

**Review of SACGHS Public Consultation Draft Report on Gene Patents  
and Licensing Practices and Their Impact on Patient Access to Genetic Tests**  
*James P. Evans, M.D., Ph.D.*

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DR. TEUTSCH: Thank you, Sarah. We do need to keep all of that in mind, of course. I think it is important to recognize also that since we do serve in multiple capacities, things where your names appear with SACGHS all should really be reviewed by the Committee.

Sarah, thank you. With that important reminder, we are ready to get started on our first agenda item.

As I think all of you are more than a little aware, the SACGHS Task Force on Gene Patents and Licensing Practices has been working for more than two years to carry out a study of the very important and largely unexplored question of whether gene patents and licensing practices affect patient access to genetic tests.

The task force began under the leadership of Dr. Deb Leonard, who has continued to serve as an ad hoc member of the group and joins us today in that capacity. Deb, thanks for your continuing service on the task force. Welcome back, as always.

Into the breach stepped one Jim Evans, on my right, assuming the role of chair at the conclusion of Deb's term. He has been ably guiding the task force's work ever since.

We have reached an important milestone in our work on this topic. Our goal for today is to decide whether the draft report that the task force has developed is ready to be released for public comment. The draft report is in Tab 3 of the briefing book.

In addition to the preliminary findings and conclusions, the task force has developed a range of potential policy options for public consideration. Jim will review the key elements of those and then facilitate a discussion of the draft report and policy options.

It should be apparent that the task force has devoted countless hours to this project. I want to commend all of the members of the task force, and most specifically Jim, for his energy, dedication, leadership, and commitment to all of this. Jim, thanks very much. Take it away.

DR. EVANS: Great. It has actually been quite a while since the full Committee has heard about our progress on the patents and licensing issues. I do want to start off by thanking everyone who has been involved in this. This has turned out to be a gargantuan task. I think that this is true for a couple of reasons.

One is that it is simply a very broad and very deep field. There is a huge history of patent law and licensing issues. Patents obviously go way back to the U.S. Constitution. So it is technically a demanding subject. We are very fortunate to have a broad range of expertise on the task force.

I think the other thing that makes it difficult is that there are many stakeholders. The stakeholders, when it comes to patents and licensing, are not always in sync with their own interests. There are sometimes mutually exclusive interests. So this becomes both a complex issue as well as one that can become contentious as well.

Again, I want to thank the task force for the many, many hours of conference calls, and some two-hour conference calls that went into three hours. I still am apologizing for that.

SACGHS Meeting Transcript  
December 1, 2008

[Laughter.]

DR. EVANS: I want to thank Steve for his guidance in this, because he has been there at critical junctures as we have come across certain issues that needed to be hammered out. I want to, especially, do a huge public thank you to Yvette Seger and to Sarah Carr, who have been just tireless. None of this would have happened without them. They are fantastic.

You can see the roster of people who have been involved in this. What I want to do today is march through these -- again, a time for apologies -- 130 slides. But we have several hours to do this.

[Laughter.]

DR. EVANS: We can discuss as we do it. I even have some humor slides I can show for breaks to wake you up.

I do think it behooves us to review what we have done and where we started with this as we go forward. The last couple of hours, what I want to do is go over this range of policy options.

The way we have approached this is a little bit unusual, but because it is such a complex and, potentially, a contentious issue, we think that the way we have tailored this will serve well the public's interest in having some framework from which to comment. At our next meeting after that public comment period, we will try to finalize our recommendations.

So, the history of this. In March of '04, gene patents and licensing were officially identified as a SACGHS priority. We deferred further effort at that point because of the NRC report, which was at that point in progress and had not come out yet. It subsequently came out, and in the fall of 2005 a small group was formed to review the NRC report and to determine whether they had done our work for us and whether we didn't need to go on, or whether there were things that it would be well for the SACGHS to take up.

During March of 2006, the NRC's general thrust was endorsed by this Committee, but there were some important limitations in our minds. Those had to do with clinical and patient access.

The NRC report was focused primarily on research. We felt at that time that we needed to investigate the issue of how gene patents and licensing play out in the realm of patient care, something that was not really a focus of the NRC. So it is not a deficiency of that report, just that that really wasn't their primary focus.

In June of 2006, we had an informational session. We decided at that point to move forward with an in-depth study that would focus on gene patents and licensing as they relate to patient access to genetic tests. We discussed the study's scope and the work plan at that point, and we established the Task Force on Gene Patents and Licensing Practices.

Then in October of 2006, now two years ago, we had the first task force meeting, where we refined the proposed scope of the study and we outlined potential approaches for the study. Shortly after that, at the full meeting of SACGHS in November, we presented the study scope and work plan, which were approved by the full Committee.

In February 2007, there was a task force meeting to discuss the study scope and work plan. We had at that time met with Bob Cook-Deegan. I want to give thanks to him, as well as to the rest

SACGHS Meeting Transcript  
December 1, 2008

of the members of his team at Duke's Center for Genome Ethics, Law, and Policy. Bob is a well-respected leader in this field.

His group agreed to develop literature review and relevant case studies to help us make some sense and learn what we could in some kind of systematic, organized way about this broad field so we could ultimately come to some conclusions that could lead to recommendations if necessary.

In March of '07, we had a special task force meeting. We had presentations by the Duke CGE and we discussed next steps.

On the very next day, at the SACGHS meeting, we had a primer session on gene patents and licensing practices, which I think many of us who only glancingly had dealt with patents and licensing in the past, say, through clinical activities, really benefitted from. It laid out a lot of the fundamentals, and the nuts and bolts on licensing and patenting, which can get quite arcane and quite complex.

We received an update from Duke, at that point, on the status of the literature review and the case study analyses.

Then, in July of '07, at the SACGHS meeting, we received a briefing on patent reform initiatives in the 110th Congress. At that time, we also had an international roundtable. This is not an issue that is by any means unique to the U.S. The issue of gene patenting and licensing has been one that has been very much front and center for many countries. We therefore felt that it would be foolish to ignore the experience of those other countries.

We received, basically, an overview of the international gene patents and licensing landscape. We reviewed the status of BRCA testing in Canada and the U.K., since BRCA has been such a visible and prominent feature of the gene patent and licensing landscape.

We studied comparisons of the patent system of the U.S. and several other countries, and we reviewed international reports and recommendations regarding these subjects.

The purpose of today's session is really three-fold. One is, we want to review and discuss the Public Consultation Draft Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests, which is in Tab 3.

We also want to review and discuss a range of policy options for public consideration. Again, because this is so complex, we did not feel that it would be fair to the full Committee, to ourselves, or most importantly, to the public, to at this point settle on concrete recommendations that we felt should be transmitted to the Secretary. Rather, what we have done is we have created a range of possible recommendations.

Those are up for discussion today and will be transmitted, when finalized, to the public. The public can use those as a framework from which to comment and make observations.

We can then come back armed with those public comments and settle on final recommendations. It would have been presumptuous, I think, of the task force, in this setting, at this point, to have come to concrete recommendations.

SACGHS Meeting Transcript  
December 1, 2008

We also want to seek the Committee's approval of this draft report, and we want to decide on the range of policy options for public consideration. These would be released for the standard 60-day public comment period in early 2009.

Now, since it has been so long since we have talked about gene patents and licensing, and because this is a field with some technical issues that need to be understood as we go forward, we thought that it would be useful to spend a few minutes reviewing the background of patents, to some extent, in general, and obviously specifically, how they relate to genes and the licensing issues involved.

Some of these slides have been taken from that earlier session in which we received a primer on gene patents and licensing. I went back and reviewed the slides of Jorge Goldstein, who was very helpful, among others, in helping us understand these issues.

Why define and protect intellectual property. If you go back to the Constitution, which we will take a quote from in a minute, it is really to promote progress in the sciences and arts. We want to promote the development of ideas.

Intellectual property protection should really be seen as something whose end is to promote the creation of additional intellectual property, to promote its use, et cetera. We want to promote the investment in ideas. We want to allow and encourage openness, and discourage secrecy, as a stimulus to further development.

This really crystallized for me as a clinician a few years ago. Those of you who are clinicians will, I think, understand something that I had not understood prior to this. In clinical medicine, we frequently talk about an artery being patent, being open. It is wide open and the blood can flow through it. I never understood why "pay-tent" was spelled in exactly the same way as "pat-tent."

[Laughter.]

DR. EVANS: It turns out that the whole role of patents is to keep the field open. So it makes tremendous sense. That really crystallized for me what the purpose of patents are. They are to keep the field open.

There is also a philosophical intent behind intellectual property, and that is to reward innovation, the idea of natural rights. If somebody comes up with something, they deserve some degree of reward for that.

The law recognizes a number of distinct types of intellectual property. One is a trademark, something like the McDonald's arches or the way "Coca-Cola" is written in script. That is a trademark, and it serves to communicate to the public what that product is and foster the advance of that company's idea.

Copyright is the protection of intellectual material. A song, a book, et cetera, can be under copyright.

Now, one of the things that patents are specifically designed to circumvent is a third way of protecting intellectual property, and that is the trade secret. Trade secrets are a viable way of protecting one's intellectual property.

SACGHS Meeting Transcript  
December 1, 2008

In fact, the recipe for Coca-Cola is probably the most famous example of that. They would have been advised early on by most people, including most patent attorneys, to go ahead and patent the recipe for Coca-Cola. It would have given them a limited-time monopoly on that.

They chose to keep it a secret, and many people would have said at the time, you're not going to be able to keep it a secret, that it's probably a bad move because it's hard keeping those secrets. They have been successful, but many people aren't. Patents are designed, then, to disincentivize, in a way, the idea of trade secrets.

If we go back to the Constitution, I think it is very important to look at what the Constitution has to say about why we want patents: "To promote the progress of science and useful arts by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries." So, really, it is the granting of a limited-time monopoly.

Again, I would point out that the purpose of this as expressed in the Constitution is "to promote the progress of science and useful arts."

Patents are really a tradeoff. The government grants a right of limited duration -- and typically in this country that is 20 years from filing -- to prevent others from making, using, selling, or importing the claimed entity. In return for this right, the patentee discloses the invention to the public, and this then presumably fosters further research and development.

To be granted a patent, one has to fulfill certain requirements. That invention has to be useful. There has to be some defined use for it. It also has to be novel and it has to be non-obvious. It has to be new and it has to be non-obvious to somebody who is "practiced in the art."

If we now zero in on the issue of patenting in biology, specifically patenting human material, there is a long history of that. It goes back almost a century. In 1911, adrenaline, or epinephrine, was patented. The courts ruled that this was a legitimate application of patent law because adrenaline had been purified and taken out of its natural environment. Intellectual expertise had been applied to do that, et cetera.

Insulin was patented in 1923 and prostaglandins in 1958. In the landmark decision of Diamond v. Chakrabarty, a bacterium was patented that had been genetically engineered to eat oil. Interestingly, that has never been used because of concerns about the environmental impact of releasing this bacterium into the environment.

Isolated genes and life forms are thus considered compositions of matter by the courts and are eligible for patenting by the USPTO. Most of the world, including Europe, China, Japan, Australia, and the U.S., allow patenting of genes, although there are significant differences in the threshold for awarding genetic patents and the criteria that must be met in different jurisdictions.

So, what is the problem? Why is there any controversy about gene patents? Why did we take this up? I think there are two reasons. I think that this is seen by many on both sides of the issue and at all points in between -- because it is clearly not just a purely dichotomous issue -- as both a moral and a practical problem.

There are many stakeholders with many different opinions and many different incentives. There are the public, patients, clinicians, industry, researchers in academia, researchers in industry itself, small innovators, and ethics-based groups. All of these people and all of these groups have some

vested interest and some positions that relate to patents and licensing of biological materials and, for our purposes especially, when it comes to genes.

These stakeholders have distinct interests. Their interests do overlap to an extent, but sometimes they are mutually exclusive. For example, we as individuals comprise the public, so we belong to more than one group of stakeholders with regard to this issue. We are all potentially patients and, unless we die before we get to the hospital, we will all be patients at some point.

Even those with no direct financial stake have an interest in commercialization if such commercialization enhances the availability of medical innovations, in this case, for our purposes, genetic tests.

This is an overview of the types of things that have been brought up on both sides of this issue, or both ends of that spectrum. It is a spectrum. It is not just a wall with two sides. There are many nuanced positions. People in one camp can agree with another camp in certain instances and disagree in others.

The perceived problems that are brought up when one begins to talk about gene patents and licensing are, and we will get into some of these, moral arguments, inhibition of research, inhibition of patient access -- for example, through effects on pricing or through limitations on volume due to a sole provider of a genetic test -- the inhibition of product or test improvement due to sole provider and lack of competition, inhibition of test verification, detriment to quality -- for example, no incentives to quality control -- and especially in the future, concerns about the creation of patent thickets.

There are many perceived benefits as well to patents and the patenting of genes. There are moral arguments on this end of the spectrum as well.

There is also the strong argument of induced investment, the idea that patents are designed to prevent what is called the "free rider" problem: somebody else does all the work but then you benefit because copying costs are low.

It compensates the need for post-invention investment, especially important in a realm where there are regulatory burdens to be met.

There is the idea of stimulating commercialization, the idea that test aggregation can be a benefit in and of itself, the idea that by granting patents and licenses one can empower the little guy to enhance innovation, and then, I think, the ever-present issue that gene patents and licensing cannot be thought of in a complete vacuum in regard to other patents and licensing.

Patents in general work pretty well in this country. They have stimulated a lot of innovation, and there is great concern that we don't want to throw the baby out with the bath water by tinkering with one aspect that then has unintended effects.

The moral and the ethical arguments can be boiled down, I think, to a couple of different positions on both ends of the spectrum. The moral objections to the patenting of genes are often phrased in a deontological or a Kantian context. That is, there is an inherent value issue at stake here. There is something inherently special about our genes. They define us in a special way that epinephrine and insulin perhaps do not.

SACGHS Meeting Transcript  
December 1, 2008

This is often phrased in terms of ownership. "No one should own your genes." As we will get into in a little bit, I think that those two things are actually separable from one another.

Those arguments oftentimes rely on a concept of genetic exceptionalism, which I think we all agree when overboard doesn't make any sense. But to some extent, genes are special. That is a balance that we have to grapple with. The very existence of this Committee, if you look at what the acronym stands for, in some ways implies that genes are special and that genetic technology has some special nuances to it which I don't think are irrelevant to this discussion.

There are also purely utilitarian arguments. There is the idea that patenting might inhibit research instead of promoting it, as is the intent. It might inhibit development and access by patients and clinicians to genetic tests.

The moral arguments for patenting genes are oftentimes, and I would say usually, utilitarian. Benefits accrue to society by harnessing self-interest via the granting of patents, and they thereby encourage innovation.

There are value-driven arguments as well. Rewards should accrue to the inventor. That is the Natural Rights argument for patenting.

One of the things I want to spend one slide of discussion on is this issue of ownership. I think that the arguments against the patenting of genes shouldn't necessarily be conflated with the idea of ownership. This is a slide essentially from Jorge Goldstein, who asked the question "Who owns your genes?" The answer, he claimed, was it depends. If they are in your body, you do. If they have been extracted and are in a test tube, the hospital, the company, or the lab owns them.

His point was that you own the tangible and the personal property, but intellectual property is in many ways divorceable from that tangible personal property and someone else can own the IP. That makes sense to me.

The effects of the current system of gene patenting and licensing on research was the focus of this NRC report that I mentioned that we spent some time discussing at a prior meeting. It addressed patents and licensing practices and primarily focuses on their effects on research and innovation. They ended up with 13 recommendations, and 12 of those recommendations had to do exclusively with research issues.

They concluded in the realm of research that for the time being it appears that access to patented inventions or information inputs into biomedical research rarely imposes a significant burden for biomedical researchers. They did have a caveat with that, however, and felt there were several reasons to be cautious about the future. That included the increasing complexity of the gene patenting and licensing practicing landscape, the potential for patent thickets due to multiplex technologies, and the impact on patient access to genetic technologies and testing.

Their final recommendation, Recommendation No. 13, had to do with concerns over independent verification of sole provider-offered tests, who limit such verification. I find that a bit of a distraction from the main issues here. I think that it is a great report but, again, all the more reason that this Committee took it up. Their choice of what to focus on from the clinical aspect, as clinicians, seemed a bit odd to many of us. Certainly, that wasn't their main goal.

A major function of the patent system is to induce investment. This is especially vital when development costs are high and copying costs are low. You don't want somebody having to

invest lots and lots of money in something so that everybody else can copy it. You need some kind of protection in that setting.

I would emphasize that the specific use to which genetic knowledge is applied affects the need for patent protection. This follows from that first bullet. I think that can all be summed up by saying that all gene applications are not created equal. There are applications of genetic technology that may have very high development costs and very low copying costs. There are other applications of genetic technology that actually have very low development costs, and thus it is hard to argue that one might need patent incentivization and protection for such uses.

I think we need to look at gene patents and licensing not as a monolithic entity. There may be a variety of different uses for such patents, some of which should, very logically perhaps, be afforded patent protection, others of which one could legitimately argue about.

The positive and negative effects of current gene patenting and licensing practices on patient access to genetic technologies was a focus of this task force. We focused on gene patents for health-related tests: diagnostic tests, predictive tests, and other clinical purposes. I will get to the definition of terms in a moment.

We wanted to look at both what we called clinical access and patient access. While we went over all of those at a previous meeting, I occasionally forget minor points that were in meetings two years ago, so we will go over those again.

We wanted to consider the effects of this on translational research. For very good reasons, translational research is in the news now. It doesn't do any good if you have advances that never make it to the bedside.

We specifically excluded drug or other therapeutic product development. That is a very different application of genetic technology and one that was not in our purview.

Here is the study plan. Those things in black, we have essentially done. We have undergone literature review, expert consultations, case studies, and have commissioned further research. We have gathered international perspectives, including identifying experts, had the roundtable I referred to, the analysis of those perspectives, and then the analysis and synthesis of the literature review, the data, the input from these experts, and the international approaches.

We tried to synthesize all that to develop this range of recommendations for further refinement and comment upon by the public. We are now at the threshold of eliciting some kind of formal public perspective. Obviously, this is something that, at any SACGHS meeting, the public can and is encouraged to make comments about.

Of course, now with the release of a draft report, we will solicit their comments in a formal way. We will then need to compile and summarize those comments. We will need to analyze those and eventually come up with a set of actual recommendations for the Secretary.

Today is in yellow. What we want to do is approve, if we can, the draft report to be released for public comment.

A couple things about terminology. We could spend days talking about what a genetic test is. A family history could be a genetic test. We obviously need some tractable, facile type of definition for our purposes.

What we settled on was that a genetic test, for the purposes of this study -- we are not trying to make any claims about any broad definition -- is any test performed using molecular biology methods to test DNA or RNA, including germ line, heritable and acquired somatic variations. This would include things like microarray technology, sequencing, TACMAN identification of a particular allele, et cetera.

We used the term "clinical access" to mean the access by a healthcare professional to obtain the tests that they feel are required or of benefit to their patients. This involves, necessarily, the issue of reimbursement and cost issues, in addition to the medical use of genetic information.

Finally, "patient access" is pretty straightforward: Can the patient get a needed genetic test.

We had a number of study questions. Some of these were answered in more detail than others for a variety of reasons: What is the role of U.S. patent policy in patient and clinical access to existing and developing genetic tests; how does a patent owner's use, enforcement, and licensing of patented genetic information affect the patient and clinical access; how does legal interpretation of the patentability and patent boundaries affect patient and clinical access to such technologies.

I think, all through this, we should keep very firmly in mind the impact and the relationship between patents and licensing. How one handles patents in the realm of licensing is absolutely critical to things related to access by patients.

We will be talking a lot about licensing practices: How are licensing practices affecting patient and clinical access to genetic information and tests; how are licensing practices affecting the ability of industry and academia to develop genetic tests; what role do technology transfer programs play in influencing clinical access to genetic tests; what kind of evidence have we found, and can we find.

If there are barriers to patient and clinical access to genetic tests, where within the healthcare system do those barriers exist; what elements of the patent system relate to these aspects of the healthcare system. With regard to the development and the translation of this type of research, in what ways do gene patents and/or licensing and enforcement practices enhance or create incentives or barriers to the development, implementation, and continued performance of clinical genetic tests.

How about cost? What are the economic data, or the studies that analyze the contribution of gene patents to the cost of genetic tests and, ultimately, to patient access and treatment outcomes; what is the evidence of positive and negative effects of gene patents and licensing enforcement practices on the cost and the pricing of genetic tests.

Quality is often brought up in this context as well: How is the quality of genetic testing affected by the current landscape of gene patents and licensing practices; how are such patents and practices impacting, and how might they impact, the ability to perform multiple gene tests, panels, and arrays.

One of the things that I want to emphasize as a clinical geneticist is that it is clear to many of us that the future of genetic tests likely lies in multiplexing and the increasingly robust technologies we have for genomic characterization and scrutiny. I think that it is very important, as we go forward thinking about gene patents and licensing, to think about how these policies will play out

in a new era where, for example, the \$1,000 genome will likely be a reality within the next few years.

What other measures and approaches could be employed to assess the direct effect of gene patents and licensing practices on patient access and treatment outcomes to genetic tests?

There have been a lot of alternative models that have been proposed to try to handle these types of things. Are some of those feasible, perhaps ones that have been developed by other countries? Are there innovations that could be applied to the patent and licensing system to enhance the benefits of the system to help ameliorate problems that are identified.

What are the lessons from parallel situations in health care and in other areas? Software comes to mind. Software has dealt, in many ways, with similar issues of enhanced or restricted access to a given technology or information.

Coming down on that huge busy slide, our study plan consisted, in part, of literature review, expert consultations, case studies, and some additional research.

There have been a number of previous policy studies. This is not a field that there is any paucity of studies and opinion on, which is something that makes it all the more daunting for our group.

Can we say anything new about this? My own view is that yes, we can, because we crafted the scope, amongst this Committee, to look at something quite specific, and that is our major charge, which is patient access to the fruits of this kind of technology. Many of the previous studies have had much broader aims.

The Nuffield Council released a report on the ethics of DNA patenting. The Federal Trade Commission, in 2003, looked at the proper balance of competition and patent law and policy. The Australia Law Reform Commission delved deeply into these issues in 2004. The Organization for Economic Cooperation and Development, in 2006, released guidelines for the licensing of genetic inventions. Then there was that oft-referred to report that I mentioned before from the National Research Council that came out in 2006.

We felt that a very productive way of trying to learn lessons about where we stand and where we are going, in the realm of gene patents and licensing, would be through commissioning case studies that we will describe in some great detail. These case studies were commissioned by us and were conducted by Bob Cook-Deegan and Shubha.

Shubha, I am just not even going to try to butcher your name. I apologize.

DR. CHANDRASEKHARAN: You already butchered Bob's.

DR. EVANS: Bob Cook-Deegan. How could I butcher Bob's name? Did I not say "Deegan"? I'm sorry, I'm sorry.

Regardless of exactly how you pronounce their names, it is an extraordinarily talented group. They are not very good at basketball, but they are great at this stuff.

[Laughter.]

DR. EVANS: They have done a tremendous job of really, I think, as best as possible, distilling some lessons from the current landscape by looking at natural experiments in gene patenting and licensing. They focused on a number of case studies which are instructive, each for their own peculiar and particular reasons, which we will go into.

They looked at breast and colon cancer, Alzheimer's disease, spinocerebellar ataxia, hearing loss, hemochromatosis, Tay-Sachs and Canavan disease, cystic fibrosis, and finally, Long QT syndrome.

These were not picked at random. These were picked for very specific purposes. They provide a nice, broad analysis of patenting and licensing formats for disease genes. They include most of the most clinically pursued tests in the clinical realm. Because of their juxtapositions, for example with breast and colon cancer in one study, they provide natural experiments for trying to tease out the role of patents and licensing.

We can learn some general lessons from these things. We can look at diagnostic development, the commercialization, communications and marketing, what the adoption by clinical providers and testing labs has been like and how it perhaps is influenced by the patenting and licensing landscape, whether adoption by third-party payers is influenced, and things like consumer utilization.

Parameters of access are multi-fold. One is whether a diagnostic test is even available, and whether improvements are available, because just having a test available isn't necessarily what you want. You want a test that is able to be improved as technology advances.

You want to see that the cost of the test is reasonable to both the provider and the patient. You want to see how quickly a test is available following discovery of a connection between a particular genotype and phenotype and how rapidly that test evolves and improves as future discoveries are made.

Finally, another parameter of that is simply the number of distinct test providers that exist. There are many factors that affect access.

Some of these are directly influenced by intellectual property rights. For example, the availability of a test following the discovery that a particular gene or mutation is associated with that disease is directly influenced by the IP landscape. The number of providers offering a test is directly influenced by how licensing is carried out, et cetera, and how infringement claims are enforced by a patent holder.

The test price directly influences access in the sense that if it is exorbitantly priced, very few people are going to be able to avail themselves of that test.

There are a number of indirect factors as well. Coverage and reimbursement in our, to use the term loosely, medical system is very important. If a test is not covered, that affects access in a profound manner.

The utility of a test for clinical decision-making is important, and the evidence for whether it has utility or not has an important impact on access.

Quality of testing services is important. Again, it is not good enough just to have a test. You need a test that is of high quality.

There are logistical issues; that is, hassle factors. If a test is very difficult to get, that is going to indirectly affect access, as will the fear of genetic discrimination.

It is amazing to me. In some ways I think the passage of GINA has raised the awareness of genetic discrimination in the public's mind. It is rare for me to go a single day in clinic without being asked about fears of genetic discrimination by a patient undergoing testing. It is amazing the impact that has. I think it, again, adds to the importance of what this Committee did in trying to promote the passage of GINA.

Now, before I start talking about the case studies, any comments? I hope people will jump in. I know this is such a shy and retiring group. We actually have two people who are literally retiring.

[Laughter.]

DR. EVANS: But I don't think anybody here is very figuratively retiring, so please hop in and comment. I don't mean to make an unbearable monologue.

So let's look first at breast cancer and colon cancer from a hereditary standpoint and the patenting landscape. No particular test has gotten more attention, I think it is safe to say, than BRCA1 and -2. Interestingly, I would add that BRCA1 and -2 are the most sequenced genes in the history of biology. Hundreds of thousands of individuals have had their BRCA1 and -2 genes sequenced. It is really a massive experiment in analysis of human individuality.

BRCA1 and -2 and the colon cancer genes have been sequenced so many times because they offer clinical utility. There is value to a patient and to a provider in knowing someone's status with regard to BRCA1 and -2 and HNPCC.

BRCA1 and -2 are genes that, when mutated, increase the risk of breast and ovarian cancer in those individuals who harbor those mutations. Broad patent rights exist to both genes and are held by Myriad

Genetics in Salt Lake City. They are the sole provider of full-sequence BRCA testing in the U.S.

Now, Hereditary Non-Polyposis Colorectal Cancer, HNPCC, or Lynch syndrome, as well as Familial Adenomatous Polyposis, are both colon cancer syndromes that differ significantly clinically, but the take-home message is that both result in an extraordinarily high risk of colon cancer during one's lifetime.

Mutations in the Lynch-associated genes, primarily MLH1, MSH2, and MSH6, as well as the FAP-associated gene, which is the APC, or Adenomatous Polyposis-coli gene, are very strongly associated with the risk of developing colon cancer. Patent rights for these genes are predominately held by nonprofit entities and are licensed non-exclusively. That is in stark contrast to the situation with BRCA1 and -2. Multiple test providers for full-sequence analysis of genes associated with HNPCC and FAP exist.

So one can immediately see you have a natural experiment here. You have similar types of predictive power from these genetic tests, in one case for breast/ovarian and in the other case predominantly colon. In one case you have a sole provider, an exclusive license, and patents that are enforced, and on the other hand you have the colon cancer situation in which you have

multiple non-exclusive licensees of that testing and it is not by any means a sole-source type of test.

Let's look first at test price. This is a good case by which to try to tease out the impact of gene patents and licensing on cost. This is something that I think surprised many of us. It surprised me. Let's march through this.

Full-sequence analysis of BRCA1 and -2 costs \$3,100. Actually, that is up to about \$3,300 now. This slide is a little out of date. HNPCC testing ranges from \$1,150 per gene to \$4,760 for sequence analysis of those three major genes I mentioned.

HNPCC rearrangement testing services vary in availability and cost. I should mention that the BRCA1 and -2 analysis includes large rearrangement analysis and, if a patient meets a certain threshold of risk, another technique that is performed to look for smaller types of insertions and deletions.

FAP testing ranges from \$1,200 to \$1,800 for sequence analysis of that gene. FAP rearrangement or dosage testing services vary in availability and cost.

Myriad not only offers BRCA1 and -2 testing, and indeed, of course, is the only one to offer that, but they also offer colon cancer testing for APC mutation detection through sequencing. They also offer Lynch-associated gene sequencing and rearrangement analysis.

Probably the best way to try to compare costs in the realm of this type of diagnostic is the cost per amplicon per segment of the gene that needs to be amplified by the polymerase chain reaction. That cost per amplicon by BRCA1 and -2 is \$38 per amplicon.

The APC gene, which again is not exclusively licensed, is available through many sources. It costs at the same place, at Myriad, about \$41 per amplicon. That includes southern blot rearrangement, insertion/deletion testing, and a couple of founder mutations for the MYH gene.

The cost of testing through the nonprofit competitor laboratories ranges from \$1,200 to \$1,600, from \$28 to \$40 per amplicon. Rearrangement testing is generally not included in that price. So you see relatively equity in the costs of these tests. Kevin.

DR. FITZGERALD: A quick question. I can understand why you picked amplicon. I didn't see some of this in the case studies, but I didn't look at them that closely. I imagine it is in there. What about the predictive levels of the tests? Are they all pretty much comparable?

DR. EVANS: Yes. Throwing out APC for a minute, if you have classic FAP you have 100 percent chance of getting colon cancer throughout your life. But if you compare Lynch syndrome, HNPCC, with BRCA, they are amazingly similar. It is about an 85 percent chance of colon cancer to the age of 80, and it is about an 85 percent chance of breast cancer if you have a BRCA1 or -2 mutation. So, really a very nice natural experiment.

COL McLEAN: I was just going to say, if you throw in the attenuated FAP studies, it washes out.

DR. EVANS: Right. What Scott is bringing up is there is a condition called attenuated FAP in which the risk is not 100 percent. So really, you lump them all together and, again, it is a beautiful natural experiment.

Yes, Sylvia.

MS. AU: I'm sorry. I forgot. Were these the advertised prices or the institutional prices?

DR. EVANS: This is if you send the box to Myriad or send it to those labs. That is a bit arcane. What Sylvia is referring to is when you send a lab test out through a laboratory, like hospitals, there is additional cost tacked onto that. This does not include that. Or, you can negotiate a lower price.

So, trying to estimate patent premiums. Lynch syndrome is offered by multiple providers, including Myriad. It is non-exclusively licensed. The cost of testing through Myriad is \$3,000. That comes to about \$50 per amplicon. That includes southern blot analysis. That is compared with \$38 per amplicon for their BRCA test. This is a within-laboratory comparison of, on one hand, the exclusively self-licensed BRCA test versus the non-exclusively licensed Lynch syndrome test.

The cost of testing through nonprofit competitor laboratories ranges from \$30 to \$77 per amplicon. It generally doesn't include rearrangement testing.

There are concerns regarding Myriad's sole provider status. Analyzing Myriad and BRCA1 and -2 has become a cottage industry. It is like the Cuban Missile Crisis; there is a book that comes out every six months. There is a study that comes out every six months on BRCA1 and -2. You can learn a lot from these, but they really get to be tedious reading after a while.

Some of the concerns include what constitutes infringement and the concerns that there is too broad a consideration of what actually is infringement. There is concern that this sole provider status limits strategies for testing.

There was a furor a couple of years ago about the possibility of incomplete testing that we can talk about if you want to. Basically, the idea was that when you have a sole provider there is presumably less incentive for that provider to offer innovative new tests that could increase sensitivity or increase specificity.

That was brought into focus when an article was published by Mary Claire King's group in JAMA that showed that a certain percentage of BRCA mutations were not detectable by the then-current procedure that Myriad used. Shortly after that, Myriad came out with that more extensive analysis that could pick up those deletions and insertions.

There are concerns regarding Myriad's patent enforcement. A 2003 survey found nine instances of enforcement of BRCA patents by Myriad. That same survey found two instances of FAP patent enforcement and no instances of Lynch, or HNPCC, patent enforcement. Enforcement actions basically serve to clear the market and drive users to Myriad's testing services.

The question arises, did the prospect of patents encourage the search for gene-disease association in the first place. If the prospect of a patent on a gene is a major driver in the discovery of that gene's association with a disease, then that is, arguably, an important benefit.

In the case studies, the precise stimulus for a breast/ovarian cancer gene search was unclear. Access to data and exclusive rights to therapeutics involving genes attracted industry funding for the search. I would point out that therapeutics and genetic testing are very different things.

SACGHS Meeting Transcript  
December 1, 2008

The development and commercialization of a test for HNPCC gene, MLH1, did play a role in stimulating research in this area. The HNPCC patents were non-exclusively licensed once they were discovered. Yes?

DR. AMOS: I was just wondering if you had looked into the issue of having access to patents and the protection it affords into incentives for investing in other genetic testing companies by investors.

DR. EVANS: In what way?

DR. AMOS: Myriad has made a lot of money with this.

DR. EVANS: Actually, they haven't. They have lost money every quarter.

[Laughter.]

DR. EVANS: Seriously, it's a very interesting story.

DR. AMOS: They are spending more on R&D than they get in revenue. But I'm just wondering, because I think that is an important thing to consider.

DR. EVANS: Right. Actually, keep that in mind because some of the other case studies I think address that perhaps better than this one does.

DR. LEONARD: One of the things that is interesting to think about is that a large proportion of gene patents are held by academic institutions. I think basically the drive there for invention is the fact that you have patients who are sick and need diagnostic or therapeutic interventions that don't currently exist, as well as the academic promotion system that requires physicians and researchers to invent and create and do research to be promoted and succeed in their own careers.

While academic institutions certainly benefit from patents that bring financial gain to the academic institution in the currently nebulous academic economic environment, that is not really the driving force for these inventions. Since the vast majority of these are held by academic institutions, and we can talk about their misuse in the licensing of these, it doesn't seem to me that the patent system drives these inventions.

DR. EVANS: I think that is absolutely true. I think that is important. As we march through these, keep in mind what Debra says. I completely agree. I think that the incentive for discovery in this realm arguably has not been dependent on the prospect of patents. We address that in each of these case studies.

The role of patents in test commercialization. Again, it is important not only to make these discoveries but to commercialize them, or at least get the tests out there so people can get them. It is not enough just to discover them. That really was the genesis of the Bayh-Dole Act.

Myriad enforces its BRCA1 and -2 patents. It serves as the sole provider. Patents for Lynch syndrome-associated genes have been licensed non-exclusively. So, has there been a difference in the commercialization? It doesn't appear so. You can get Lynch syndrome testing in a variety of different venues. You can get BRCA testing at Myriad.

How do patents and licensing practices affect price. As the sole provider of BRCA1 and -2 testing, the main effect of the patent really comes down to testing volume. Presumably, the business plan that Myriad is pursuing is that they are able to get a higher volume. Therefore, they are content with a lower price and getting that higher number of users, versus if they were to charge a higher price and have fewer users.

There is another externality in this whole economic equation in genetic testing that hinges on the bizarre aspects of our medical care system, and that is the issue of third-party payers. If you own a patent on a gene and you don't license it and say, I'm going to be the sole provider, there is also a limit on what you can charge because, except for the 47 million people who don't have insurance, people are used to having insurance pay for their medical tests. You have to keep that in mind as you price the test, and that is another externality that is important to consider here.

DR. WILLIAMS: The other point to consider relating to this is that part of the Myriad business model was that the full sequencing test was really going to be an entry for what they anticipated would be a large number of family members that would have targeted sequence analysis, which would then also generate revenue. Of course that is a lower-priced test, but you could argue that the marginal profit on that test is higher than the original sequencing.

Now, part of the issue relating to their current business and profit relates to how many family members they thought would avail themselves of the follow-up testing, and that is an issue. But that does impact that top price.

DR. EVANS: It sure does, yes.

So, what is the potential that the patent might cause some future harm. I think that while, as Yogi Berra said, making predictions is difficult, especially when they are about the future --

PARTICIPANT: Niels Bohr said that.

DR. EVANS: Oh, it was Niels Bohr. He is a much higher authority, actually.

[Laughter.]

DR. EVANS: The question I think we have to keep in mind is, obviously we are not going to be able to know what the landscape will be like in the future. But I do think we have to try very hard to anticipate problems that loom large.

Now, Myriad could conceivably file patent applications for new mutations identified in these genes. I actually think that is quite unlikely. There have been thousands of individual mutations that have been identified. I don't think that is a realistic fear.

On the other hand, I think that we have to think hard about whole genome sequencing and how it will have an effect on this whole landscape. We are already able to do whole genome genotyping at a million loci in an afternoon. I think most people realistically feel that in the next few years we will have whole genome sequencing at some feasible realistic price. How is that going to interact with the fact that, by some estimates, 20 percent of your genome is staked out in patents.

Case No. 2 is the Alzheimer's disease study, which has its own particular lessons that can be learned. There have been essentially four genes associated with Alzheimer's disease in humans. Three of those genes are what we call high-penetrance, low-frequency genes: Presenilin-1 and -2

and the Amyloid Precursor Protein. These are genes that, when mutated, result in an extraordinarily high risk of early Alzheimer's disease. Mine will be kicking in this afternoon, but hopefully we will be done with this session by then.

In contrast to that, the ApoE gene is polymorphic in the general population. One allele of the ApoE gene, the ApoE-4 allele, is predisposing to run-of-the-mill, garden-variety Alzheimer's disease. If you have an ApoE-4 allele, or if you have two ApoE-4 alleles, your risk is higher than it would have been otherwise for Alzheimer's disease, but there is no deterministic aspect to this like there is in Presenilin-1 and -2 or Amyloid Precursor Protein mutations.

ApoE-2, on the other hand, is protective of Alzheimer's disease. One sees a lower risk for those lucky individuals who carry one of those polymorphisms.

Broad screening is not recommended for any of these genes. You test those three first genes, Presenilins and APP, if your patient is in a family that has early-onset Alzheimer's at a very high prevalence in the family.

ApoE-4 is an allele that is shared by many of us in this room. It is generally considered that it is pointless at this point, and perhaps harmful, to just engage in screening of the population for the ApoE gene. That could change. That could change, for example, if preventive measures came to the fore which could be applied in individuals who were at higher risk. But right now nobody is really recommending ApoE screening in the general population.

On the other hand, its recommended use is to confirm a diagnosis in individuals who have already developed dementia. It is not a very clinically useful test, but it at least theoretically could help you have some increased confidence in your diagnosis of Alzheimer's disease in an individual patient.

ApoE testing, interestingly, is also available for cardiovascular risk-determining purposes, but that side effect, if you will, of also learning about your Alzheimer's risk is one that plays out in such a manner that very few people get ApoE testing.

Patents have been issued in the U.S. relative to testing for all four of those genes. Duke University holds three methods patents on ApoE testing which are licensed exclusively to Athena Diagnostics.

Athena charges \$475 for their ApoE testing. You can see the range of prices there among other labs.

I would point out, just so people don't get confused, that the test for ApoE is a very different test than something like BRCA or Lynch. That is really what underlies how much cheaper this test is than those other tests.

Health insurance companies differ over whether to cover Alzheimer's disease testing or deny claims on the ground the tests are still experimental.

DR. LEONARD: Just so you don't think it is just Canadian laboratories, when the University of Pennsylvania laboratory was stopped from doing ApoE testing we were charging \$125.

DR. EVANS: That is important.

So, did the prospect of patents encourage the search for gene-disease associations. The case study indicates that the prospect of a patent really was not needed to stimulate research in the area of Alzheimer's disease.

How about the role of patents in test commercialization? Patents provided a mechanism for aggregating patent rights from disparate academic groups and consolidating that testing.

Now, whether that is a plus or a minus depends on which side of the fence you are talking about. I think you can argue that aggregation just in and of itself is not necessarily a good thing, though in certain circumstances it can be useful and it can be a good thing.

It was intended, according to the patent holders to this exclusive licensing, to limit the testing to individuals already diagnosed with dementia. That is, they felt that patents were a mechanism by which they could help ensure proper use of this test clinically. I'm not sure how well that has worked.

So, how is price affected. It is unclear how Athena's enforcement of this exclusivity affected price, although, as Debra just mentioned, the University of Pennsylvania's prices, before they were prohibited from testing, as well as the Canadian providers', were significantly lower. Price information wasn't available for the Presenilin-2 and Amyloid Precursor Protein. Yes.

MS. DREYFUSS: Can you clarify what you mean when you say the patent is helpful in aggregating the tests? If there would have been no patents, any one company could have given all the tests.

DR. EVANS: I think that is a fair statement.

MS. DREYFUSS: So I don't understand what the word "aggregation" means.

DR. EVANS: Bob, do you care to comment on that?

DR. COOK-DEEGAN: The argument goes that it prevents others from entering the market if you make the investment in entering it first. That is the argument. So you aggregate the patents and you prevent other competitors from being able to enter the market.

MS. DREYFUSS: Either that is an argument about free riders or it is an argument that says you want to achieve economies of scale and that way you don't have any competitors. But it is not really an argument that without the patents you couldn't offer all those tests.

DR. EVANS: In fact, there are a lot of common examples. Look at something like Lynch syndrome. You have aggregation without patents.

Yes, Lori.

DR. PRESSMAN: The business reason to do it is that the aggregate market might be larger than if it is fragmented.

DR. EVANS: Yes. So, how about the role of patents and licensing in the availability of the test. It is unclear whether Athena's monopolies will benefit or harm availability in and of themselves. Athena offers two programs that reduce out-of-pocket cost of testing. One is their Patient Protection Program that limits the cost that a patient will have out of pocket to 20 percent of the

test. Now, for this test, that is, arguably, not a huge amount of money, but keep this in mind as we go on.

They also have a program called Athena Access that offers free or low-cost testing to some patients. Yes.

DR. LEONARD: As a clinician, have you ever been able to access this program with Athena?

DR. EVANS: Let's hold off and get to that in a minute because I will answer that question when we are talking about SCA.

What is the potential that the patent may cause future harm. It isn't clear whether multiplex tests would infringe on the patents in this particular case, and it is not clear whether direct-to-consumer tests like Navigenics would infringe on patents by indirectly assessing Alzheimer's risk.

This is interesting. I Emailed Bob about this just a few days ago. It looks like in the Navigenics test that what is being tested is a SNP that is about 14KB from the ApoE gene and it is tight linkage disequilibrium. So my thinking was that, actually, that particular application may not infringe. But certainly, with sequencing of that region I would think you would have a pretty clear case of infringement.

Spinocerebellar ataxia is a really bad disease. All these diseases are not ones I would sign up for, but this would be really low on my list. It is a rare subset of neurological diseases, and it is characterized by loss of cells in the cerebellum. That is the region of the brain that really controls your spatial orientation, the way your body knows where your limbs are, et cetera.

These can be inherited in a variety of mendelian patterns. It is a genetically heterogeneous group of diseases with dozens of genes responsible for clinically highly similar conditions. I think it is really important that we all remember this issue of genetic heterogeneity going forward because it is going to come up over and over again as we talk about genetic testing and patents.

When you see a patient who looks to have spinocerebellar ataxia, in most cases you really cannot figure out which of the many, many genes -- there are, I believe, 34 genes that have been identified so far -- except in rare circumstances, might be mutated in your patient. What that obviously means, then, is you can't just say, I'm going to sequence this one gene, or I'm going to sequence these two genes. You have to sequence or look at a bunch of genes to try to find the mutation.

There are population differences in the prevalence of various mutations. For example, in the Mexican population, there is a higher prevalence of SCA10. Spinocerebellar ataxia accounts for only about 5 percent of the ataxic population.

Ataxia just means that you are doing this when you walk. You can't walk, you can't maintain balance. There are many reasons for ataxia, with these particular syndromes representing a minority of the etiologies.

There is testing available for 15 variants of SCA. Athena holds the patent or exclusive license to 12 patents that identify the most commonly occurring variants, constituting about 60 to 80 percent of SCA cases in which it looks like there is a genetic underpinning.

They were granted a non-exclusive license by Baylor for one of those genes, SCA10, and they have been aggressive in the enforcement of this exclusive license. It is widely assumed that they are the sole distributor of these tests.

How about price? This is an expensive test. Yes, this is your question.

DR. LEONARD: No, no. Can we go back to the previous slide? I would like to point out, while they may currently be the sole provider, there was actually a consortium of laboratories that worked on SCA testing, the best ways to do it and how to offer it. The vast majority of those labs are no longer in business.

DR. EVANS: Right. The market has been cleared. We will get to that. That's right.

Testing for individual genes can range from \$400 to \$2,300. Again, remember that issue of genetic heterogeneity. I saw a patient last week who clearly has SCA, but there were no real defining characteristics of her disease that allowed me to pick and choose and say, oh, we need to sequence this gene to figure it out.

Therefore, what one typically needs to do is the complete ataxia panel. It is a compilation of 13 tests that covers the most commonly identified mutations. It is \$7,300 dollars. That is an expensive blood test.

Now, there are these two programs to reduce out-of-pocket costs of testing. One is this Patient Protection Program, limiting to 20 percent the out-of-pocket expenses for a patient whose insurance doesn't cover the test.

Now, I would just point out that 20 percent of \$7,000 is over \$1,400. That is significant. For the population of patients that I see, that is a prohibitive amount of money.

The Athena Access offers free or low-cost testing to some patients. I have never had personal success -- and this is answering your question, Debra -- in getting this done. It is a laborious procedure with the documentation that is required.

I'm sure it is done. I'm sure it is a solution. It is certainly not the solution for getting access to these tests. Scott.

COL McLEAN: Just two points. One is that it still is within the prerogative of a provider to go one test at a time and not do the panel. That is a practice of medicine, if you chose to do that. Being forced into doing a package deal is, in a sense, a limitation of your prerogative, as a provider, to do whatever strategy you want to create. I wouldn't recommend it.

DR. EVANS: It is your prerogative, but look at these prices. I do this every time I see a patient.

COL McLEAN: It is cost effective to do them all at once.

DR. EVANS: Yes. If you guess right, you save money. But if, as is likely, you guess wrong sorting these out clinically, you end up spending more money by doing the tests one at a time.

COL McLEAN: But if somebody added to the panel things that you clearly didn't think were indicated on a clinical basis, you would be forced into doing something you weren't interested in.

SACGHS Meeting Transcript  
December 1, 2008

DR. EVANS: That is true. So it would be nice to be able to do a menu to pick and choose. Yes, that is a good point.

COL McLEAN: The other point I would like to bring up is that in the military healthcare system patients are never going to pay out of pocket for any component of a testing panel, so that 20 percent rule wouldn't really be a benefit.

DR. EVANS: Right. But obviously, most people aren't in the military healthcare system.

COL McLEAN: No, but I'm representing them, so I wanted to speak up.

DR. EVANS: I see.

[Laughter.]

DR. EVANS: Exactly. The solution is we should all join up. Mara.

MS. ASPINALL: Just a comment about the Athena Access program or the Broad Access program. I, as a non-physician, have not tried to access it but have tried to manage that program. With the anti-kickback rules and the requirements that you need to do to continue to have open and equal access, it is extremely difficult to actually have the ability to have those tests open. There are some who have interpreted that that you actually need to get the tax return of the patient to do that.

DR. EVANS: Oh, yes. W-2s are required.

MS. ASPINALL: I think as we talk about whether anyone has successfully accessed that, it may be difficult but not necessarily a futile endeavor to do it. Several of the companies have come, and I don't know if they will testify to this in this meeting, but they have talked publicly about allowing access to be open, making that procedure not so burdensome to the company but, more importantly, not so burdensome on the patient to truly have to submit a tax return to get free or low-cost testing.

DR. EVANS: I think your point is well taken. I haven't looked at this firmly. I just know from my experience that the access is difficult with this program. I don't know why. There could be all kinds of reasons.

MS. ASPINALL: I just didn't want to imply that it was their specific program or any one company's program. In Medicare you have to go by these rules and the tax return hurdle is just ominous.

DR. EVANS: It has been my experience as a physician that all of these programs are extraordinarily cumbersome, and I'm sure there are reasons like that that cut across from company to company.

So, did the prospect of patents encourage the search for gene-disease association. That really was not addressed or addressable well in this study.

How about the role of patents in test commercialization? Various patent holders exclusively licensed their patents for different SCA gene variants to Athena, which then developed various

SACGHS Meeting Transcript  
December 1, 2008

genetic tests, including a testing panel. Athena has a non-exclusive license, as mentioned, from Baylor for that one particular gene. Yes.

DR. LEONARD: But while the patent is encouraging the search, I think almost all of these are from academic institutions.

DR. EVANS: Yes, I believe they all are.

DR. LEONARD: Right. So I don't think they were out there going, come on, you guys, do this research so we can get the patents.

DR. EVANS: I agree with you. I think your point is well taken. I think one of the things that maybe we need to stress in the report that was not is the other incentives that exist in academia which have proven highly successful in incentivizing gene discovery, et cetera.

DR. LEONARD: I hate to be corny, but most of us became physicians because we cared about patients and health care and making patients better. Sometimes that doesn't mean taking care of one patient at a time but it means finding better ways of curing diverse patients, which is why we do research.

DR. EVANS: I completely agree with you. I don't, though, want to imply from this Committee that people who go into non-academic pursuits don't have those same goals.

DR. LEONARD: But they do have a business model behind their activities.

DR. EVANS: Yes.

DR. ROHRBAUGH: I would like to make a comment. From Lori's side, I think it also shows how complicated this is in that her numbers showed 78 percent of the DNA patents were owned by for-profit companies, only 22 percent in the non-profit community, and of those, only half designated government funding.

The other complexity is defining what is a DNA patent. Her study shows that there is not a good correlation between defining a definition of DNA patent and gene diagnostics, which makes it even more complicated.

DR. EVANS: Yes. And difficult to tease out lessons. That's right.

I think we have covered that slide. Next is the role of patents and licensing practices in test availability and this aggregation point that Rochelle brought up.

I think that it is a prima facie case that Athena's aggregation enables a single laboratory to test for many variants that contribute to a rare syndrome. I think, however, it remains an open question as to whether such licensing is necessary for aggregation testing. I think we all agree that having a single source to do the testing involved in SCA makes sense. I don't want to have to send six different tests to six different labs to get SCA testing.

But I think it is very much an open question as to whether that wouldn't occur anyway without exclusive licenses. In fact, if you look at HNPPC or Ehlers-Danlos syndrome, there is plenty of precedent for aggregation of tests, including what Debra has mentioned for SCA, prior to enforcing the exclusive licenses for such clinical aggregation.

SACGHS Meeting Transcript  
December 1, 2008

DR. LEONARD: Right. Every laboratory that was doing SCA testing practically, as new genes were discovered, were bringing online that new test. In fact, most laboratories were then going back and retesting all their patients who had been negative for the previous ones. If they found a positive, they would call the clinician and say, maybe you want to order this new test on your patient. Some labs would even give that result out for free. It depended upon the IRB approval process under which they were doing the development of the new test.

So it was being done in aggregate anyway, one new gene at a time.

DR. EVANS: That is why I added that bullet. That's right.

So, what is the potential for future harm. Athena's consolidation of IP-related SCA results in an effective monopoly. The enforcement of their patent rights, or their licensing rights, has been aggressive, leading several labs that might have or were offering SCA testing to avoid offering those services. The lack of competition raises concerns of reduced incentive to improve testing services.

One clear example of hindrance to access that has come up a couple of times from clinicians, and this is something I'm hopeful that the public will flesh out as we release this draft report, is the situation in which a major third-party payer does not have a contract for whatever reason with a sole provider of a genetic test.

For example, MediCal, which covers a lot of people, is the state Medicaid program in California. It does not have a contract with Athena. Therefore, they can't get SCA testing done, period. It is as simple as that. There is no alternative testing available because Athena has been aggressive in limiting the ability of other labs to offer such testing. This is, I think, a clear example of hindrance and one that is a problem. Yes.

DR. LEONARD: Can we just change the word "several" labs? It was "many." "Several" indicates to me, one, two, or three. It was many labs that were doing SCA testing that were shut down.

DR. EVANS: Maybe we could find out how many. Right.

The next case study regards hearing loss. There has been a huge amount of interest in defining the genes that contribute to hearing loss because it is such a profound problem for toddlers and babies.

There have been at least 65 genes, probably more, that have been implicated in hearing loss. Mutations in five of those genes comprise a significant bulk of hearing loss cases. We have Connexin 26 and Connexin 30, as well as SLC26A4 and then these two other genes bulleted.

Genetic testing is available through multiple providers for those five genes listed above. Three of those five genes are not patented. Those are Connexin 26, SLC26A4, and MTT51.

The test prices don't appear to correlate with patent status, as I will show you in a minute. GJB2 testing is licensed exclusively to Athena but is offered by at least 10 other providers. MTRNR1 testing is licensed exclusively to Athena but is offered by six nonprofit providers.

So it would appear that there is a lack of enforcement at present. Clearly, there is a potential for problems if enforced. Yes.

SACGHS Meeting Transcript  
December 1, 2008

DR. FERREIRA-GONZALEZ: There are some changes that are happening for hearing loss testing that I can tell you about from experience in my own laboratory more recently.

There are laboratories other than Athena Diagnostics that can offer Connexin 26 testing. The reason that they have been able to offer these tests is because of another company called Third Wave Technologies that gives us a way to detect a specific mutation, Delta-35G.

Athena holds the rights of the patent. Third Wave has decided not to provide those reagents anymore. It provides an alternative method for detection, but my laboratory will not be able to offer this type of testing anymore.

DR. EVANS: Will not be able to offer it?

DR. FERREIRA-GONZALEZ: Yes. Because now we have no way to address the Delta-35G.

DR. EVANS: Why has that transpired; do you know?

DR. FERREIRA-GONZALEZ: There is no economic incentive for the company, I guess, to provide those reagents for those 10 laboratory providers.

We have developed the test. We have generated the insight or knowledge of how the testing is done and developed some of the limitations, so we can very easily talk to our providers about that. So this landscape might change very rapidly since these more recent developments.

DR. EVANS: Yes. I don't know if that is distillable in a paragraph, but at some point if you could shoot us a paragraph about that, that would be very valuable.

DR. LEONARD: This has been a very recent development. Maybe Steve could comment on the interaction between the FDA and Third Wave because it is not just this test but several tests that have stopped being offered by Third Wave, and they are affecting my laboratory as well.

DR. EVANS: What I'm trying to figure out here, and maybe you two can tell me, is how does this interact with the patent and licensing issue. Was this a pure business decision that was independent of that or is there a reason to believe that this is meshed?

DR. LEONARD: No, I think your Oversight of Genetic Testing document is having an effect. I don't know if it is the effect that you want.

DR. FERREIRA-GONZALEZ: There is the issue that Athena holds the patent to the Connexin 26. The Delta-35G mutation is the issue here. There is no market, according to Third Wave, for them to continue. First, they cannot offer this specific reagent anymore, and they decided not to go through the FDA.

DR. EVANS: We are focusing on patents and licensing. Whatever you can shed light on from that standpoint. I think the issue of genetic oversight, which overlaps a little bit -- and we will talk about that in a minute -- is important but is not our focus.

DR. FERREIRA-GONZALEZ: There is another issue that I became very acutely aware of. As you provide genetic testing services, you learn a lot about the genes and the mutations and the advantages and not only continue to do research on identifying new mutations of polymorphisms but also how you implement the testing and so forth.

SACGHS Meeting Transcript  
December 1, 2008

I have not seen across any of the studies what the impact is of public genetic knowledge. Some of these sole providers know a lot about how to implement the testing and the limitations of this testing, but that is not translated to the local level, where the primary care physician might have a question that is easy and more accessible to your local laboratorian, clinical professional, or laboratory professional that actually is doing the testing.

DR. EVANS: You maintain there is an inherent value in local testing.

DR. FERREIRA-GONZALEZ: Yes. I haven't seen in any of the case studies that you have here if you have been able to look at what the impact is on public genetic knowledge.

DR. EVANS: We did not really look at that.

DR. FERREIRA-GONZALEZ: I think that is an important issue to look at not only from the patient's genetic knowledge or even the clinical provider's, but as to the testing.

DR. EVANS: To play devil's advocate there, I would point out that one of the things that, for example, Myriad has done is they have been extraordinarily active in contributing to the database. We have learned an immense amount about BRCA1 and -2 largely because of their willingness and efforts to do that.

So I think that your point is well taken. There are arguments on the other side that having large-volume labs can provide some benefits.

DR. FERREIRA-GONZALEZ: But the trickling down of the information of the clinical use of the tests sometimes get lost in translation, I guess. I think that has a different value to the general knowledge base of the genetic disorders. How do you actually work with a clinician or healthcare provider who has specific questions about the test? We don't have local area laboratorians with the knowledge because we don't offer the tests.

DR. WILLIAMS: I want to get back to the first point that Andrea and Debra were bringing up so I can make sure I understand it, since I am not someone that is living this day to day.

It sounds to me like with the Connexin and the Delta-35G that this was, if you will, a safe harbor within the broad patent in the sense that there was something relating to detection of this specific mutation that somehow avoided the methodology of the patent that is now licensed exclusively to Athena. They weren't comprehensive enough to cover all possibilities and so this was able to be promulgated.

Now the situation comes about that if you are not able to use this because you are losing your ASRs or whatever, then that will default and the landscape is going to change very rapidly. That particular safe harbor is really going to disappear, not legally but because you just logistically won't be able to get the things to do it that way. Is that accurate?

DR. EVANS: Steve.

DR. TEUTSCH: It relates to this education and knowledge base. That is, if you have a patent and someone has a reasonably exclusive license, there is a reason to promote it to get the value out of that. Of course, that happens in other industries.

SACGHS Meeting Transcript  
December 1, 2008

To what extent do we know anything, then, about this local knowledge versus the benefits of having someone who is actually going to go out there and do that promotion to make sure that people are aware and doing it. Obviously, not everybody has a high-quality genetics expert locally.

DR. EVANS: Right. It is a double-edged sword. Speaking personally as a clinician, I don't typically see most of the information put out by commercial labs that do this as necessary for me to decide what tests to have done.

Now, that said, I happen to be immersed in genetics as a clinical geneticist. So one could argue that there is a role for laboratories to send out detail people and "educate" physicians, which could then increase the availability of that test to appropriate people.

The danger, of course, is that you go too far the other way and you end up actively selling the test to people who don't need it and then misusing the test. It is a slippery slope.

In general, I would maintain -- though this is just my own opinion -- that physicians adopt typically the things they need to adopt as they practice. I am skeptical of an excessive reliance on profit-motivated education, if that makes sense.

DR. WILLIAMS: Again, since we are picking on one particular provider here. To the issue that you brought forward with the SCA testing and the fact that it is clinically challenging to be able to distinguish between the different types, there is another panel offered by that provider for Charcot-Marie-Tooth, where there is a great ability to be able to distinguish the different types of Charcot-Marie-Tooth based on clinical and EMG findings.

They still offer the panel and they detail the panel to neurologists saying the easiest thing to do is just order the panel, whereas you really can clinically say, this is the gene that I should be testing. It is a very different scenario. It might be one that would be worth contrasting.

DR. EVANS: That is an interesting point. Mara.

MS. ASPINALL: I appreciate that, Jim, as you said, it was your opinion, but I guess I would just take issue with the idea that it is profit-motivated in the same sense whether it is a university, a for-profit, or a not-for-profit. The idea is to get the information out.

The drug companies may be a good or bad example, but 85 percent, at least in cancer and true of virtually every area other than pediatrics, of practicing physicians don't have access to a geneticist, or community hospitals don't have the access that many people have.

The question in terms of judgment call is where do you draw the line. What about websites? Websites, I think many people think about as being educational. They sell as well. The number of people that are actually out there talking to physicians about these tests is relatively small.

I think if you look at the DTC advertising market, you could see that doctors are, quite frankly, impacted, whether it is indirectly or directly through their patients. But it is an effective way to get the message out. Sometimes there is under-use and sometimes there is over-use.

I just didn't want to characterize it that way. Certainly they are out there to ensure that people know the tests are out there.

SACGHS Meeting Transcript  
December 1, 2008

DR. EVANS: I didn't want to imply that there isn't a legitimate case to be made for the education of physicians by detail. I think you can make that case. I think it is also empirically evident that that is regularly abused and may not be the best way to educate physicians. It isn't to say that it couldn't work well. But anyway, that is a long discussion.

MS. ASPINALL: Maybe we could talk offline about the empirical evidence.

DR. EVANS: Right. Scott.

COL McLEAN: I just wanted to agree with Marc regarding the bundling of tests that sometimes are clinically inappropriate.

DR. EVANS: If we look at the price of hearing loss, this was not broken down by amplicon, which is probably the best way to do it. But the genes in yellow are those genes that are not patented. The two in white are ones that are under patent and exclusive license.

I would just point out that, again, this recurrent theme of genetic heterogeneity is very operative here in hearing loss in that we simply can't usually tell what genes might be mutated in a child with hearing loss.

DR. LEONARD: Can that analysis be broken down by amplicon?

DR. EVANS: I'm sure it can.

DR. LEONARD: That is an overall price for each test?

DR. EVANS: It could be a misleading comparison. I don't know how many amplicons are in, say, SLC26A4.

DR. FERREIRA-GONZALEZ: It depends how you do the testing.

DR. EVANS: Shubha has something to point out. If you would come up to a microphone.

DR. CHANDRASEKHARAN: On the last slide, I would like to point out that not all the costs that you see are for full-sequence analysis.

DR. EVANS: Which one; this slide?

DR. CHANDRASEKHARAN: Yes. Some of those are for mutation testing.

DR. FERREIRA-GONZALEZ: But with Connexin 26, the way 10 laboratories are approaching that -- I was going to do that -- is that you first look for the Delta-35G. If they don't have it, then you reflex to sequencing. So it will be more difficult to make the breakdown.

DR. CHANDRASEKHARAN: I wanted to say that for MTRNR1 and MTTS1, the prices that you see are for mutation testing. For the rest it is full sequence analysis.

DR. LEONARD: Connexin 30 is full sequence?

DR. FERREIRA-GONZALEZ: No, it should not be full sequence.

DR. CHANDRASEKHARAN: It is not full sequence, no.

DR. LEONARD: So 26 is full sequence and PDS.

DR. CHANDRASEKHARAN: PDS is full sequence analysis.

DR. LEONARD: Those are the more expensive ones. So we have to look at the method of testing.

DR. CHANDRASEKHARAN: That's right. We can do price-per-amplicon analysis for the ones that are full-sequence analysis.

DR. FERREIRA-GONZALEZ: I think it would be very interesting to see the price per amplicon because usually for Connexin 26 you should not do more than one or two amplicons.

DR. CHANDRASEKHARAN: That's right. Exactly. We can do that. We do have that information.

DR. EVANS: Yes.

DR. WILLIAMS: The one thing that is going to be interesting given what Debra and Andrea said is that there are a lot of us that believe that you shouldn't do Connexin 30 unless you find something in Connexin 26. If Connexin 26 is going to now be under the purview of an exclusive test, it really in some ways won't matter from the convenience perspective that you raised earlier if other laboratories are available to do the Connexin 30 testing because it is not under patent.

DR. EVANS: In a way, that is reflective of another problem that could loom in the future, and that has to do with the holdout issue. Say there is a disease that has 11 genes associated with it. You can have the right to test for 10 of those, but if that one gene that you can't test for comprises any reasonable percentage of the cases, your inability to do that renders your panel worthless.

DR. STANTON: I believe several people have raised the issue of what is an appropriate measure. I would just like to put on the table that -- and Jim and I spoke about this briefly -- we need to come up with at some point some comparative index. I have been working on the mathematical model and I have run out of my own mathematical abilities.

But an amplicon against a societal need or a patient population needs to be balanced because Debra's point is telling. In an academic setting where smaller patient populations may be present, or a specific patient may need some sort of service, versus a large-scale genetic test where there are millions of patients, those indexes may not be normalized relative to each other. We need to somehow factor that in.

I just wanted to bring that up because, in comparing these numbers, they are not always going to be consistent or even comparable unless we somehow normalize for patient population.

DR. EVANS: Great. Maybe we can work that out.

So, did the prospect of patents encourage the search for SCA gene-disease associations. They didn't appear to hinder research efforts in the area, nor was the prospect of patents a primary driver of the research, as concluded in this case study. Some genes and some methods were patented to preserve potential commercial interests in tests that could be developed in the future.

The role of patents in test commercialization. The diagnostic tests for both the patented and the unpatented genes have been developed and are offered clinically by multiple providers. The conclusion of this study was the demands for testing or institutional interest in hearing loss research really were the primary factors in determining whether diagnostic testing for a particular gene was offered as a clinical service.

How do patents and licensing practices affect price. The cost of hearing loss tests don't appear to correlate strongly. I think the caveats that Brian brings up and the caveats that Shubha is going to address are worth looking into. I think probably that conclusion will remain, but we will see.

How about availability? The lack of correlation between patent status and test cost is evident, and the lack of utilization data. We really don't have data on that.

The potential that patents may cause some future harm in this area. The enforcement of exclusive licenses could result in reduced access. There is little doubt about that. It is unclear how patents will affect access to gene chip or microarray-based diagnostics. I think it depends on two things. One is technically how that is seen from a pure infringement standpoint, but the other is how aggressively licensees choose to enforce their patent rights.

Again, I will keep coming back to this because I don't think we should lose sight of it. Robust sequencing, which is more and more the rule of the day, I think will present great challenges to a genetically heterogeneous disorder like this with various patent and licensing claims. Andrea.

DR. FERREIRA-GONZALEZ: We have for hearing loss at least 10 providers for now. How does that compare or differ from the sole provider, where we are starting to see an issue of access for individuals that cannot pay for the testing, versus having the 10 providers? Some of these are nonprofit organizations that actually might do some of the testing and have different venues to provide the testing. I don't know if you have looked into these particular issues with these two examples, BRCA1 or the SCA and the hearing loss.

DR. EVANS: Not per se in those terms. Debra.

DR. LEONARD: I think looking at future potential harm, we need to bring in Marc's point, and Andrea's, that the landscape may change very abruptly if those 10 labs disappear.

Secondly, Connexin 30 testing shouldn't necessarily be done unless you have done Connexin 26. When that is under exclusive, sole provider status, then it also could change the landscape of how the testing is done.

DR. EVANS: Right. Now, moving on to hereditary hemochromatosis, this is a common autosomal recessive disorder. It has relatively low penetrance, in part dependent upon how you define "penetrance," either from a laboratory standpoint or a clinical standpoint.

It results most often from mutations in the HFE gene. This is a disorder in which individuals keep too much iron. We evolved mechanisms to acquire iron from our environment because it is an extraordinarily important mineral. In fact, it is so important that we didn't evolve mechanisms to get rid of iron. The only way we get rid of it is through sloughing cells in our GI tract.

Individuals with mutations in the HFE gene have a subtle shift in their iron balance and they retain too much iron. That iron deposition over many years can cause a variety of disorders, like diabetes, heart failure, and, probably most importantly, liver failure, cirrhosis.

SACGHS Meeting Transcript  
December 1, 2008

It results most often from mutations in this one gene, HFE, and it was discovered and was patented by a start-up company in the mid 1990s. There has been an exceedingly complicated history of business transactions with who owns the patents and licensing, et cetera. Uncertainty has existed about to what extent patent rights would be enforced throughout the history of much of this story.

Testing is currently available through multiple providers. That was not always the case. Exclusive licensing and a single-provider model ruled for a time in the HFE history. A 2002 Nature article concluded that hemochromatosis testing had "failed the test of socially optimal access." Yes.

DR. LEONARD: I think in parallel to the business history, which is complex, there is a parallel scientific history of hemochromatosis testing. When it was discovered, it was thought that doing this testing may be warranted in a population screening mechanism. It has been demonstrated through very large studies that having the HFE mutation is similar to the ApoE-4. It puts you at higher risk potentially, but if you have it it is not predictive.

DR. EVANS: It is not determinative.

DR. LEONARD: Exactly. That process evolved over time in parallel with this going from exclusive to broad testing. So what happened early on is in the context of a test that we thought would be really important medically with enforcement and exclusive licensing and a single-provider model, and it became something where the science evolved and then the ability to do the test evolved.

DR. EVANS: Right. In a way, it intersects with the whole idea of clinical utility. I would phrase what you said as the idea that it was thought in the early days that this might have clinical utility for screening populations. It has really not turned out to be the case.

Now, interestingly, there was a call in the Annals of Internal Medicine about three or four months ago to do basically a case-finding approach, to do limited screening of populations. So we still see recurrent calls for that type of thing.

But suffice it to say that, yes, in addition to the complex business history of this, there has been a complex scientific history in which it turns out that knowing somebody's mutational status can be important. It does not appear at this point, most of us would agree, applicable for the general population.

There are really two alterations in the HFE gene that account for the vast majority of individuals with hemochromatosis, and that is C282Y, the substitution of a tyrosine for a cystine at 282, and H63D.

These are specific sites that can be analyzed. You don't have to sequence the whole gene in the vast majority of cases. Methods for analyzing those mutations and a kit were patented by Mercator Genetics, which was subsequently acquired by Progenitor. Other patents in the same family were issued between 2000 and 2006 and were assigned to Bio-Rad. Patents include diagnostic methods for a panel of less prevalent mutations, polypeptides related to the HFE gene, and associated proteins.

DR. LEONARD: Jim?

SACGHS Meeting Transcript  
December 1, 2008

DR. EVANS: Yes.

DR. LEONARD: S63C and S65C. Because of the 63 and 65, you can tell they are close together, and they have a similar impact. Is S65C patented?

DR. EVANS: I'm not aware that it is. I don't know. Bob, do you know? Shubha?

DR. COOK-DEEGAN: I shouldn't say unless I have the patent in front of me.

DR. EVANS: I don't know. Shubha, grab a mic.

DR. CHANDRASEKHARAN: There is another holder of patents. I believe it is Waltrop, Inc., separately. It is an individual who owns patents. It is incorporated. They own two more mutations. I do not know if that includes S65C, but I do believe that some companies have had to get licenses from them. Third Wave, which used to offer NESR, had to acquire licenses both from Bio-Rad and this other entity. So I believe some other mutations may also be under patent.

DR. EVANS: The prices for targeted testing of those two major alleles varies based on the technology used. You can see there the cost range from a subset of providers, from \$158 to \$467.

DR. LEONARD: I don't mean to be too detailed, but this creates a scenario where there was a company providing a test kit. So from a laboratory perspective, you had to use that test kit because they were enforcing. They only did H63D, and their test didn't take into account the S65C. You could get wrong results from a test kit that you were forced to use because of patent enforcement. It created a very bad situation for laboratories.

DR. EVANS: Right. Debra, I don't know technically how the public comments work, but you are a member of the public, too, right? I'm trying to write them down, but if you could summarize some of these things so we can get them in the report, that would be great. Just a few bullets at some point. Do you mind?

DR. LEONARD: Can somebody remind me?

DR. EVANS: Yes. I'm jotting these down.

DR. LEONARD: There is also my talk that I gave, back when I was on SACGHS, at one of the very first sessions on gene patenting.

DR. EVANS: What I'm getting at, though, is that we have massive information. Targeted things like this will be very helpful.

DR. FERREIRA-GONZALEZ: I think Debra is making a very, very important point. Here we only have examples of inherited disorders. Clearly, there are other acquired somatic genetic changes related to cancer where we are forced to use specific test kits from a patent holder or licensee of the patent holder that have very questionable quality. We are not allowed to use other technologies. So this goes beyond just this point.

DR. EVANS: Yes. That is a very important point that we did not have in there. I want to make sure we include that.

So, did the prospect of patents encourage search for gene-disease association. This is actually a very complex question when it comes to hemochromatosis. The prospect of patents and revenue from diagnostic testing, I think it is fair to say, probably stimulated research. It induced investment for the creation of this company, the start-up company, whose business plan centered on the identification of candidate genes for a number of diseases, including hemochromatosis.

This should be seen especially in the context that Debra raised of the idea which was prevalent about this time that identifying this gene might lead to reasonable calls for population-wide screening. In other words, there was thinking that this might be an extraordinarily high-volume test.

It is also true that three additional groups were pursuing similar approaches for hereditary hemochromatosis gene identification. Once the association was found and was published, there sprung up many laboratories developing these tests for the mutations based on that original Nature genetics article. As soon as that association was discovered, there were many labs that were offering this testing because it is a relatively simple test.

So, how did patents and licensing practices affect price. It is really unclear how much variability in price can be attributed to the licensing issues, but the role of patents and licensing practices in test availability is more clear-cut. Patent enforcement did clearly remove preexisting competition when the patented test first appeared in the testing market. In other words, a substantial clearing of the market was engaged in.

At the moment, genetic testing for hemochromatosis appears to be widely available, though I think the caveat that you bring up about suboptimal testing that doesn't detect the other allele is germane to this.

What is the potential that patents may cause some future harm. Marc.

DR. WILLIAMS: I just have an issue that I will bring up before we leave hemochromatosis.

DR. EVANS: We are about to leave it. This case study really did not address future harm. I think this is, again, the type of thing that Debra and Andrea bring up. Marc.

DR. WILLIAMS: The point I was going to make was that there are analogous issues in the syndromes of iron overload to that in Alzheimer's, where there are other rare genes such as Ferritin heavy chain and the transparent receptor-2 that are much rarer and much more deterministic. So given what you did with the presenilins and APP and ApoE, you might be able to do something in this landscape that would also be analogous to that that might add value.

DR. EVANS: I think that is a good idea. The one thing I would add, though, is that we could research this landscape for the next 30 years, especially as it keeps moving. We could have a permanent job on the Committee. Boy, that would be fun.

[Laughter.]

DR. EVANS: But I think that with the blemishes and with things that could be assigned to the future, it still is very important that we come to some conclusions here. Brian.

DR. STANTON: Is that second allele subject to a patent, Debra? I couldn't hear that.

DR. LEONARD: We don't know.

DR. STANTON: We don't know. So my question is, if there are alleles that are subject and others are not, and the license requires you to use a test kit, I'm trying to understand why that would preclude you from doing a separate test for the other allele. That would be a negative impact.

DR. LEONARD: Because you don't do a 65C by itself.

DR. STANTON: So it is a logistical issue.

DR. LEONARD: It is not clinically relevant. The H63D and S65C are much less penetrant even than the major mutation, which still is not very penetrant.

DR. STANTON: But you are not precluded per se from doing it? It is just not relevant.

DR. LEONARD: Not that I'm aware of.

DR. FERREIRA-GONZALEZ: I think it would increase the cost because you have to add in one more test.

DR. EVANS: Julio.

DR. LICINIO: I have a question. With all of these efforts on our whole genome sequencing, there is the project for the \$1,000 genome. Very soon it may be cheaper to sequence the whole genome than to do a few of these tests. Can you sequence the genome with all these patents? That is the question.

DR. EVANS: I'm not a patent attorney. Maybe Rochelle should weigh in on this. If an exclusive licensee holds that license and says, we are the only ones who can test for this, we sequence the gene, that is how we do the test, I find it very difficult to imagine that they are not going to take umbrage at the idea of somebody sequencing the whole genome, which happens to include the gene that they have their whole lab based upon. I can't imagine that that wouldn't be infringement in some way.

DR. WILLIAMS: There is precedent in the microarray area in that some microarray companies have now been asked to remove the information that they have around the Duchenne muscular dystrophy locus because there is now a patent held on looking for subtle insertions and deletions in the DMD gene that involve a high-density microarray. They are now saying you have to pull this off of your microarray chip. So I think that that is extremely analogous to the whole genome situation.

DR. EVANS: I think it is.

DR. WILLIAMS: I agree with you. I think this will become a nightmare.

MS. DREYFUSS: I asked the 23andMe people what they do, and they are walking a very fine line. They actually tell people that if there is a mutation that they have, that they have to then go to the company that owns the patent on the mutation to do another test, even though, I imagine, clinically the test is not required. So this is a real problem.

DR. EVANS: Yes, it is. I would just add that the 23andMe, Navigenics, and DeCODE situation is a little different because you are looking at SNPs and you could argue that that doesn't infringe. What I would say is that when it comes to sequencing, which is the future of this kind of analysis, it seems to me a slam dunk that that is infringement.

DR. LEONARD: Since there is a discussion in the report on whole genome sequencing in fairly great detail, I think it would be very nice to do a cost analysis of the impossibility of ever having a \$1,000 genome because of the royalties that would need to be paid on all the genes that have been patented. I think that there should be a royalty calculation for the \$1,000 genome project, even if you could do it from the perspective of the cost of the testing. It would cost you \$25,000 because of the royalty payments.

DR. EVANS: It seems to me that one doesn't even need to do any actual calculation. It is quite obvious that sequencing the whole genome would infringe on multiple patents. You would have to make so many assumptions in a cost analysis. I don't think we need to do a cost analysis.

DR. LEONARD: Maybe one sentence could be added to say that because that point I don't think is made in the report.

DR. EVANS: Right. Now, we are going to keep going until 10:30. Then we are going to have a break, as scheduled. Then we will finish the case studies and go on from there. I think this discussion we are having is very valuable.

Tay-Sachs and Canavan disease. For any of you who, as a hobby, have followed the gene patent arena, you are probably salivating now because Canavan has been particularly infamous in the history of gene patenting. These are both recessive neurological conditions that are prevalent to a greater extent in the Ashkenazi Jewish population than others. HexA is the operative gene in Tay-Sachs disease, and ASPA is the gene that, when mutated, gives rise to Canavan disease.

DNA-based carrier screening is available for Tay-Sachs and Canavan disease. There is a highly effective enzyme test that was developed in the 1980s for Tay-Sachs and is still in use because it is an extraordinarily practical test to use. In many ways, it is actually superior to the genetic test.

HexA was patented by the NIH and it was never licensed. ASPA gene was patented by Miami Children's Hospital, with licensing arrangements that were eventually determined by a confidential out-of-court settlement, so no one is privy to the details of the settlement. That throws up some major opacity to our analysis of this case.

If you look at the full sequence analysis for Tay-Sachs and Canavan, they are roughly similar. Targeted mutation analysis is almost identical. The enzyme assay, or analyte test, is again almost identical.

Did the prospect of patents encourage the search for gene-disease association. The prospect of patents clearly did not motivate the inventor of the genetic test for Tay-Sachs disease. She has talked about that and she has published on that very point.

The case study doesn't address whether Canavan researchers were motivated by the prospect of obtaining a patent, though it is fair to say that family groups were very involved in the Canavan research and were not motivated by developing and retaining a patent to any developed test.

SACGHS Meeting Transcript  
December 1, 2008

The Tay-Sachs patent neither helped nor hindered commercialization of the Tay-Sachs gene test. The impact of Canavan patent on commercialization ultimately is unclear, in part because of the out-of-court settlement.

For Canavan disease testing, significant problems arose with the original licensing scheme. It imposed high fees and use restrictions capping the number of tests that could be done by a licensed laboratory. This scheme was the focus of a good deal of dismay by the Canavan community. Ultimately, an out-of-court settlement was reached that provided for more thorough testing or more available testing.

Regarding availability for Canavan testing, problems ruralizing did arise under that original licensing scheme, which imposed these fees and use restrictions. It, however, did not remain in place because of this legal battle and the ultimate confidential out-of-court settlement.

Genetic testing for Tay-Sachs is widely available. However, the biochemical test is generally preferred. That is an interesting point. Genetic testing isn't always the best way to test for something. In fact, usually we do genetic testing when we don't know enough about the biochemistry of something.

Somebody had a comment. Debra.

DR. LEONARD: The Canavan case points out an interesting situation in which you can have people who are not medical practitioners enforcing medically important patents in ways that no healthcare provider would ever do. I saw versions of contracts with the University of Pennsylvania which basically banned the University of Pennsylvania from doing any Canavan testing on University of Pennsylvania patients even by sending it to another laboratory.

DR. EVANS: Yes. They totally shut out UPenn patients.

DR. LEONARD: Of course, we didn't sign a contract, but it just shows the outrageousness that can arise and actually has arisen. So it is not a theoretical or hypothetical situation. It is absolutely real and what can happen to medically important patents under the current situation, which, in my opinion -- and this is only my opinion -- should not be allowed.

DR. EVANS: This will be a matter for the public comment, et cetera. One counter-argument to that is that this is the way these issues are resolved, and it was ultimately resolved. So one argument would be, that is why we have courts to resolve these things. That would be the one argument that is used to basically say that this was an example of the system working. It was working in a cumbersome and in an unwieldy way, but ultimately working.

I will just leave it at that because different people can have different takes on that, let's just say. Rochelle.

MS. DREYFUSS: These are not worked out in a systematic way. With Canavan, I think the family had some claim that they were the inventors of the patent, and so there was a question whether the patent would be valid since they weren't on it.

Each of these requires some sort of unique argument. With BRCA in Europe, there was a typo in the application. It is not like we have legal doctrines that say problems will arise and here is the way that they are solved.

SACGHS Meeting Transcript  
December 1, 2008

DR. EVANS: Yes. It is very ad hoc.

MS. DREYFUSS: Saying that you have a counter-argument is to ignore the fact that these counter-arguments are completely ad hoc.

DR. EVANS: I agree with you, but I think we need to try to represent the range of arguments that have been brought to bear on this.

So, what is the potential that the patent may cause some future harm. It is highly unlikely that the NIH will begin enforcing its patent on Tay-Sachs gene prior to its expiration in 2010. The effect of Canavan disease patents on future clinical access is hard to assess due to this closed settlement. The Canavan Disease Consortium has made a public statement that research uses are not subjected to liability for infringement, so specifically looking at research uses.

Let's stop here. It is 10:30. We will resume in 15 minutes, at 10:45. We will do the last two case studies and then move on.