*. But the problem is that the language of the claim is extraordinarily broad, impossible to determine without reading into the claims much that is not stated in them or only ambiguously framed in the patent specification. Based on our analysis, these claims seem to fail under Section 102, and if not there, then probably under written description, enablement, or both (Section 112).

Myriad’s patents are not the only ones we have found with this style of claim. The problem is not common, but we do find such claims in the patents that have been enforced by Myriad and Athena against diagnostic testing laboratories. After *Mayo v Prometheus* and the demise of broad method claims, such oligomer claims may be the main ones constraining some DNA diagnostics. The problem is consequential if these claims are the main ones that matter in some DNA diagnostics. I conclude this is sloppy claims drafting and inadvertent granting of very broad claims masquerading as subordinate claims during examination.

The service-monopoly business model is the main bone of contention

The debate about gene patents has centered on what is patentable, but even the most anti-patent critics generally concede that patents in some circumstances serve socially beneficial ends. And even staunch defenders of patents would concede that monopolies, even temporary ones, can get in the way of progress. If patents are not always good and not always bad, then patents must be doing something useful sometimes, but can also hinder progress. The question is not whether they should exist but what they should cover and how broad they should be. What they should cover is the center of both *Mayo v Prometheus* and *AMP v Myriad*. But those cases will not entirely resolve the question of

patent breadth, which involves examiner judgments that irreducibly entail uncertainty about how the rights granted might be used or abused.

Myriad Genetics and Athena Diagnostics are the two most conspicuous firms whose business models depend on strong patent protection for one or several genes related to particular conditions, such as breast/ovarian cancer or specific neuroendocrine disorders inherited in a Mendelian fashion.

Athena's and Myriad's business plans rest on a service monopoly model that has proven to be highly controversial, in large part because the "blockbuster" model depends on strong patent enforcement. In the case of diagnostics, that means enforcement against university clinical laboratories and nonprofit health systems such as Mayo, as much or more than other competitor firms. It is Myriad and Athena that have been most in the line of fire in the debates over gene patents.

Athena Diagnostics began as a commercial testing service for Duchenne muscular dystrophy. Some of the physicians and scientists involved in discovering the *dystrophin* gene concluded that genetic testing warranted commercial testing through a new startup. Athena has since diversified into other neurological and endocrine disorders, generally on a model of securing exclusive patent rights from academic research institutions for the relevant genes.

Myriad was founded the year after Mary-Claire King's team identified a region on chromosome 17 that could explain the inherited risk of breast and ovarian cancer in some families. Myriad won an intense race to clone and sequence the actual gene on chromosome 17. Finding the mutated gene on chromosome 17 was not Myriad's only R&D effort, but it was high on the list. Myriad has since diversified into genetic testing for other cancers, for companion diagnostics, and for years aspired to become a drug company, spinning off its therapeutics arm after an Alzheimer's drug failed in clinical trials. (That therapeutic company has essentially disappeared since.) BRACAnalysis®, the first-line *BRCA* test, however, is still overwhelmingly the source of Myriad's revenues. Most of Myriad's revenue is attributable to BRACAnalysis® alone (\$405 of 496 million total revenues in FY2012), \$110 million in the most recent quarter, and 79 percent of total revenues for the first quarter of FY2013 [16]).

The service monopoly model has worked mainly in the United States but less so elsewhere

Myriad is now expanding into Europe, with headquarters in Zurich, a lab in Munich, and offices in Spain, Italy, and France. The business model in Europe will have to be different, and likely less patent-dependent, because:

1. The claims allowed by the European Patent Office were much narrower than in US patents;
2. Compulsory licensing provisions weaken patent-holders rights in Belgium, France, and Switzerland (and these provisions were written specifically with *BRCA* testing in mind [17]);
3. Patent enforcement will have to be country-by-country; and

4. Many countries have organized health systems that can push back as monopsonists against a firm whose sole provider model has proven effective only in the United States. (Even in the US, its business model may prove to have rested on patent claims that the courts decide should not have been granted. Myriad has already lost its broadest patent rights, on methods, and could lose most of their broadest composition of matter claims in *AMP v Myriad*.)

In Australia and New Zealand, Myriad secured initial patent rights roughly comparable to their US rights. An Australian company, Genetic Technologies Group (GTG), sued Myriad for infringement of patents on intervening sequences, and the result was an agreement making GTG the exclusive licensee for *BRCA* testing in Australia and New Zealand, where it now operates a CLIA-certified genetic testing laboratory [18]. GTG, in turn, gave its *BRCA* testing rights as a “gift to the people of Australia,” allowing the laboratories in Australia’s provincial health system to test royalty-free. When GTG’s then-CEO announced an intention to change this policy in summer 2008, a furor erupted. In October 2008, the company backtracked, restoring its pledge not to enforce its patent rights. Cancer Voices Australia mounted a lawsuit that went to trial in February 2012 (decision pending). An extensive set of hearings and draft bill from the Australian Senate were other results of this controversy.

In Canada [18] and in the United Kingdom [19], *BRCA* patent rights have not translated into a service monopoly. The main reason is not differences in patent scope, but the presence of pushback from the provincial health systems (in Canada) and National Health Service (UK). There are differences in strength and breadth of patents in different jurisdictions, but the stories have not played out through patent litigation or licensing. Instead, the story has been health systems making decisions about how to conduct testing that in some cases very likely entails infringement of claims as granted, but no litigation to find out if the infringed claims are valid and so no case law by which to interpret the scope of patents. The absence of patent litigation may be in part because a patent victory would still not resolve whether genetic tests would be paid for by the health systems in question. Myriad would in effect be suing its own biggest customers. This sometimes happens in law, but it is not always wise to litigate on one front when you can lose on others.

Several conclusions can be drawn from this history of how patent rights have been used (US) or not used (other jurisdictions) in genetic testing. One is that patents are clearly not the only or most important factor determining whether genetic testing is available. Genetic testing evolves from a complex research and clinical system. Tests are available in different jurisdictions. Despite roughly similar patent criteria, the role of patents has been big for Myriad and Athena in the United States, and a much smaller part of the story elsewhere. Can we conclude which is better or worse? I know of no credible way to answer this important question without an extensive and expensive empirical comparative study that no one is motivated to undertake.

Taking the case of Myriad, it does enjoy some advantages that make its entry into Europe possible. It has an efficient operation and can quickly return results in clinical reports. It can reach payment agreements with national and private health systems analogous to those it has with US payers. It has patent rights on some specific mutations, albeit in some

cases only for specific populations (Ashkenazim). And it has its large proprietary database built from almost a million tests. But for the reasons noted in the first paragraph of this section, Myriad will almost surely not develop a service monopoly in Europe comparable to its US position. It will compete mainly on other grounds, with patents likely less prominent than in the historical development of its US business model. Europe should benefit from a high quality new testing service, and Myriad will benefit to the degree it succeeds in gaining market share and expanding the market.

Both harms and benefits of patenting have been overstated

My main conclusion from our case studies is that both the harms and the benefits of patents have been wildly overstated. This may seem a bit namby-pamby to say, but it may be helpful to exclude the absolutist positions of pro- and anti-patent factions. It is quite clear that there are some benefits to having patents. The prospect of patents invited the involvement of companies to do research that yielded fruit, for both hemochromatosis and breast/ovarian cancer. Mercator Genetics discovered the *HFE* gene underlying the most common form of inherited hemochromatosis. Myriad Genetics and its collaborators won the race to *BRCA1*, and the race for *BRCA2* a year later ended in a dead heat between Myriad and a British team. The hunt for both *HFE* and *BRCA* involved many publicly funded groups. But the winners were companies drawn into the game by prospect of patents. For most other gene hunts, the discoveries have been made by academic groups (who go on to get patents in many cases, but the funding is generally from government or nonprofit sources). Myriad's most important gene discovery in effect made the company a successful startup, and commercial success of the resulting test continues to be the main source of revenues to diversify the business plan.

There is no doubt the genes in our case studies would have been discovered and fairly quickly, even without the private R&D. The alternative of trade secrecy is simply not an option when there is a robust system of publicly funded research. When a gene or mutation is there to be found, it will be found if someone has a reason to find it. The disclosure function of patents is therefore weaker in human genetics than many other domains, because there is a strong base of publicly funded research. Moreover, as we have seen, patents on molecules and methods breed trade secrets in the form of proprietary databases born of a service monopoly.

So while the prospect of patents sped the process and rewarded the winners, as noted above, patents clearly were neither necessary nor sufficient to discover or develop clinical testing of genes for Mendelian conditions. Myriad officials have been widely quoted as saying the firm has spent half a billion dollars on R&D for its *BRCA* tests[9]. That figure should be interpreted carefully, since Penn, Mayo, OncorMed and other laboratories had *BRCA* tests on the market before Myriad and cannot possibly have spent more than a fraction of one percent of what Myriad claims. So the figure cannot refer to cost of making the service available that would not otherwise exist. More detail about the nature of the R&D and what it cost would improve the debate.

Continued conflict is foreseeable. Establishing a deliberative process may be wise.

Patent law is a blunt instrument that moves slowly. The starting gun to find genes underlying inherited risk of breast and ovarian cancer went off in October 1990 when Mary-Claire King found genetic linkage to a putative *BRCA1* gene on chromosome 17. Twenty-three years later we are holding a roundtable and awaiting a court ruling about ongoing conflicts over the legal rights emanating from research that took place between 1990 and 1995. The *BRCA* patents challenged in *AMP v Myriad* will begin to expire in 2014 and 2015. (Myriad has rights to some mutations through 2028. The later patents are increasingly narrow. Other *BRCA* patents may be yet to come.) In 2012 we learned in the CAFC phase of *AMP v Myriad* that the broadest claims—the method claims on detecting DNA alterations—should never have been granted. We will know in summer 2013 whether that is also true of the claims on isolated DNA molecules. That feedback loop is 15-19 years. This is not a feature; it is a bug. There is nothing good about how slow and expensive the process is.

Slow feedback is tolerated not because it is good but because the alternatives are worse. It appears patent incentives do some work, even in DNA diagnostics. People in the know disagree sharply about whether the benefits justify the costs, but the range of disagreement has narrowed in the process of elevating the utility and written description thresholds in 1996-2001, patent reform in 2005-2010, and during the litigation cycles for *Mayo v Prometheus* and *AMP v Myriad*. It is now confirmed that DNA molecules, when altered, can be patented, and that some methods can be patented, just not with claims as broad as have sometimes been granted.

It is the nature of patent law that it entails judgments in examination and patent prosecution while technical fields are evolving rapidly, followed by clarification of the scope and strength of protections through litigation. The system is not optimal or quick, but it does work to a degree. Patent critics have no practical prospect of dismantling the system, and few outside of academe seem to want to do that; defenders of the system, however, can hardly point to a 15-year monopoly based on invalid claims as a good way to go about business. There are many lessons for different actors in the system.

For the USPTO specifically, matching the kinds of claims being granted to the prevailing norms of jurisprudence will remain a continual challenge. Indeed it may get harder, as the uncertainties of bioinformatics and software will be more relevant because interpretation of biological information has become another chokepoint in addition to DNA molecules and methods. Computation is essential. The notorious difficulties in software and information technology may prove as difficult or more so than the gene patent debates. My colleague Arti Rai has some examples showing that the rigor of patent examination varies in technology classes, and such rigor is a cause for optimism. The central challenge for USPTO will remain ensuring that rights granted correspond to inventions disclosed in the face of uncertain and unstable jurisprudence. More easily said than done, but still a challenge that is not distinctive to genetics and genomics.

Many of the broader problems—and most of the problems that are truly distinctive to genetic diagnostics and risk assessment and the future of whole-genome analysis—are not going to be solved through the expertise of patent lawyers or courts, although such experts will be part of the process. Patent law will confront other bodies of law and other goals of a health care delivery system beyond patent protection, and will draw in constituencies that do not consume patent law as their daily bread. Knowledge of how genomics is actually finding its way into real-world uses is needed to understand how patent law and patent prosecution and administration have their impacts. Given that one controversy after another has washed over the system, starting in 1991 with EST patents, then utility and written description guidelines in the wake of *UC v Lilly* (Section 112 concerns), then uncertainty over obviousness (*KSR v Teleflex*), and now attention to patentable subject matter (*Mayo v Prometheus* and *AMP v Myriad*), it seems safe to predict continuing controversy.

Conflicts over DNA patents in diagnostics and research have been almost unremitting for three decades. This suggests that some systematic method for drawing on expertise throughout the federal government, including USPTO and NIH and the National Institute of Standards and Technologies, at the least, might be a wise investment of time and effort. The process may not be smooth and consensual—deciding the Solicitor General’s position in *AMP v Myriad* did not produce consensus, although it did yield a position—but having a systematic process to think through policy in a domain of consistently intense conflict seems better than not. The hardy perennial nature of conflicts surrounding DNA patent policy may warrant a deliberative process within the executive branch to interact with the judicial and congressional branches, and with external constituencies.

A deliberative process cannot shorten the lag time from discovery to court ruling, but it might be able to lower the likelihood of litigation in the first place if it could successfully anticipate where patent examination may be creating zones of ambiguity ripe for litigation or by addressing points of friction where examination practice collides with policy preferences of research funding agencies (as it did with EST patents).

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