



Roundtable on Genetic Diagnostic Testing

US Patent and Trademark Office

Madison Auditorium
600 Dulany Avenue
Alexandria, VA

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

Robert Cook-Deegan, MD
Research Professor
Duke Institute for Genome Sciences & Policy
Sanford School of Public Policy

Subhashini Chandrasekharan, PhD
Misha Angrist, PhD
Mollie Minear, PhD
Lane Baldwin
Center for Public Genomics
Institute for Genome Sciences & Policy
Duke University

Thursday, January 10, 2013

This statement is based in part on research funded by the National Human Genome Research Institute (P50 HG003391), the Marion Ewing Kauffman Foundation, and the Duke Endowment. From 2004-2009, the NHGRI grant was co-funded by the US Department of Energy. This statement does not necessarily reflect the views of the funders.

Introduction

Thank you for inviting me to participate in today's roundtable. I am a physician-molecular biologist with some background in public policy research. I am a research professor at the Institute for Genome Sciences & Policy and the Sanford School of Public Policy, Duke University.

I am giving you my own perspective here. My views do not reflect the National Human Genome Research Institute, the Ewing Marion Kauffman Foundation, the Duke Endowment, the US Department of Energy, or others who have funded our research. We thank them for their generosity, but you should not blame them for my mistakes or attribute my views to them. Indeed, this is not merely the usual disclaimer, as I will make some judgments that even the others who have helped prepare this statement do not necessarily share, so the views truly are very much my own

We have been studying the impact of patenting and licensing practices affecting clinical genetic testing since 2006, when we were asked to do some policy-oriented case studies for the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS). SACGHS had decided to do a project on how patenting and licensing affected clinical access to genetic testing in the United States, under a task force chaired by James Evans, which then led to an SACGHS report published and submitted to Secretary Sebelius in 2010, three years ago [1].

We have continued to work on themes related to today's roundtable through research studies published in the open literature and by organizing public events. We

have established a website¹ that includes a longer version of this statement as well as other links that are relevant to today's roundtable. We also have two webpages devoted to the ongoing case *Association of Molecular Pathology, et al. v Myriad Genetics et al.* (hereafter *AMP v Myriad*).² I also want to alert you to some ongoing lines of work that may inform decisions going forward.

Subhashini Chandrasekarhan, Ph.D., is leading an effort under the working title “patent speed bumps on the road to whole-genome sequencing?” This project is intended to address whether claims in US patents that have already been granted (and whose validity is subject to evolving jurisprudence in *Mayo v Prometheus* and, perhaps, *AMP v Myriad*) will or will not be infringed by doing whole-genome sequencing. We include single-molecule methods and genome-wide approaches. It turns out that while many lawyers (both practicing and those doing legal scholarship) have firm opinions about the extent of infringement liability, the firmness of opinion does not mean agreement. Expert practitioners and scholars truly disagree on how claims will be interpreted in court, and there is little case law precedent to guide interpretation at the necessary level of granularity. Our main audience for this work is researchers and clinicians who are incorporating such whole-genome analysis into clinical practice. This research is intended to bound the uncertainty: to identify what is known and not known about the answer to the first question Judge Bryson asked Gregory Castanias (Myriad's chief litigator) in the first oral arguments before the Court of Appeals for the Federal Circuit (CAFC) in *AMP v Myriad* (which was then *AMP v USPTO*, CAFC docket 2010-1406, 4

¹ <http://www.genome.duke.edu/centers/cpg/sec-27-study/>

² <http://www.genome.duke.edu/centers/cpg/Myriad/>, and <http://www.genome.duke.edu/centers/cpg/BRCA-resources/>

April 2011). Judge Bryson asked if sequencing the entire genome of an individual would infringe Myriad's claims as granted. The litigants in the case disagree on the answer, and that disagreement is found among other experts. Yet it is a question highly pertinent to those engaged in many approaches to whole-genome analysis and multi-gene testing frameworks that are being introduced into clinical research and medical care. The analysis centers on how patent claims might be interpreted, and which claims will remain valid in the wake of recent and pending court decisions such as *Bilski v Kappos*, *Mayo v Prometheus*, and *AMP v Myriad*.

One of the main findings from our work over the past seven years is that the policy framework has often centered on what is patentable subject matter. Yet what is done with intellectual property is just as important as what can be patented. In the real world, it is not just what is patented but how patents are used. Most controversy in gene patenting has centered on service monopoly business models. These are indeed enabled by patents on genes (and depend critically on what kinds of claims are granted in "gene patents" of various kinds). But we have studied several cases in which patents on genes have not caused controversy. Mollie Minear, Ph.D., is taking the lead on describing how patents on the *CFTR* gene were licensed. We regard it as a success story for licensing practices that allowed widespread and rapidly evolving approaches to genetic testing for an inherited disease, cystic fibrosis; yet it also accommodated exclusive licensing for one approach to gene therapy, nonexclusive licensing for alternative approaches to gene therapy and development of novel cystic fibrosis therapeutics, as well as humanitarian licensing in the hunt for drugs to treat diarrheal diseases that afflict millions of children around the world.

And finally, Lane Baldwin is writing up a paper that compares and contrasts Genentech's development of Herceptin® to Myriad's development of BRACAnalysis®, its first-line genetic diagnostic for testing inherited susceptibility to breast and ovarian cancer, the main reason that Sec. 27 of the America Invents Act was included in the law. These are two patented medical products aimed at a similar patient constituency, but how Genentech and Myriad responded to initial conflict with disease advocacy organizations and interacted with health professional organizations is starkly different. Our focus is how Genentech's narrative was constructed as heroism and Myriad's as villainy and avarice. Again, we will share that paper once it is in final form.

I will focus the remainder of my statement on some questions pertinent to today's roundtable, emphasizing points that emerge from our own research and that others may not address to the same extent. We have prepared a longer version of this written statement on our website at <http://www.genome.duke.edu/centers/cpg/sec-27-study/>.

I will start with two kinds of activities—verification testing and research—that have been the focus of most disagreement and controversy. The disagreement includes the extent of impact and the importance of exclusivity. The controversy extends beyond that into whether the patent law is the proper instrument to decide such matters, if that means patent law trumps other bodies of law and other policies that affect health care decisions.

I will then turn to verification of genetic test results in more detail, and explain how the frame of the debate that has played out before USPTO has focused on the easiest and least important aspects—whether one can get an accurate assessment of one's genotype—but in fact the much more important and pervasive problems are about

interpretation of genetic data. In that framework, patent rights do affect access to data, interpretive algorithms, and doing biological and clinical studies to explore the meaning of genetic variants; this is much closer to where the wave is breaking in clinical genomics today than accuracy in DNA variant detection *per se*.

A final observation before proceeding to address the questions before us. This study is being done for Congress by USPTO, under the shadow of a recent and forthcoming Supreme Court decision that will frame relevant jurisprudence. All three branches of government are involved, and several organized constituencies are also engaged: patent lawyers, companies, doctors, testing laboratories, universities, and patients and people at genetic risk (which is really all of us). Congress is presumably interested primarily in possible statutory change, and there are indeed statutory options such as those recommended by the Secretary's Advisory Committee Report [1].

There are also options for USPTO itself. As will be apparent below, some of the uncertainty over the scope of gene patents is due to the kinds of claims being granted, some of which are now clearly invalid after *Mayo v Prometheus* (very broad method claims) and perhaps (depending on what the Supreme Court decides between now and July) after *AMP v Myriad* (DNA molecules corresponding to sequences found in nature). The courts are defining some boundaries, in a complex back-and-forth series of decisions between the CAFC and the Supreme Court that affect interpretation of patentable subject matter, obviousness, enablement and written description. USPTO is operating in turbulent waters, as it often does (and this gene patent storm may seem tame compared to software and infotech). It seems likely that there will be ongoing activity in the form of re-examination, litigation, interference (for pre-AIA patents and applications) and post-

grant opposition (for post-AIA patent applications). I suspect that writing the report mandated by Section 27 has made it apparent to USPTO that much complex information leavened with legal uncertainty needs to be transmitted down to the level of examiners and USPTO's administrative oversight apparatus.

I do not believe, however, that government is only remedy for some of the policy conflicts. Research policy, verification testing, and data-sharing practices are three domains where industry norms and practices could be flexible and responsive to technical change. My own sense is that we are here today because of a problem of collective action. Constituencies—in *Mayo v Prometheus* and *AMP v Myriad* these include testing laboratories, physicians and people wanting to get genetic tests—have turned to the courts and to Congress to resolve problems that would be more efficiently and perhaps more effectively addressed at the level of norms and practices than binding legal precedents and statutes. That is, I conclude that we are here today in part because of a failure of political process, and all of us are partially to blame.

Does verification testing infringe?

It is quite clear that the answer to this question is yes. The disagreement is about how much it matters, and what constitutes verification.

Myriad has addressed verification testing in several of its court documents, and their main argument is that verification testing is just not much of an issue. Myriad has not licensed out initial testing that involves sequencing both *BRCA1/2* genes. Rather, it has licensed rights to test for specific mutations, and this is the most common form of verification testing (but see below; follow-up mutation

testing is not by any means the only kind, or even the most important kind). It is not clear to us, despite having inquired several times, what kind of follow-up testing is permissible and what is not. How many mutations have been licensed? All? Some? We have learned of informal, and sometimes written (but not public), agreements between Myriad and other laboratories that permit follow-up testing. My conclusion is that this is generally handled case by case, and sometimes through letter agreements or tacit practices. None of the policies is, however, public or transparent; licensing terms are not shared. How are clinicians supposed to proceed?

When an issue has risen to the level of congressional attention it is well past time to have more formal policies. This is not an issue just for Myriad, although Myriad and Athena Diagnostics (which has many test for neuroendocrine and other disorders) are probably the largest testing services that would be affected. This cries out for attention from the many companies and nonprofit laboratories, trade organizations, and health professional societies now involved in or soon finding themselves involved in genetic and genomic testing.

One option that has always been on the table is to have a formal policy of allowing verification testing for any patient who has already paid a laboratory that has exclusive patent rights for initial testing. This could become a legally actionable policy if someone raised a legal challenge under the doctrine of patent exhaustion. From the example below, it will be clear that such a policy might help a bit, but it will not solve the system-wide problems. The virtue of company-by-company policy is that it is relatively quick and easy. Individual companies could follow a policy

permitting verification testing by stating it does not incur infringement liability.

They could do so at very little risk to their business practices. Indeed it is a mystery to me why they have not. A need for verification testing is not common, but it does occur; pretending it is not a problem is not a viable policy.

Industry-wide norms could be developed by experts familiar with how genetic testing is carried out in practice, and the situations in which follow-up testing and interpretation are needed. This would be a step up from company-by-company policies, and completely compatible with them. The major companies involved in genetic testing as well as the associations of clinicians who order tests, patient groups that want the tests, and laboratories that would do the verification testing could work to develop some guidance.

The main counterargument to having formal verification testing policies has been the danger to patent-owners of a gray market emerging. Patent owners are understandably wary of policies that might impose costs or weaken presumptive rights, and permission for verification testing would indeed complicate the process of patent enforcement. But the fact remains that in any particular case it would be possible to establish who had been paid what through whom for which genetic test. Under the current chaotic process that labors under real fear of infringement liability, data are not shared and testing is secretive. Everyone is worse off and genetic tests are underpowered. A company that has been paid to do its initial test is on very thin ice arguing that others cannot subsequently do tests the patent-owners do not themselves do; and yet that is the result of current non-policy. The

logistics are not insurmountable, and it is a question of consensus on importance, political will and political process, not feasibility.

Does research infringe?

Here again, the answer is clearly “yes,” under US law. No one disputes that many thousands of articles have been written that specifically study *BRCA1* or *BRCA2*. Myriad has only sued a few of the authors of those studies (and four of them were initial plaintiffs in *AMP v Myriad*). Myriad has sent letters to another unspecified number. Athena has never sued, to my knowledge, but it has sent letters to many professionals who engage in research. The for-profit arm of the nonprofit Clayton Foundation has also threatened legal action, although to my knowledge has never filed suit.

In Europe, only studies of specific *BRCA* mutations would infringe patent rights because the claims are relatively narrow. Even there, however, some studies that include people with the common deleterious mutations would technically infringe. Several jurisdictions in Europe, however, have exemptions from infringement liability for research use. Studies of how the gene works, for example, might not infringe, or testing in the context of clinical trials. And several countries (France, Belgium, Switzerland) have explicit compulsory licensing mechanisms. For studies in the US, and jurisdictions without clear research exemptions, such research is technically an infringement because it entails using methods or making molecules covered by patent claims. But suing over basic research is rare—in part because there are mainly benefits and no damages to the patent-holder—and the question

then becomes how to define the boundary between clinical research and genetic testing that might affect the market for commercial testing.

Under a patent regime, decisions to enforce patents are at the discretion of the patent-owner, and decided case-by-case. This is subject to court interpretation, but in genetic testing there is little relevant case law and the mere threat of a lawsuit has been sufficient to clear the market of competitors without legal challenge until *AMP v Myriad*. In effect, patent-owners decide the scope of activities covered by their patents; this is of course how patent law works. In the low-margin business of genetic testing, however, the main reason there was no law case law for ten years was the high barrier of litigation, addressed only when the American Civil Liberties Union bankrolled the litigation.

This is hardly a satisfactory solution to a pervasive system-wide issue. In some jurisdictions, there are research exemptions from infringement liability, but such exemptions are generally narrow. They would not exempt uses likely to arise in clinical research that involves genetic testing, or if they were broad enough to do so, they would probably also weaken patent incentives in DNA diagnostics. Trying to solve this problem through a statutory research exemption, diagnostic use exemption, or through case law seems unlikely to produce a fully satisfactory solution, although the uncertainty could certainly be reduced considerably.

A diagnostic use exemption from patent infringement liability, as recommended by SACGHS, solves the problem for researchers. It also, however, weakens the patent incentive for private R&D in the diagnostic space. That makes it

a difficult political sale, and an unlikely prospect for statutory change because there will be no consensus.

The problem here is when and how to respect patent rights while also allowing freedom to do clinical research that is beneficial to the health care delivery system as a whole; it is a policy problem, and only in part a legal boundary problem.

To my eyes, this is another area in which collective political process would be better suited to addressing the problem than case law or statute. In ten years of controversy and debate about whether gene patents hinder research, most of the attention has focused on what is patentable and the morality of patenting, but there have only been occasional (and relatively general) efforts to find common ground to set norms and practices.³ Point 2 of the “Nine Points” in particular bears on diagnostics, and urges exclusive licensing only in exceptional circumstances where exclusivity is needed to get a product to market, clearly not the case in the Mendelian genetic tests we examined (since there were already laboratories offering the test before the patent-holders, and not by free-riding on the patent-holders disclosures; independent discovery is the norm here). No trusted

³ Some laudable examples include: (1) the “Nine Points to Consider in Licensing University Technology” 2. Bienenstock A, Association of American Medical Colleges, Association of University Technology Managers: **In the Public Interest: Nine Points to Consider in Licensing University Technology**. In. Stanford University and Association of University Technology Managers: Stanford University and Association of University Technology Managers; 2006., (2) NIH’s “Best Practices for the Licensing of Genomic Inventions” 3. Office of Technology Transfer NIOH: **Best Practices for the Licensing of Genomic Inventions**. In. Bethesda, MD: National Institutes of Health, US Department of Health and Human Services; 2005., and (3) the “Guidelines for the Licensing of Genetic Inventions” from the Organization for Economic Cooperation and Development 4. Organisation for Economic Cooperation and Development: **Guidelines for the Licensing of Genetic Inventions**. Paris: Organisation for Economic Cooperation and Development; 2006.

intermediary has emerged to formulate policies to enable clinical research to proceed while also accommodating the rights and interests of patent holders.

My own assessment is that there is no process for setting norms, to which companies might be held to account, so each company does what it deems to be in its own best interest, although many decisions have system-wide effects on genetic testing. Some norm-setting would be welcome, at least creating benchmarks for flagging deviations from practices that a group of experts agree would be good for the system as a whole, with the best interests of *patients* held foremost. This would be a pathway for soft regulation. Shaming the companies that deviate from the norm would be the main enforcement mechanism. That might or might not change behavior. Without such voluntary action, however, the alternative is statutory change along the lines suggested by SACGHS. One benefit of congressional attention is to raise the stakes, so that a political process might emerge. That is, threat of statutory change might induce better industry behavior regarding research use and verification testing, or at least a process for flagging outlier practices that are problematic.

Initiate a process to formulate guidelines for research use and verification of genetic and genomic tests

I believe that designating an organization trusted by the relevant constituencies to formulate principles and practices for both research use and verification testing could address many of the most contentious issues. A consensus study could also explore how such principles could be put into practice by the various stakeholders. There are several real-world models of how this can work:

the National Academy's guidelines for stem cell research [5, 6] and standards for publication and data-sharing in genomic research [7, 8].

If my diagnosis is correct that the remedies are more readily pursued through principles and practices rather than statutory or case law, then the crucial missing element is a trusted intermediary to formulate the principles and sketch out how to implement them. The USPTO is not the proper place to resolve this, because its core expertise is patent examination and oversight, and those are not the elements missing in the system. This Section 27 study might nonetheless be the instigator of the next step. This task is larger and more complex than any academic group can credibly undertake, but it is the bread and butter of the National Academies, in this case some combination of the National Research Council and the Institute of Medicine.⁴

“Verification” is not just about accurate test results

Verification of a clinical genetic test result entails three steps:

1. Accurate identification of a genetic variant,
2. Interpreting the clinical significance of that variant, which sometimes requires
3. Further experimentation or clinical observation.

1. Accurately identifying DNA variants

To illustrate the importance of having backup system for verification, let me use a couple examples. At the March 2012 Charlotte workshop organized for USPTO in conjunction with the annual meeting of the American College of Medical Genetics, one of the clinical geneticists explained that a sample from a patient with an autosomal recessive neuromuscular disorder was sent to Athena in 2005. Athena

⁴ For purposes of full disclosure, I worked at the National Academies 1991-2002 in various capacities at the Institute of Medicine, National Research Council, and National Academy of Sciences.

reported one variant of unknown significance in a disorder in which one would expect symptoms only with two deleterious mutations, affecting both copies of the relevant gene. The clinician remained strongly suspicious because of the inheritance pattern and clinical profile. Three years later, through collaborations in Europe, another lab did testing of the same gene in this patient and found two mutations. The clinician wanted to use the results clinically, and thus use a CLIA-approved laboratory (testing had been done in a research protocol). He/she sent the sample for repeat testing at Athena. He/she also sent it (quietly) to another laboratory testing service that is CLIA-approved. Athena reported the same result as its first test (one variant of unknown significance). The clinician was disturbed to find that the mutation reported as “unknown significance” by Athena was actually characterized in the literature as deleterious. And when confronted with two other laboratories showing a second deleterious mutation, Athena discovered that second mutation fell underneath one of the primers used to amplify DNA for the Athena test. The primer was not binding to the DNA, and so the DNA bearing the mutation was not being amplified. No error was detected because the patient’s other chromosome had a normal (wild type) sequence at that position. At that point, Athena acknowledged the error. The virtue of systematic clinical protocols is that they are rigorous and done exactly the same way time after time. But every protocol has flaws.

BRCA testing faced a controversy in 2006 when a paper in the *Journal of the American Medical Association* revealed that insertions and deletions larger than those detected by Myriad’s BRACAnalysis® accounted for a clinically meaningful

percent of mutations [9]. Myriad was already aware of the problem and was developing what became its second-line BART® test to detect such rearrangements. It was nonetheless a clear illustration that no genetic test is complete. Until and unless we get to error-free genome analysis, every test will miss some mutations—and we may never get that far.

This leads to a second aspect of detecting mutations. If a deleterious mutation is found, then the case is straightforward. However, when the test result is negative for BRACAnalysis®, the clinical decision tree branches, and right now it branches in a way that makes no clinical sense in the long run. If the clinician suspects there is still a mutation to be found, Myriad can do its second-line, \$700 BART® test. But an equally plausible second choice is to send a sample to Ambry Genetics, the University of Washington, or another laboratory that offers multi-gene deep sequencing. This can detect mutations in any of another 10 to 20 genes associated with inherited risk of breast and ovarian cancer (and often other cancers as well). It would cost the same to also sequence *BRCA1/2* at the same time, but these tests—at least the ones offered in the United States—leave out *BRCA1/2*, presumably to avoid infringement liability. Some combination of the patient or their health system pays for two expensive tests when one comprehensive deep-sequencing test would be clinically optimal.

Every laboratory makes mistakes. The issue of verification testing at the level of mutation-detection is not common, but neither is it rare. It can and does happen and will continue to do so for the foreseeable future. The main problems are technical pitfalls and incomplete clinical information, but patent rights also are

directly constraining second-line testing for those whose initial genetic test does not show a deleterious mutation but clinical suspicion of a clinically meaningful DNA variant persists. And patent rights may also hinder multi-gene deep sequencing approaches that will surely be preferable to current methods in the next few years. The outcome will depend on how patent rights are deployed; but multi-gene testing will not fit smoothly and cleanly with service monopolies on genetic testing rights covering one or a few genes.

2. Interpreting the clinical significance in light of extant data

While preparing my statement for today's event, I have been interviewed by many journalists. One of them brought to my attention a statement from Myriad's CEO, Peter Meldrum. Robert Langreth's Bloomberg News story on December 28, 2012, included this sentence: "There has never been a reported case in which Myriad wrongly told that a woman she had a cancer-causing mutation,' he [Meldrum] said [10]. The danger here is that the operative word is "reported."

I suspect that the clinical and scientific staff at Myriad would wince if they read Meldrum's quote. It may be useful to go through a case in which Myriad did what Myriad's CEO said has never been reported. We do our work under a certificate of confidentiality, and I will be characterizing a case that was brought to our attention by a lawyer on behalf of a client whose name I do not know and did not ask. The case illustrates how "verification" is much more complicated than just accurately detecting a DNA sequence variant.

The chronology is this. A woman with apparent risk of cancer (based on family history documented by genetic counseling in 2007) sent in a sample for

BRACAnalysis® testing in 2008. Myriad reported that she had a deleterious mutation in *BRCA1*, with 87 percent lifetime risk of breast and 44 percent chance of ovarian cancer. In 2009, fifteen months after getting her *BRCA* results, she had both breasts and ovaries surgically removed to reduce her cancer risk. Six months after her surgery, her physician got a letter saying her mutation had been reclassified from “deleterious” (i.e., associated with high risk of cancer) to “unknown significance.” Two years later, her lawyer contacted us. She was still highly apprehensive about what the test result meant, wondering if she had sacrificed her ovaries and breasts for no apparent purpose. Her lawyer asked for advice about next steps.

I spent a day going through various databases, and also solicited input from various experts in our network. I spent another day exploring the literature and available databases in preparation of this statement. The client’s *BRCA1* variant was reported eleven times in the Breast Cancer Information Core (BIC), the largest *BRCA* mutation database. The same mutation was also flagged in the BioBase® as being associated with breast and ovarian cancer, uterine cancer, Fanconi’s anemia (but also for lower risk of breast/ovarian cancer in one report). And the Human Gene Mutation Database in Cardiff flagged it as a deleterious mutation with citations to two papers, one from Australia and one from Europe. One 2012 study used the mutation as a “positive control” for splice variants—that is, a clearly deleterious mutation to which others would be compared.

Of the eleven reports about this mutation in BIC, ten were from Myriad. All of Myriad’s BIC reports dated from 1999 to 2004, the year Myriad stopped

contributing to public mutation databases. The vast majority of Myriad's testing has taken place since 2004, however, and if the early reports approximate the mutation frequency, then Myriad has probably come across this same mutation fifty or more times since. However, in contrast to the information I was able to glean from various databases that indicated the deleterious nature of this mutation, Myriad has proprietary data that is not openly accessible that formed the clinical basis for reclassifying this variant, and we will know the justification behind their reclassification only if they care to share it or publish it.

In examining the databases, I was doing what every laboratory or medical geneticist would do—interpret the result based on extant information. The information in public databases is woefully incomplete. And this is true for *BRCA1*, one of the most intensively studied genes in the human genome. The uncertainty for genes attracting less study will be greater.

This is a story that will play out in gene after gene for the coming decades, until we have databases that are friendly for clinical use, accurate, and comprehensive. Current databases fail on all three counts.

The databases I solicited are actually *research* databases, and have explicit statements that they contain inaccuracies and should not be used for clinical purposes. But of course they are the only sources of relevant data so every sophisticated clinician uses them, but with caution because they really do contain many errors. We will be discovering many, many genetic variants whose clinical

significance will only become apparent if data about many people are shared and are linked to clinical outcomes.

Proprietary databases guarded as trade secrets are antithetical to this goal. The policy upshot is to create incentives or obligations to share clinically relevant data. The relevance to patent law is that patent rights are what give rise to these proprietary databases. This is good to the extent that it expedites collection of the information in a central place because all testing is being done and reported by a single laboratory. It is bad because proprietary databases silo information gene-by-gene and company-by-company, with strong incentives for data-retention and weak incentives for sharing. It thus sets up a prisoner's dilemma policy problem.

3. Experimentation and clinical observation to assess variant function

To bring our case history up to date, in preparing this statement, we went back to the patient's lawyer and some experts in our network. One of the researchers believes this patient was analyzed for RNA transcription of the *BRCA1* gene, and results indicated the reported mutation would indeed produce a defective protein. That would mean Myriad's initial call was right and their reclassification was not. RNA expression is a kind of testing Myriad does not do, and I am not sure Myriad knows the results in this case, although they are relevant to clinical interpretation. Certainly no one was going to call Myriad in advance to ask permission. The possible answers from Myriad are "no," "yes," or "yes with conditions." "No" and "yes with conditions" would be unacceptable, and the clinician and the laboratory involved are concerned primarily with reducing the uncertainty haunting this woman. Moreover, any contact with Myriad would construct a trail documenting

willful infringement. Asking permission is not a viable solution in this clinical scenario.

If the RNA transcription testing had not produced results, then other options were also available. A consortium called the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) was assembled to interpret genetic variants of unknown significance (VUS) in the *BRCA1/2* genes (<http://enigmaconsortium.org/>). In some cases, that may entail experimentation or supplemental clinical observation studies. One can test other members in the family, or wait for others with the same mutation to enter the database, and make better interpretation in light of more data. Myriad offers free testing to family members of a patient with a VUS, for example.

Another approach is to introduce the mutation into animal models or cell culture, and look for effects. Or knock out the gene, and then introduce the suspect mutation to see if normal function is restored (in which case it is not deleterious). This can be done in fruit flies, yeast, fish, mice, nematode worms, and other model systems. No one approach will consistently yield a result, but often a multiplicity of approaches can shed some light. This is a network benefit of data-sharing and a collective virtue of science. But it relies on a huge and diverse network of researchers. No one laboratory can do all such analysis, no matter how motivated and wealthy. Mutations housed in a proprietary database simply will not be explored except when the particular company decides to do so. Under the current regime, however, laboratories tell us about follow-on testing at risk of infringement liability, and Myriad and Athena are simply not trusted to act in patients' best

interests if it conflicts with business interests—or even if it does not. It leads to a shadow world of genetic testing deliberately not shared with patent-owners and rarely reported in the public literature.

Several key points emerge from this story.

One is that we have found quiet, surreptitious verification testing in every case study. One problem is that a patient has to find a physician or laboratory who knows the network and can get help with testing and interpretation; presumably many patients never get there and none of us would know. Sometimes clinicians who collaborate closely with the patent-holders do this. Sometimes verification testing is open, but more often, it is a concealed process in which clinicians and laboratories deliberately risk infringement liability. It is one reason our research is done under a Certificate of Confidentiality granted by the National Institutes of Health. This is not a proud achievement of the patent law, or a testimony to the foresight of the genetic testing industry. Those who own the patents also own this problem. They could solve it themselves, but have chosen not to.

Second, it shows how patent exclusivity has led to the development of proprietary databases whose exclusivity will not expire when the patents do. There is nothing illegal about it, but there is certainly something unseemly. Myriad did not announce its decision to stop sharing data and create a proprietary database. It did not notify its customers, its informed consent documents do not make this clear, and when I give public talks, this is not something women who have been tested are happy about.

In our case example, all the public sources for this mutation indicate it is a deleterious mutation, and for the woman's sake, at this point that would actually be good to know, given her surgeries. She would have proactively addressed an actual risk. The worry here is whether the proprietary data on which Myriad based its reclassification is accurate and better than that available in the open literature. That is still a possibility, but the system cannot make that determination. If the open literature and the lab that did the RNA analysis are right, then the mistake here was the reclassification step by Myriad. (But from Myriad's perspective, this would be awfully close to having told a woman she was at high risk, and notifying her after multiple surgeries that this might be wrong—the very situation Mr. Meldrum claimed has never been reported.) The more likely outcome here is that the reclassification is wrong. But we simply do not know and cannot query the relevant information to find out without voluntary data from Myriad, because that would require identification and disclosure that then raises the prospect of willful infringement liability.

If Myriad had a formal policy permitting verification testing and research use, which some of us have urged since 2000, this would not be an issue. By retaining its legal options, Myriad is undermining clinically relevant information exchange that in my view is more important. I also believe its long-term business interests would actually be served by having a formal policy. They have already been paid to do their form of testing, and engaging others would improve their test.

Finally and most importantly, this case illustrates a deep pathology in the current system. There is no way to find out what is actually going on in this case because the data and algorithms underlying the reclassification from “deleterious” to “unknown significance” are not public. The laboratories involved cannot be expected to notify Myriad lest they incur the wrath of Myriad’s lawyers and find themselves defendants in a lawsuit. Trust in the company is so low that this is a real issue. This is not a situation that anyone will want to defend. But it is the situation in our world.

1. Secretary's Advisory Committee on Genetics HaS: **Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests**. In. Washington, DC: Secretary's Advisory Committee on Genetics, Health and Society, Office of Biotechnology Activities, National Institutes of Health, US Department of Health and Human Services 2010.
2. Bienenstock A, Association of American Medical Colleges, Association of University Technology Managers: **In the Public Interest: Nine Points to Consider in Licensing University Technology**. In. Stanford University and Association of University Technology Managers: Stanford University and Association of University Technology Managers; 2006.
3. Office of Technology Transfer NIOH: **Best Practices for the Licensing of Genomic Inventions**. In. Bethesda, MD: National Institutes of Health, US Department of Health and Human Services; 2005.
4. Organisation for Economic Cooperation and Development: **Guidelines for the Licensing of Genetic Inventions**. Paris: Organisation for Economic Cooperation and Development; 2006.
5. Daley GQ, Ahrlund Richter L, Auerbach JM, Benvenisty N, Charo RA, Chen G, Deng HK, Goldstein LS, Hudson KL, Hyun I *et al*: **Ethics. The ISSCR guidelines for human embryonic stem cell research**. *Science* 2007, **315**(5812):603-604.
6. Council NR: **Guidelines for Human Embryonic Stem Cell Research** Washington, D.C. : National Academies Press 2005.
7. Council NR: **Sharing Publication-Related Data and Materials: Responsibilities of Authorship in Life Sciences**. Washington, D.C.: The National Academies Press 2003.

8. Council NR: **Evolution of Translational Omics: Lessons Learned and the Path Forward**. Washington, D.C.: The National Academies Press 2012.
9. Walsh T, Casadei S, Coats KH, Swisher E, Stray SM, Higgins J, Roach KC, Mandell J, Lee MK, Ciernikova S *et al*: **Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer**. *JAMA : the journal of the American Medical Association* 2006, **295**(12):1379-1388.
10. Langreth R: **Myriad Stymies Cancer Answers by Impeding Data Sharing** In: *Bloomberg News* New York, NY; 2012.