Review of SACGHS Draft Report:

Gene Patents and Licensing Practices

and Their Impact on Patient Access to Genetic Tests

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[PowerPoint presentation.]

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.

[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 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 primmer 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.

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 primmer 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.

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.

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.

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.

DR. 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.

DR. 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.

DR. 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.

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.

DR. 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.

DR. 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.

DR. 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 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 HNPCC 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.

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 MTTS1.

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.

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.

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.

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.

DR. 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.

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.

DR. 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.

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?

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.

DR. 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.

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.

DR. 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.

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

DR. 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.

[Break.]

DR. TEUTSCH: If folks could take their seats. I hope Paul is on the phone. His flight got canceled from the West Coast last night. He will be joining us, hopefully, later, but he has to be on the phone, and so will be heard if not seen.

Jim, please lead us through.

DR. EVANS: Let's keep plowing through this. We have this session prior to lunch and then we have two hours after lunch. I would like to devote that entire two hours to going over the range of policy options one by one.

We are finishing up the case studies with two interesting cases. One is cystic fibrosis, the other is Long QT syndrome. Now, CF is a recessive disorder that affects about 30,000 Americans. About one in 20 of us is a carrier for a cystic fibrosis mutation. When we inherit two of those, we have the disease. What it means is there is an overwhelming likelihood that somebody in this room carries, for example, a heterozygous mutation for CF.

Delta-F508 is the name of a particular mutation in the CFTR gene which is present in about 70 percent of cases and at least one copy. The early detection and screening for CF does, arguably, allow for better disease management, although there is no cure for CF.

DNA-based carrier testing and newborn screening is available and is endorsed by medical professional societies. I think 35 or 37 states, at last count, engage in CF testing as one of the newborn screening panels.

Patents for the CFTR gene mutation and methods for detecting those mutations are held by three entities: University of Michigan, the Hospital for Sick Children in Toronto, and Johns Hopkins, again reflecting the big role of universities in this landscape.

All of these patents are non-exclusively licensed. So this case study gives us a way to look at the landscape of, in biogenetic terms, a relatively common disease for which there are patents held but no exclusive licenses involved.

The testing price varies over the 64 laboratories that offer some type of CF testing. The full gene sequencing offered by a subset of those laboratories ranges from $1,200 to $2,500. Targeted mutational analysis -- for example, looking for the Delta-F508 gene, which in half the cases will be there in two copies, and one can employ targeted analysis -- costs between $84 and $595.

That price range, however, is influenced by the fact that there are a number of different panels that one can order. One can order a panel of seven or nine mutations that are fairly common, all the way up to a panel of several dozen. Then the most exhaustive type of analysis would be full-gene sequencing.

With regard to whether the prospect of patents encouraged the search for gene-disease associations, it does not appear that gene patents were an important incentive for CFTR gene discovery.

The parties involved in commercialization, both researchers and funders, agreed to pursue patent protection so that broad access to CF genetic diagnostics could be encouraged through non-exclusive licensing strategies. In a way, my understanding is that the history of the CF patent issue is that these were, in a way, preemptive patents that were taken out by the discoverers so that they could control matters and make sure that broad access was available.

There is no evidence that patent process affected the speed of genetic test development. There were, however, interference proceedings that weren't resolved until 2002, fairly recently in the big scheme of things considering when it was cloned.

How do patents and licensing practices affect price. Lab-to-lab comparisons are difficult because of this range in services. You can get whole gene sequencing. You can get a variety of different panels that look at different mutations. You could, for example, if you wanted, get precise, targeted mutation analysis as well. Andrea.

DR. FERREIRA-GONZALEZ: These are practices of

pricing on diagnosis for cystic fibrosis. Have you looked at the pricing for carrier screening, since there is a specific panel that has been recommended?

DR. EVANS: No, that is not included for carrier screening.

The role of patents and licensing practices and the availability of this testing is pretty clear. It is offered by 64 laboratories nationwide. There is no evidence to suggest that the CFTR patents and the broad licensing have limited consumer utilization.

With regard to future harm, development and commercialization of new tests and techniques have continued a pace. As techniques for genomic analysis have progressed, they have regularly and rapidly been applied in the context of cystic fibrosis. Broad, non-exclusive licensing practices have clearly been compatible with competition as well as innovation, as evidenced by the fact that there are 64 labs offering a variety of different products.

Therefore, I think it is quite fair to say that patents and licensing practices of the CFTR gene most likely will not result in future harms to CF genetic

testing.

The last case is one that is still in flux. Hence the disclaimer. Long QT syndrome is a shifting and currently changing landscape. The authors of this case study are continuing to update the report. I don't want to imply that the conclusions or interpretations in the following slides are final. We do not know the whole story when it comes to Long QT, and there seem to be surprises that regularly pop up with this situation.

Long QT is an interesting, from a clinical standpoint, and a tragic, from a clinical standpoint, condition. It is a mendelian condition. That is, it is inherited in a mendelian type of pattern. It affects about one in 3,000 newborns. For those of you who aren't geneticists, I can tell you from a genetics standpoint it is not rare. We are used to dealing with rare diseases.

There are mutations in 12 susceptibility genes that account for about 75 percent of familial Long QT syndrome. Mutations in three of those genes account for the vast majority of cases.

It is called Long QT because when one looks at the EKG of somebody with Long QT syndrome, under certain

circumstances and at times, one of the intervals between those little blips is prolonged between the Q and the T waves.

Unfortunately, the EKG is not sufficient to make the diagnosis in many circumstances. You can't just do an EKG and determine whether the sibling of this child who died suddenly and turned out to have Long QT syndrome is affected. It really matters clinically. If that sibling is affected, they may need an implantable defibrillator. They obviously need very close follow-up.

If, on the other hand, they did not inherit this condition from the parents, then they can forego screening and procedures.

So, clearly, this ability to diagnose Long QT is, with no hyperbole, a matter of life and death for the families in which it is being transmitted.

Moreover, knowing the particular mutation involved can guide therapy. There are particular genes that have a more malignant phenotype than others and necessitate the implementation of an automatic defibrillator at an earlier age, et cetera.

Testing is offered through Clinical Data

Corporation. That is a subsidiary of PGx Health. The FAMILION Service was launched in 2004 for Long QT testing. Prior to the launch of the FAMILION Service, there were at least two other fee-for-service providers of genetic testing for this syndrome, screening approximately a third of the five genes' combined coding sequence.

The story behind Long QT is difficult to unravel and it is still being unraveled. The majority of these genes were discovered by a researcher at the University of Utah in the '90s. The University of Utah exclusively licensed its Long QT syndrome patents to DNA Sciences for a period of several years, from '99 to 2003.

Then in 2003, DNA Sciences and all of its assets were purchased by Genaissance Pharmaceuticals. Genaissance Pharmaceuticals launched commercial testing in 2004. In 2005, they were acquired by Clinical Data, Incorporated, a subsidiary of PGx Health. If you guys aren't lost at this point, let me know.

Clinical Data has since overseen the rapid growth in commercial testing for this disorder, and there has been rapid growth.

Testing is offered by Clinical Data Corporation

for $5,400 per patent and $900 per confirmatory test in additional family members. The cost per amplicon is $74. That is a bit of an outlier compared to, for example, the $38 per amplicon test of, say, BRCA.

Did the prospect of patents encourage the search for gene-disease associations. That prospect didn't appear to stimulate a race for gene discovery, most likely because of the relative rarity of Long QTS and the presumed small market for such genetic testing.

With regard to the role of patents in test commercialization, there was perceived value in the Long QTS IP as both Genaissance and Clinical Data appear to have made testing for Long QTS a substantive part of their genetic testing business plans. Both GeneDX and Boston University, however, it should be noted, offered fee-for-service testing from 2001 to 2002, before patents were enforced, suggesting that IP certainly wasn't the only incentive to offer this service.

I think that gets back to a recurrent theme that clearly patents are by no means the only reason, or even a reason, that many labs pursue such analyses.

So, how do patents and licensing practices affect

price. The test currently costs $5,400 per index case and $900 to confirm that test in other family members. So you find a specific mutation in a child. Say you want to discover whether the siblings have it. It costs $900 to look for that particular mutation.

It is more expensive than most comparable testing. As you will recall, BRCA confirmatory testing targeted for an individual mutation costs about half that and, on a per-amplicon basis, the initial test is also more.

There is incomplete coverage of the test by most payers, and the role of patents and licensing practices in test availability is hard to sort out. Enforcement actions of DNA Sciences and perhaps those of Genaissance from 2002 to 2004 may have adversely affected consumer access. There is concern that there was a period of time during which testing was not available at all due to the sole provider-enabled exclusive licensing.

This is a serious issue with a condition that can result in sudden cardiac death and for which there is an intervention that is available if you know it. Moreover, it is difficult to diagnose, if not impossible to diagnose,

without DNA analysis.

Clinical Data doesn't offer prenatal genetic testing for Long QT. So this gets to the more general issue of concerns about an exclusive licensee offering one genetic test but not offering another type of related test that many individuals may want. So the issue of prenatal genetic diagnosis is a complex and a somewhat controversial issue in our country as a whole, but nevertheless there are certainly people who elect to pursue prenatal testing for a host of conditions. It is up to an individual licensee whether they want to offer it or not. If they are the sole licensee, that can obviously create problems.

That takes us into the realm of potential future harms. To date there is no evidence that a virtual Long QTS monopoly has had a stifling effect on the development of an improved test. Oftentimes noted is the exception of allelic dropout. This is a problem that is inherent to PCR-based tests. I'm not sure how unique it is to this particular situation. Andrea.

DR. FERREIRA-GONZALEZ: I was just curious to see if this company also has a program that allows individuals that cannot pay for that test to have access to the

testing. Have you looked into that?

DR. EVANS: I don't know. Mara, do you know?

DR. ASPINALL: I don't know. We may have some representatives here who can talk to that. But again, it is the same problem. If you want to offer access to the test you need tax returns. You need to go through a major process to do it, and most patients are not able or willing to share that level of financial information.

DR. FERREIRA-GONZALEZ: But those who decide to do it, do they have that capability?

DR. TEUTSCH: I don't understand why that is the case. For drugs you don't need that level of documentation.

DR. ASPINALL: It is a great story. It is actually different for testing than it is for drugs. In many examples, and I know we didn't look at drugs in this instance in terms of patents, but it is an area where there is non-comparability in terms of the anti-kickback and the rule about providing services, for which the requirements are actually higher so there is no sampling technique. It may go back to a point about 10 years ago, but the challenge is very great in terms of offering this.

DR. EVANS: I would go on record personally as saying that I don't think the answer to our cost issues and affordability of genetic testing or, for that matter, other types of things in medicine, is really going to be solved by those kinds of programs.

Clinical Health has been criticized for its difficulty in processing paraffin-embedded samples from deceased individuals. I'm not sure how relevant that is personally because that is not routinely done in many situations. It is very hard to get payment. Who is going to pay for analysis of a dead person's tissue, et cetera. So I'm not sure how valid that particular criticism is. It is not something that clinically is done very often.

DR. LEONARD: But wouldn't this be done in the setting of BRCA testing?

DR. EVANS: Very rarely. Very rarely.

DR. LEONARD: Because you always have to have the proband.

DR. EVANS: Yes. I would say it is almost never done.

So, what is the potential that this patent situation may cause some harm in the future. Clinical

Health has declined to add genes to its Long QT testing panel or sublicense rights to its panel to other companies due to the rarity of mutations in the other genes. Now, they currently test for mutations in five genes, and rare mutations in seven other genes are known to predispose to this same, oftentimes clinically undifferentiatable syndrome.

I would add this is not unique to Long QT and is unlikely to be able to be linked directly to the patent licensing issues. This is a common dilemma in clinical genetic testing. When is it worth adding an assay for a gene that plays a very rare role in a disorder. So, to some extent, this dynamic is a natural result of the nature of genetic heterogeneity. I think hemochromatosis is a good example of that, in which HFE is the major player but things like Ferroportin can occasionally cause a similar condition. I think this is more a nuanced issue with regard to Long QT.

DR. WILLIAMS: Jim, just a clarification. Does Clinical Health hold the patents on the rare genes?

DR. EVANS: Shubha, Bob? I think that Utah holds all the patents involved in this. What has happened, and

that gets to the next point, is that there has been exclusive licensing of different loci to different licensees. There has not been, that I can make out, a really broad, coherent policy with regard to this. So I think Utah holds the patents to all these genes.

DR. WILLIAMS: The harm would then result from holding a patent, not developing the test, not making it easy for somebody to develop the test, and then having people that literally do not have access to testing because the test is not available or being developed.

DR. EVANS: That is precisely where harm could come up: when you have a patent holder that has refused to license a particular gene to somebody else who, even though it is for a rare subset of that disease, might be willing to test for it.

DR. TEUTSCH: We might invite some comments from the audience.

DR. EVANS: Paul Billings, and then to Bob. Paul?

DR. BILLINGS: I just had two quick questions. On your slide, are Clinical Health and Clinical Data the same thing?

DR. EVANS: I believe so.

DR. BILLINGS: I think it is a mistake. I don't think it is Clinical Health.

DR. EVANS: It should be Clinical Data.

DR. BILLINGS: Yes. Clinical Health doesn't exist. You may want to correct that.

DR. EVANS: Yes, we do need to correct that.

DR. BILLINGS: Secondly, the Long QT syndrome is caused by mutations in ion channels and there are, as you say, quite a number of them. There is no evidence that we have found them all, by the way. Some of these patents are owned by the University of Utah. There may be others that are either out there that are as yet uncaptured or may be also unknown.

DR. EVANS: Great. Bob.

DR. COOK-DEEGAN: I was just going to make a technical point about what we can and what we cannot say about the intellectual property situation. It is not too hard to find patents and who was originally assigned a patent because you can get that from a public database. The crucial information that we don't have in this case, and we know that we don't have the full story, is the

exclusive licensing status of some of the key common mutation patents. It has been brought to our attention that there might be a potential mutual blocking situation here.

DR. EVANS: Right. Lori.

DR. PRESSMAN: This is such a great example of where diligence might be the fix that I wanted to jump in and suggest it. It has been proposed that very broad, non-exclusive licensing would be the fix because then there would be many parties who would eventually aggregate all 11. Another potential fix is more nuanced exclusivity but incentivizing their adding the additional mutations that, if they don't add, they lose rights. So, add or lose.

DR. EVANS: That is a good preview in the range of policy options that we present. You will see a progression. You will see a range from more and less nuanced fixes for these kinds of things that we envision.

DR. ROHRBAUGH: In terms of the comment Marc made, if a technology had government funding and is not being developed, that would certainly be something appropriate to consider.

DR. WILLIAMS: One other thing to note with this

particular case study that is also unique to this case study is that this is the single case study that you have presented where there is a strong financial incentive from two other stakeholders. It is the ordering physician, who is usually a cardiologist, who will presumably be able to generate revenue relating to implantation of devices, and the device manufacturers, who obviously will benefit from that. Of course, there is still a wide variety of opinions about who should get the defibrillator, ranging from everybody that carries a gene should get one just in case, to more of a selective issue.

But the amount of money associated with these devices and with the insertion of these devices is not trivial and in fact dwarfs the cost of the genetic test.

DR. EVANS: That is a very good point. That is a very interesting point. Mara.

DR. ASPINALL: Two comments, one to Marc's comment. I'm not familiar with the medical history there, but just because there is a financial incentive on people's part doesn't mean they do the wrong thing. The implication there is how that works through the system.

DR. WILLIAMS: No, I understand that. One of the

things that we have frequently argued to peers about is that for the vast majority of genetic tests that we are ordering there is no personal financial incentive for ordering a test or not ordering a test. It really is for the patient. This is not the case with this particular test, and that is something that could in fact promote a broader use of testing that might be defined as inappropriate.

DR. EVANS: It is an interesting issue.

DR. ASPINALL: Fair enough. I think that, more broadly, testing is probably the one area that there is no financial incentive broadly. In drugs there is an incentive. On devices there is an incentive to go back. But that is the fundamental basis of our system. Virtually all of the other interactions have some financial incentive for the ordering physician or the institution. That was Point No. 1.

Point No. 2, first let me say thank you for your presentation and giving it in such a broad, open-minded way, looking at the various issues with all of the questions. I think the way that it was put together was very helpful.

One of the things, though, that I would suggest -- and I know we talked about it a little bit in the Committee -- as we move forward with the case studies, is with that last question, do patents have the potential for future harm, we should also have the potential that the patent has future benefits. We had talked about it at one point but it seems to have gotten lost in there.

The Long QT one is an example. Earlier we spoke about the role of the people in the field going out. In this case, we talk about the fact that, without education of physicians, many physicians are not aware of this, much less have an interest in doing it. I think that is there now. Right now we are laying out the situation. There are some that work one way and some that work another. I think we need to ask the question both ways.

DR. EVANS: I think that is a point very well taken. Alan.

DR. GUTTMACHER: I would just like to quickly add, I think the example of the financial interest in the Long QT syndrome is a very illustrative and important one. I would also point out, though, that even for other testing there may be a financial implication. That is, people tend

to like and refer to physicians whom they perceive as doing something. That is the reason why people often write scripts at the end of an exam, to make the patient feel like you have done something.

For many folks in genetics particularly perhaps, ordering a test is doing something. I think that there may be a less overt, more subtle, but still somewhat of an economic interest in doing something.

DR. EVANS: That is a good point. Even BRCA1 and -2, you find a mutation in somebody and they have bilateral mastectomies. We are talking about a major financial incentive from that perspective.

DR. ASPINALL: I think that that is a very fair point, but typically you hear from physicians that, the time to do the test, send it out, interpret the test, speak to the patient about it, forget even genetic counseling, often none of that is being paid for. So the incentive may be to do something, but the actual time it takes to go through that is actually a loss rather than a gain.

DR. GUTTMACHER: Medical genetics is based upon losing money on each client you see and somehow making it up in volume.

DR. EVANS: In "Catch-22," Milo Minderbinder says, "I lose money on every sale. It's just the volume that keeps me in business." I never understood that comment until I got involved in medicine, and it is exactly right. We lose money on every sale. It's just that because we are perceived as being needed and people demand it, we somehow survive.

DR. ASPINALL: The perception of that changes a little bit for those in medical genetics, for whom it is done, but the vast majority are done by non-geneticists.

DR. EVANS: We are going to try to march through preliminary conclusions that we have made in going through this.

Now, I would emphasize what we have tried to do here is, among the task force in these grueling conference calls, come up with some of the lessons learned and the preliminary conclusions that we can make. I do not want to imply that these are the only lessons that one could learn. We are trying to present a balanced type of set of conclusions.

I would start out by saying that it is not so much whether a genetic diagnostic test is patented or

unpatented, but rather, how the patents are used and enforced that result in potential barriers to clinical access. I think that a good example of that is something like CF. CF has broad access. It is patented. It has been how that patent is used that has allowed for such broad access.

The findings from the case studies suggest that it is this use and enforcement of IP rights that ultimately affect access.

Controversies are most likely to occur when the interests of medical practitioners and patients aren't taken into consideration during license processes and when exclusive licenses are issued. I think that is pretty clear. It is in those realms of exclusive licensing that we run into problems. It is in realms like Canavan where there was a disconnect between the patients, their families, and the individuals who were setting policy with regard to the use of those patents.

I think that it is surprising but demonstrable that there is no clear relationship between patents, license exclusivity, and the price of a genetic diagnostic test. The evidence from the case studies don't reveal any

exorbitant patent premium or, for that matter, they don't even reveal a patent premium for most of these genetic tests that were patented and even exclusively licensed relative to tests that were either unpatented or non-exclusively licensed. This was a surprise to me, but I think it is relatively uncontrovertible from the analysis when you look at things like price per amplicon. It is surprising, but I think it is true.

Now, why is that. I don't know. It could be because of third-party payers. It could be because of the quest for volume in lieu of price per test. Andrea.

DR. FERREIRA-GONZALEZ: I think some of the testing that you looked at to compare the pricing were sequencing tests. There are not that many providers, so there is no significant amount of competition among laboratories to be looking at price changes.

The third one is the third-party payers. They act as kind of regulators. They decide how much they are going to pay.

DR. EVANS: To me, that is probably what answers that question.

DR. FERREIRA-GONZALEZ: But again, if you have,

for example, more laboratories competing for the sequencing, maybe the prices might go down. We have seen from $76 for some of the testing down to $48.

DR. EVANS: But those aren't clearly related to the patent status.

DR. FERREIRA-GONZALEZ: But I think you may need to see the number of laboratories that are offering the tests.

DR. EVANS: But we see a lot of laboratories in many of these situations that do offer testing. Look at HNPCC. Look at CF.

DR. FERREIRA-GONZALEZ: CF is different.

DR. EVANS: I think you are right about the etiology of this, that it most likely relates to third-party payment, to CMS, et cetera. But for whatever reason, we don't see a big patent premium.

DR. WILLIAMS: I think one of the nuances relating to third-party payers is that you may also find differences in laboratories depending on whether or not they will accept specimens from Medicare and Medicaid. A laboratory that takes all comers will charge a higher per-test price because they know they are going to be losing

money on those payers because of the current payment structure, which we will go into ad nauseam on the coverage and reimbursement side, or have already done that.

But if you, as some do, don't accept those payers or you just say, we are going to bill the referring laboratory or the institution and not bill a third-party payer, you can afford to charge less if you are getting dollar per dollar as opposed to looking at a discount where you have to build that into your price structure.

Looking at the test price has so many variables associated with it that, while I don't disagree with your conclusion, I think that we shouldn't necessarily be so sanguine, either.

DR. EVANS: To be honest with you, I think it is hard to disagree with this conclusion. The facts are the facts. There doesn't seem to be a relationship. I think the reason for that is complex.

DR. ASPINALL: Patent holders range from for-profit, not-for-profit, universities, and individuals. So there is no "they" that are all one type. To me, it is not surprising. It is like any other piece. If you look at drugs or if you look at services, the relative prices and

margins vary, period.

DR. EVANS: Thus far, there is no strong evidence of large-scale and long-term barriers to clinical access to genetic tests within the current gene patenting and licensing landscape. Case studies do document several instances in which access to genetic tests may have been impeded due to a sole provider not offering a test for a period of time, disagreement regarding test cost and royalty payments, inability to combine services for testing multiple mutations, and this problem that arises when there isn't a contract between a sole provider and a major payer.

I want you to pay attention to the nuanced nature of this statement. What we are trying to say is that there are not strong, large-scale, long-term barriers that have arisen due to the patents landscape. At this point, while there have been problems and while there are problems, I think it is also fair to say that in most cases genetic testing is available at what appear to be reasonable prices for most things. Yes.

DR. FERREIRA-GONZALEZ: I think it is a very strong statement here. It might be that we are lacking some of the information. Some of your case studies are of

limited nature. So I think we have to be careful with that strong statement that there is no strong evidence. I don't think we have enough data.

At the annual meeting of the Association for Molecular Pathology, there was very nice work presented where patients at Louisiana State University were not able to get access to BRCA1 mutations even though they had very strong positive clinical information.

DR. EVANS: Right. I'm going to say two things. Where you lay the blame for that lack of access is important. I completely agree with you that the field is opaque, that the absence of evidence is not evidence of absence. I think that is a very important point that we will get to in a minute. Bear with me because I think we address some of that real soon.

DR. FERREIRA-GONZALEZ: I'm sorry to keep coming back to the BRCA1 mutation, but I think if you had more providers that could offer that test we might have access to that.

DR. EVANS: Andrea, that isn't borne out by what I think is probably one of the strongest case studies, when you compare colon cancer and BRCA.

DR. FERREIRA-GONZALEZ: In colon cancer you have more people offering the test, some of which are nonprofits.

DR. EVANS: Right. But they cost the same.

DR. FERREIRA-GONZALEZ: They cost the same, but I'm not talking about the cost. I mean the access to a group that cannot afford the testing.

DR. EVANS: Bear with me. Again, these are nuanced. I'm not trying to say there are no problems. What I'm trying to say is there is not a pervasive, huge problem and people are generally able to get tests. But I think that has to be countered by this following slide.

There is an important typo that was corrected in this. Your hard copies do not reflect this very important "no" in the first line.

At the same time, there is also no evidence that gene patents and exclusive licensing practices provide powerful incentives for the development or availability of genetic diagnostic tests.

In contrast to the situation for the development of therapeutics, the threshold for developing diagnostics is low. Clinical need and academic interests serve as the

predominant drivers for the development of genetic tests. It is evident that in most cases diagnostic tests are quickly offered without the need for patents or exclusive licensing. You can look at CF, hemochromatosis, BRCA, Ehlers-Danlos syndrome. You could go on and on.

The incentive structure could change as the regulatory environment for genetic tests evolves. That is something we have to keep in mind. But patenting does not seem to be required for driving discovery of genetic associations or the proliferation of clinical laboratories which offer a given test.

I think, as we will get to in a minute, this is a very important point. One has to think about what the purpose of patents and licensing is. People can differ about what those purposes are. But if the purpose is to have tests available and to promote innovation, it is arguable that we have uncovered no evidence that suggests that exclusive licenses and patents are necessary. Yes.

DR. ASPINALL: If you would go back? I'm not sure it changes the conclusion, but you say "The threshold for developing diagnostics is low." I think it is important to, at a minimum, say "is lower than

therapeutics." But it is increasingly changing. Several companies have spent in the tens of millions of dollars. One spent $100 million. Is that a billion dollars? No. But the relative benefit is not like it once was or like it is perceived and portrayed.

DR. EVANS: Right. That is why that third sub-bullet, I think, is important. We can talk about that more as we get into the various policy options. I think the incentive structure could definitely change with regulatory requirements.

I do think that the phenomenon of clearing the market, which has occurred so many times in the history of gene patents and licensing, is empirically instructive to us. What it tells us, I think, in no uncertain terms is that tests get developed. We find an association and entities that do not have deep pockets -- clinical labs and academic environments -- quickly fill the gap and start offering testing. Then what exclusive licenses do is they clear the market.

I think when that happens over and over it is telling you something important. It is telling you that you don't really need incentivization to get these tests

out there.

DR. ASPINALL: That may or may not be true. I guess I'm making a different point. Regardless, if the incentives don't change today and they don't change in the future, the first statement about the cost for developing diagnostics is rapidly changing and some would say already has changed.

DR. EVANS: That is why Sub-bullet No. 3 is there.

DR. ASPINALL: I'm saying it is not related to the incentive structure. If the incentive structure never changes, the hurdle to make a diagnostic that is clinically accepted today is changing or has already changed. I think if you look at the IVDMIAs that are on the market and what is public information, it is tens of millions to do that. So the third point may also change that, but it is a separate issue because today the incentive is what it is.

DR. EVANS: That makes sense.

DR. ROHRBAUGH: Jim, I think that is a strong statement in that there hasn't been a look at the null set. What is the negative. What is not being developed adequately because it is not being patented and licensed in

this way. By selecting examples of products that are developed, it is a selective set and not looking at the null set.

Also, there may not be a powerful incentive, but I think there are those who would agree that there is an incentive. I certainly know of companies who would say, we are not going to spend several million dollars even on certain clinical studies if there isn't some degree of exclusivity.

DR. EVANS: That is, again, why I think of these two slides as a spectrum. I think that there has been disagreement with both of these slides, which is exactly what we wanted, because they present the strongest statement of both sides. I think the reality of these situations is nuanced.

DR. WILLIAMS: The point I would make to John's reference to the null set is that were there not issues relating to that, particularly in the rare disease area or the ultra rare disease area, we wouldn't be investing in something like a SEP program through CDC to try and bring some of these tests to the market.

So, at least in the ultra rare disease community,

there are definitely some places where incentives would be necessary to bring that in. Perhaps you could argue that patenting is not an adequate incentive to bring those forward just because of the volume.

DR. EVANS: Yes, Lori.

DR. PRESSMAN: I would just ask Bob and Shubha a question about Myriad. I thought there was some suggestion in some of the phone calls that there has been desirable behavior at Myriad where they correlate genotype to phenotype. Do you think that that in any way was incentivized by their position? I guess, could some exclusivity further incentivize such clinical utility?

DR. EVANS: That is an interesting question. I don't know. Bob, Shubha, do you have any insight into that?

DR. COOK-DEEGAN: I don't know how to answer the question about whether patents are related to that. It is clear that Myriad did that. It is also clear that it is not a universal finding for all of our case studies. So I don't know what to make of that. It is cool that they do it. Is it related to the fact that they are the sole provider? I think it probably is related in some ways. I

think it is also related to the constituency community they are dealing with and all sorts of other variables.

DR. EVANS: I think that it is instructive to think for yourself about what do you feel the purpose of patents and licensing is. I think this is, arguably, a question that reasonable people will differ on. But the answer to that question is incredibly important in how we go forward in crafting policy. It gets to this.

Are patents and, for that matter, exclusive licenses an inherent right? Is it that we should be able to have these patents and these exclusive licenses as a value in and of themselves, or do they exist as a tool to achieve some other, positive goal?

I think that is important because it all turns the threshold of action. If one says that they need to accomplish a goal, then that second slide that says, it doesn't seem that there is a lot of need for these things, weighs very heavily. If one feels that patents and exclusive licenses are an inherent right, then that first slide that says, there aren't huge problems, rises to a greater significance. Rochelle.

DR. DREYFUSS: I didn't chime in earlier when you

talked about the goals of patent law. You did put in this notion that people have an inherent right or a moral right to patents. I would say that is an odd statement about American law. I don't think American law recognizes a moral right to intellectual property.

DR. EVANS: So, the Natural Rights argument that people discuss?

DR. DREYFUSS: The Natural Rights argument, to the extent it exists, mostly exists for copyrighted works or where a piece of a your personality is involved. But even that is more a statement of European or civil law intellectual property, not American law intellectual property.

In fact, I would say it is quite the opposite. Thomas Jefferson, who was in some ways the founder of the patent system, was very skeptical about the idea of needing intellectual property rights at all. He has a letter in which he talks about the fact that if I have a candle and I light yours, I have not diminished my own fire. I have only added more to the world.

So, if anything, that moral claim goes the other way in American law. Ideas are things that should be

shared if there is no special utilitarian right to keep it not shared. The copyright clause which you put up on the board is purely utilitarian, to provide for the progress of science.

DR. EVANS: That is exactly what I was going to go back to. The U.S. Constitution is totally utilitarian in its context. It says "to promote the advance of arts and sciences." It says nothing about inherent rights. I think that is important.

DR. DREYFUSS: The notion that a state could create its own patent rights, that has completely been quashed by the Supreme Court.

DR. EVANS: Kevin and then Mara. Kevin.

DR. FITZGERALD: I don't want to juxtapose European law and tradition versus American because I think in the European law tradition you would get a different sense of that. But I don't think you have to set this up as an either/or. This can be a both/and. One doesn't necessarily have to have an exclusive natural rights framework. One could argue natural rights within a larger framework, which I think is what they do in the European tradition. So it would be seen as a both/and.

DR. EVANS: This comes from your own Kantian/Mill type of thing. Mara.

DR. ASPINALL: On this philosophical issue, the only thing that I would add is, my understanding of it is that is why there are time limits. Time limits are the balance in patents. Whether you call it a right or a privilege that is owned, that means that you have it for a certain period of time and then it is broadly open. That time period was put in place and recently revised in the U.S. and internationally to be able to say reward but then step away and ensure broad access.

DR. EVANS: The second bullet, how does patenting and health care differ from patenting in purely commercial arenas. I think this is also germane to what kinds of policy recommendations we ultimately come up with. Is health care the same as a widget, to use the economic jargon. I would maintain that no, it isn't, that there are other important considerations in health care.

I think that that is demonstrable that we hold different views about health care. We have examples like the Ganske-Frist bill, which implies, I think, quite clearly that we separate healthcare issues when it comes to

patents and licensing in some ways from more purely commercial arenas. I think that, again, these are important things for us to think about as we go forward with a possible policy range.

Is the patenting of diagnostics inherently different from other uses of patents. Since diagnostics elucidate something about an individual, is it relevant to ask whether discovering that information through a diagnostic test should be treated differently or should be controlled in some manner. I think those are, again, reasonable things to take into account. I think people will differ on those.

Maybe, Rochelle, this is a good time for you to speak. We had a conversation at the break about my statement at the start that patents of genes are a fact in every jurisdiction that has looked at it. Rochelle countered I think really instructively.

DR. DREYFUSS: I think the notion that genes are patentable is very heavily dependent on this idea that what you are doing is isolating something from nature and purifying it. Those are the cases that you cited. They were all cases where you isolated and purified something,

so a great deal of human intervention was required and that made something different in kind from what was in nature.

Now, all of those cases are about therapeutics. They are about actually purifying something and then you have a nice little liver pill or whatever that you then swallow. It is the isolated substance which is the thing that is commercially valuable and the thing that the patent protects.

When you are talking about DNA, you are sometimes talking about the same things, perhaps. There might be some therapeutics that you do with DNA. But in actual fact, the isolation and purification of it is not the commercially valuable thing. It is the information content of it that is commercially valuable. When you are talking about diagnostics, that is what you are talking about: utilizing the information content, not utilizing the purified version of the DNA sequence or whatever.

We really haven't had any cases on the question whether that itself is patentable. The Supreme Court has recently, in two cases about things that are quite different, hinted that pure information may not be something that is patentable.

So one question here is whether or not the information content is patentable or just the actual substance. A related way of thinking about it is, even if you get a patent on the DNA, what is going to be considered infringement. Is use of the knowledge going to be considered infringement.

I think there is some real question at this point based on a couple of Supreme Court cases and based on a federal circuit case about how far the patents on this stuff actually go.

DR. EVANS: I think that is a really interesting issue. One thing that we need to keep in mind is that our power as an advisory committee to the Secretary lies in making concrete recommendations. Those issues will be decided by the courts and they are out of our control.

DR. FITZGERALD: I also think Rochelle makes a good point. I thought the Metabolife case indicated the opposite.

DR. EVANS: Could we actually wait on the Metabolife case? Because we are going to talk about associations.

DR. FITZGERALD: Oh, you are. Okay.

DR. DREYFUSS: I guess I disagree about that. You like evidence-based medicine. I agree when I'm a patient that that is the way I would like to be treated. But law doesn't always work quite that way. Law works on looking at the pros and cons of different positions. Is the potential harm greatest this way or greatest this way.

So this kind of data, these case studies that Bob worked on and the conclusions of this Committee, could weigh very heavily for a court. Bracketing this when it is really an issue that is very much at the forefront right now seems to me to be a mistake.

DR. ROHRBAUGH: Jim, I think there are also a lot of other patents that one could imagine and that exist around diagnostics, not just DNA. You mentioned biological and biochemical assays as well. There are formats and other kinds of things.

We are also in a time period of a bolus of DNA patents that will eventually expire. Perhaps the number of new DNA patents is diminishing and ultimately will come to an end, and so we will be dealing with a different set of patents with respect to diagnostics and their framework and also in light of the judicial and statutory interpretation

of utility and all these other cases.

So it is a period in time looking at DNA. Patents issued, many times, long ago and were licensed in the past, and we are looking at the consequences today. What happens today will be different in the future.

DR. EVANS: Debra.

DR. LEONARD: The committee also looked at international perspectives. Bob and I were talking this morning that it is not only Ganske-Frist. Bob knows this better than I, but Belgium and France also have diagnostic exemptions. So the Ganske-Frist type of concept of accepting healthcare practice from patent infringement lawsuits includes diagnostics there where we excluded those. So there is precedent internationally for this kind of thing.

DR. EVANS: Absolutely. They include diagnostics in that kind of exemption.

Moving on with preliminary conclusions, the regulation of IP rights may not necessarily be the optimal primary point of action for resolving problems regarding quality of genetic testing. We put this in here because frequently as you read about the controversies regarding

gene patents and licensing the perceived and potential detriment to quality is brought up.

The argument is made, reasonably, that perhaps with a sole-source provider one is unable to have the kinds of quality control that are inherent when there is competition. This was touched upon by Recommendation No. 13 in the NRC report regarding verification.

What I would argue and what I think came out of our task force discussions is that intellectual property rights and their application are in some ways a peripheral matter with regard to quality. They perhaps are not the best place to focus if one is concerned about quality. Issues related to quality are perhaps better assessed through mechanisms that address quality instead of trying to do it in a roundabout way.

I think that this Committee has weighed in on it. It is a complex issue. But I'm not sure, and I think that the sense of the task force was, that quality perhaps takes our eye off the ball and isn't so much an IP issue. What people do have to say to that?

DR. WILLIAMS: Yes. The other way of stating that would be to say if we had a robust oversight of

genetic testing quality and practice, I don't think this issue would arise within the context of a patent discussion. I would agree with you that I think that the quality issue is a very poor lever to try and say we shouldn't have patents. It really is reflective of another problem in the system. We have addressed it, and I think you are right on.

DR. FERREIRA-GONZALEZ: I think there are two different issues on the quality where you have external proficiency or alternative assessments for performance and quality. What I'm concerned about here is something that we discussed earlier for hemochromatosis where the design of the assay was limited because of the patent.

DR. EVANS: But that is not a quality issue. That is an exclusion of ability to test issue.

DR. FERREIRA-GONZALEZ: It plays into the ability to identify the disorder.

DR. EVANS: I think we are using "quality" in different senses here. I'm talking about quality as in does this test do what it says it does, is it robust enough to detect, et cetera. That is a different issue than, we can't test for this condition because it is under exclusive

license.

DR. FERREIRA-GONZALEZ: But if you are going to use a test to detect specific disorders and you are not allowed to add another mutation that would allow you to really detect the disorder, it is an issue of quality.

DR. EVANS: I disagree. I don't think for these purposes we want to broaden quality in that way. I think that is an issue of can you test for this allele.

I think when we talk about quality maybe what we need to do is define quality in a more precise way for this.

DR. FERREIRA-GONZALEZ: I'm going to go back to this specific issue because it is not the quality of actual analytic validity. I'm okay with that. But you might be missing the issue.

DR. EVANS: Right, right. What I'm getting here too is mainly analytic validity issues. That is a great way to think about it. Thank you.

The field of genetic testing is rapidly evolving and the existing landscape of patents and exclusive licenses might cause significant problems in the future. I think there are a few things we can probably all agree on.

Imagine that.

Most diseases with a genetic component are genetically heterogeneous, which necessitates multiplex testing. This is not up for argument.

Technology is rapidly moving towards the ability to engage in robust, deep genomic analysis. Here is where the interpretation comes in. I think that patent thickets may become more of a logistical problem as multiplex testing increases.

This seems to be rather obvious to me. Maybe other people want to argue with me on it, but it seems to me that, as you test more and more genes, if some of those genes are exclusively licensed or patents are held and not licensed, you have a problem.

I think what is really looming is this issue of sequence analysis, which will materialize. I think that you can argue about whether it will be three years or 10 years, but I think most of us agree it is going to happen. It is very hard for me to envision this not being a serious challenge to the current system of patents on individual genes and exclusive licenses.

I knew Brian would raise his hand. Brian.

DR. STANTON: I'm just going to ask two questions, rather than make a statement. The question of patent thickets, the examples of the 802.1N, the new network standard that has been preliminary forever, could be considered a patent thicket. The DBD standards could be considered a patent thicket where standards of patent pools came up.

My question would be, I don't know whether there is evidence of patent thickets occurring. If there are, the community, or at least the commercial community, doesn't know how to deal with them. So I think that there is a potential issue, but I'm not sure that the solutions are not in the toolbox.

DR. EVANS: Right. I think that is very fair. This is a concern that I think may arise in the future. Now, whether the remedies currently exist to get around them or not, I don't know. I'm skeptical, but there are people who know a lot more about the patent system than I do. So I would love to hear how they are going to get around that.

Kevin is next.

DR. FITZGERALD: Just on that note, if I remember

correctly, somebody brought up a similar kind of example talking about the HD TV. There were 1,100 different patents and everybody gets their little piece. I thought that was brought up as an example.

DR. EVANS: I think it was in software. Software development is an example of where there has been great potential for this. I think as we get into the policy recommendations that we have to look closely at other models that might get around that.

Who is next? Rochelle is next.

DR. DREYFUSS: I wouldn't draw too much happiness from these other examples.

[Laughter.]

DR. DREYFUSS: Think about the DVD, for example, or the HDTV. You have a patent on a tiny piece. You have no product unless you agree with everybody else. Nothing comes out unless everybody agrees. But if you have a patent on a gene, you can still market your test. There is absolutely no need to agree with everybody else because you can still go out there and market.

Now, there might be good reasons to want to agree, but you are not driven to it in the way that you are

all in all of these other examples. That has been the problem in agriculture, where there are some places where you are seeing some of these pools. But the pools are much harder to create because of the fact that people can make money even if they are outside the pool. You don't need everybody else to market a genetic test.

DR. EVANS: Incentivizing a pool is very difficult in this context.

DR. DREYFUSS: It is completely different.

DR. FITZGERALD: On that note, I agree that is an issue that we have to look at. However, as you talk about moving ahead to the $1,000 genome, and we are also keeping personalized medicine out there as the horizon toward which we are moving, when we get a greater sense of what is out there in the "healthy" population, my guess is the relative simplicity with which we look at some of these supposed deterministic genetic conditions is going to become a lot less deterministic.

So even if somebody does have a patent even on the CAG repeats in Huntington's, we may discover in the population that there are people sitting out there with 42 or 45.

DR. EVANS: We already know about the vast majority of them.

DR. FITZGERALD: Right. But things will become less deterministic rather than more. In that case, then you are incentivized, in a sense, to engage with other people to get the information in order to pull together in an integrated fashion, which is what personalized medicine is supposed to be anyway.

DR. EVANS: It is hard for me to see how that is going to solve what Rochelle brings up.

DR. WILLIAMS: To Kevin's point, even though the association studies are showing genes of relatively low level of effect, the reality is the market for those is enormous compared to any of the case studies that we are looking at.

DR. EVANS: Perhaps. I don't know. I would still say perhaps. We have no idea clinically if assessing somebody at a 1.3 relative risk for diabetes is ever going to be valuable.

DR. WILLIAMS: I would argue that we do have examples not in the DNA realm but certainly in the protein realm, looking at things like CRP and HPa and some of those

sorts of things.

DR. EVANS: I think those exactly prove my point. They are of minimal clinical utility, for the most part.

DR. WILLIAMS: Although the new APP3 guidelines suggest that they are going to be very important in terms of what LDL target you treat for. There is relatively good evidence around that.

Again, the issue here is not necessarily the science but the convincing and the uptake. We know that the adoption curve for physicians in terms of new testing is relatively slow. So it may take 10 to 20 years, basically.

But the bottom line is, once it does take off, it takes off very strongly. So I wouldn't necessarily again be sanguine that because we haven't seen high adoption of some of these biomarkers at the present time that that doesn't mean within five years that we are going to see that.

DR. EVANS: Absolutely. I think we could. But again, I don't think that takes us out of the realm where we should be sanguine about the prospect of patent thickets and holdouts. I think that this is a looming problem.

That is my impression. Alan.

DR. GUTTMACHER: I think it is a very good slide because it helps prevent us from being generals fighting the last war. The case examples we went over this morning I think are very useful and very informative, but of course by definition they examine the past. This field really is changing very quickly.

A point that Marc made before, that Claire Driscroll from NHRI has made to me eloquently, is of course that many of the patents which we have talked about are going to expire very soon. Then when we look forward, we really do need to think about the time of being able to sequence the whole genome.

At that point, there will still be some of these which will become an issue, but the larger problem in terms of patenting then is going to be simply the technology of the genome analysis and how that is patented and licensed. I think we have an opportunity now to look forward to that. If we are going to make recommendations or other kinds of things, we should make sure that those are recommendations which look forward and emphasize how we deal with that kind of perceivable but not yet here world, as opposed to simply

how do we fix the past.

DR. EVANS: That is a good point. Who is next? Lori.

DR. PRESSMAN: Around the technique and the physical sciences, there is a lot of competition, which I won't get into.

On that slide, I wonder if instead of "patent" you should put "information thickets." One concern is to be mindful of creating incentives for people to disclose phenotypic to genotypic correlations. Those won't be patented.

DR. EVANS: Or will they? Association patents. Maybe we should weigh in on that.

DR. PRESSMAN: Maybe they will be patented, or there will be secret databases. That seems like something really not good because those don't expire.

DR. EVANS: Right, right. Brian.

DR. STANTON: I was just going to advise the Committee that in March of next year when the new cabinet comes in, the new patent bill will be coming up again. One of the things they will be considering, as somebody mentioned, is the Lab Corp. case, which deals with the

simple correlation and what the standard is. That will be on the table, or is supposed to be. The leadership has been saying in the Senate that they want to bring it up in the next Congress.

I just wanted this Committee to be aware of that. The next meeting is, I think, in February. There might be some chance to bring your opinion to the Senate.

DR. EVANS: Thank you. Marc, then Debra.

DR. WILLIAMS: This relates to the point that Alan made about looking to the future. I think the other thing that we have clearly been promulgating is that in order to make any of this work, at least for common disease variants, it is going to require robust clinical decision support in terms of combining information. That of course in some sense now is being treated as a device in and of itself. That is another area that, whether or not combining that information is going to actually be a device and patentable, will also dramatically impact how we are going to be able to use this information.

DR. EVANS: Preliminary conclusions. I think this one is a fairly straightforward one. The field is opaque. It is difficult to assess the current landscape of

gene patents for diagnostic purposes, associated licenses, and whether the IP rights are directly affecting clinical and patient access to diagnostic genetic tests. I think that is pretty clear.

The lack of transparency also has implications as well for the future. When it comes to multiplex testing, how does a potential provider know if their test even infringes on another's rights. We even jumped beyond that when we said that we might have infringement problems. How are you going to know, as you develop this test, if you have infringement problems. In other words, the transaction costs of this begin to rise quickly because of this opacity.

I want to explain something because I think that unless we frame this correctly there could be considerable misunderstanding about what we are trying to do with this range of potential policy options.

We are not saying as a task force or, if we approve such a range, as a Committee that this is what we are telling the Secretary. This is a very complex landscape. We are trying to frame the issues with a range. Some of them are virtually "mom and apple pie" kinds of

things. Others will have vociferous objections from some people. But I think it is reasonable and instructive to bracket this field and put out a range of options.

I will say it again. Some of these will be mutually exclusive. Some of these will be ones that depart considerably from what I think and what you think, but I think it is reasonable to have them out there and get public comment. Then, next time we can have a really friendly conversation about what should go into the final recommendation.

We have divided this range of options into eight categories. They are categorized by the nature of the action, how the change would be effected, and the entity to whom the recommendation is directed.

The categories of potential policy options include advocacy efforts by key stakeholders to ensure access, enhancing transparency in patents and licensing, filling data gaps, federal efforts to promote broad licensing and patient access, licensing policies governing federally funded research to facilitate access, study federal implementation of IP laws or recommendations related to that, improving and clarifying PTO policy, and

finally, seeking or recommending statutory changes be sought.

Again, why present this range? To present a number of options to the public to help frame the issues. The public perspectives will then help guide formulation of final recommendations to the Secretary. Yes.

DR. FITZGERALD: Just a procedure question. My sense is from this what you are saying is you are looking at this issue as at the same time complex and yet opaque. You want to get this feedback without necessarily indicating that the next meeting is going to be the meeting where this report is finalized. It could be, but it may not be.

DR. EVANS: It is not so much that. It is that we feel like just putting out an unstructured call for comments would be far less productive than putting out a framework of possible options that people can then comment on.

The other side of the spectrum would be to just have come up as a task force with the recommendations. That would not be fair to the Committee and it wouldn't be fair to the public. I think this is a nice amalgam of

that.

But we do very much hope to move along quickly on this. There is 60 days for public comment. Then we will have some more of those really fun conference calls and we will come up with something. Then, in a full meeting we will nail down our recommendations.

DR. ASPINALL: Just to clarify the process, we are going to have public comment live today with people? No?

DR. EVANS: We will.

DR. TEUTSCH: But not on this.

DR. EVANS: Some people may comment on this. The main public comment will be in that 60-day period.

DR. ASPINALL: That is what I wanted to understand. It will be written comments like we have had on the last couple.

DR. TEUTSCH: Yes. It is the formal process.

DR. EVANS: Then we will do all that laborious culling.

DR. ASPINALL: Then we may have live comment at the next meeting as well.

DR. EVANS: We always have live comment.

DR. ASPINALL: Right. But then we will be looking towards finalizing this or putting it in writing at the next meeting.

DR. TEUTSCH: Correct. But we really want the public comments in writing before then so that we have as much as we are going to have so that we can reach some recommendations.

DR. ASPINALL: That is what I wanted to clarify.

DR. EVANS: The public has 60 days.

DR. ASPINALL: After this meeting, the documentation we have talked about today will be available for public comment.

DR. TEUTSCH: Yes. Once we approve it today.

DR. EVANS: Once we approve the draft.

DR. TEUTSCH: It will go out for that purpose.

DR. EVANS: Let me keep moving here because we will need all the time we can get.

I will just make a plea for balance at the start. I don't think this is a particularly controversial statement, but the patent system in this country works pretty well. We should be mindful of unintended consequences that could result from suggested changes. It

is the baby and the bath water argument. We don't want to muck up the whole system by trying to fix things.

On the other hand, if there are problems or likely future problems, I don't see it as unreasonable to recommend judicious policy changes. The key is balance. We need a proportional response to identify problems and potential problems. That would be my plea.

The questions for the following draft options are the following. I want you to keep these in mind as we go through them. Are there policy options that should be added, removed, or modified prior to releasing the draft. We have heard some suggestions. We could get that input. I'm sure the task force came up with the perfect document, so I can't imagine there would be changes.

Is the range of policy options presented supported by preliminary findings. Are there any other issues that need to be addressed in the report before it is released for public comment. Overall, and with the understanding that further editing may be needed, is the draft report ready to be released for public comment in early 2009 for that 60-day period.

With those kinds of instructions in mind, let's

tackle the first ones. Some of these, as I mentioned, are kind of "mom and apple pie" types of things.

"With regard to advocacy efforts by key stakeholders to ensure access:

"A) In order to optimize patient access to and the quality of genetic tests, stakeholders -- that is, for example, industry, academic institutions, researchers, patients -- should work together to develop a code of conduct to encourage broad access to technologies through licensing agreements for the diagnostic use of gene patents."

Comments?

DR. LEONARD: But, given the discussion of quality, I think the quality issue --

DR. EVANS: Right. As I read it I thought, wait a minute, why do we want "quality" here. Why don't we leave that out. "Patient access to genetic tests." Mara.

DR. ASPINALL: I have some issues with a number of these, but I'm wondering whether it makes sense to edit these or really leave them as they are and then have the comments on them.

DR. EVANS: That is a good point.

DR. ASPINALL: I think this presumes a lot of things. Otherwise, we will never get through it.

DR. EVANS: Right. I don't want to do too much wordsmithing here because the whole purpose of the subsequent phase of this is to get people's input. I do think that [we should discuss] if there are really substantive reasons not to have things or ones to add. I think your point is good. Unless there are huge issues, I think we should proceed.

DR. ASPINALL: The only issue that I will say is, that implies that as a result of the patent system we don't have broad access, which some of the case studies said we do and some of the case studies said we don't.

DR. EVANS: It says "in order to optimize." I don't think this necessarily implies it is bad. I think that we want the most access possible.

DR. WILLIAMS: The other point I would make relating to the quality thing and the reason to maybe recharacterize it or restate but not take it out, is the point that Andrea brought up before that some of us include within the general term of "quality" the idea that if you are not operating certain parts of the test, that affects

what might be considered to be the utility of that test. So you might want to characterize that as utility as opposed to quality, leaving out the "analytic validity" piece of it.

DR. EVANS: So, how would you phrase that?

DR. WILLIAMS: "In order to optimize patient access to and the utility of."

DR. ASPINALL: Can I ask, does that include the issue that sometimes we are having very many companies or labs doing one test who actually may have lesser quality because there are variable, different standards and not a clarified ability to show one reference standard?

DR. WILLIAMS: You are talking about analytic testing?

DR. ASPINALL: Yes.

DR. WILLIAMS: That is not what I'm talking about.

DR. ASPINALL: No. I'm saying it should include that as well if you want to include that.

DR. WILLIAMS: No, that is a different issue.

DR. EVANS: That was the point. We wanted to separate analytical validity from clinical utility and

clinical value.

DR. FERREIRA-GONZALEZ: We were talking about adding different mutations, Mara, here that will have different clinical utility. Clinical utility will cover that portion of being able to only detect 95 percent of the mutations versus 50 percent or not being able to add that mutation to the panel.

DR. EVANS: Kevin.

DR. FITZGERALD: It might be helpful for our own reflection if you add into (A) that HHS should bring together these stakeholders to develop a code. Then we find out from the public whether they think HHS is the place actually to do that or there is some other group to do that.

DR. EVANS: We could say "should work together (perhaps facilitated by HHS)."

DR. FITZGERALD: Just put that in there so we get that feedback and we can see whether that is the place that that is supposed to happen or not.

DR. EVANS: "B) When different stakeholders -- for example, academic researchers, industry, and patient organizations -- work together to advance the

identification of gene mutations and the development of diagnostic tests, the owner of any resulting invention should consult with those stakeholders regarding whether to seek patent protection and how any resulting patents should be licensed."

Does that seem controversial to anyone?

MS. AU: What is the action step on this one? Who is enforcing this?

DR. EVANS: Believe me, we get to ones that have big teeth. Have no fear. This is a recommendation. This is a statement that we should all get along.

DR. WILLIAMS: Actually, this is a statement. It is not really a recommendation. The recommendation could be that DHHS provide a role or a forum by which the stakeholders could actually get together and discuss these issues.

DR. EVANS: That is interesting. Maybe we could consider that as another option to put out there on the table.

DR. BILLINGS: What I don't understand about this one is, I thought the patents were held in some level of secrecy until they were filed. How are we going to have

these discussions within the context of how patent information is handled?

DR. EVANS: I think what this is saying is that when different stakeholders work together to identify a gene and develop a test, the owner of the resulting invention should consult. I think that it doesn't preclude not consulting. It is a recommendation or a suggestion that this is the most beneficial way of proceeding.

DR. BILLINGS: But when? After the filing, before the filing? When, exactly?

DR. EVANS: I don't know. We didn't approach it that way.

DR. TEUTSCH: It is probably not about whether but it is about how it gets implemented.

DR. BILLINGS: This actually has something to do with marketing of tests.

DR. COOK-DEEGAN: Paul, this is Bob. I think what this is trying to get at -- I'm not absolutely sure -- is let's use the Huntington's disease and cystic fibrosis model. The constituencies were at the table when the decisions were made about how and when to file patent applications. The fact that something can be secret does

not mean that it has to be secret. In this case they were not.

That is in contrast with the Canavan case, which I presume is what this is mainly aimed at. Don't screw up your relationships with the constituencies that contributed to your invention.

DR. EVANS: Maybe Paul's objections could be overcome by saying instead of "the owner of any resulting invention," "those stakeholders should consult with one another regarding whether to seek patent protection. I think that would get around some of the ambiguity that, Paul, you highlight there.

DR. ASPINALL: Either way, there may be patents in process that people may not choose to share. I think you could phrase it either way, but as a live entity under today's system there very well may be things that people do or don't want to share. Maybe some would say, I don't want to sit here because I don't want to learn things that will impinge upon this.

I think in and of itself this is meant to be draft and then to have more substantive comments on it later. I think Paul's point is a good one as to how

logistically this will work. There are those who may want to do it but they are unable to.

DR. EVANS: Right. So, what if, instead of "the owner," we said "those stakeholders should consult with one another." This is more of a general admonition in the field.

DR. LEONARD: Actually, this could be a recommendation to patient organizations, when they are beginning to interact to advance identification of gene mutations and the development of diagnostic tests, that they proactively make their input a condition of their involvement.

DR. EVANS: That is a little different. This is an admonition to, really, all those stakeholders. I think you are right. It is instructed by our experience with the Canavan experience, where this didn't happen. Now, I don't know whether us just saying, you should play well together, is going to do anything.

I don't want to dwell too much on this because these are "mom and apple pie." We want people to get along. I think it is useful for our Committee to mention this, but I think when we have things that have no

enforcement we shouldn't spend that much time. We do have to break for lunch. Mike.

DR. AMOS: I just want to say, to the extent that this is sent to the Secretary of Health and Human Services, what is an actionable statement that we can make to get to the point where the Secretary can set up a commission or set up a forum to promote this. "Where possible, HHS should promote," blah, blah, blah.

DR. EVANS: That is a really good point. Maybe at the lunch break we can do that.

DR. ASPINALL: In thinking about it, something like that may be necessary at least post granting of patents because I think there is an aspect of this, which I don't think was the intention, which is restraining free trade. If you haven't filed your patents you can't say, I'm going to file this one first, so-and-so is going to file this one second.

DR. EVANS: Yes. Collusion is not something we want to encourage.

DR. ASPINALL: So if part of the idea is, you have these patents, so how do we make the world better for health care. It may be after granting as opposed to before

granting. That gets to Paul's issue as well.

DR. EVANS: At the lunch break we can talk about that. We are going to have to finish up with this one and then go to lunch. Joseph.

DR. TELFAIR: My question is more of a point of both clarification and information. It is a feasibility question. I agree with the statement made about what is actionable, but I have to back up and ask the question how realistic is this? Maybe it can be answered here. Do we have adequate information about how often this actually occurs in the development process such that we could spend reasonable time getting this done?

It seems to me that if we are going to make this a recommendation, it should be a strong enough recommendation on accessible data and information that we can actually say, do something about it. If it's just not done often enough, [it may not] even be something that is reasonable to consider.

DR. EVANS: Again, I think that the case studies clearly demonstrate there are times that when this didn't happen there were problems. I don't think it is unreasonable to admonish --

DR. TELFAIR: I'm sorry. That is not what I'm saying. I'm just saying I recognize from the case study that it happens sometimes that it's not. I'm just worried about when the "not" occurs.

DR. AMOS: My guess is that it is not going to happen that many more times for individual genes. It might, but when you start multiplexing these tests and trying to put them together on one platform, the issues are going to become very, very complex. That is something I think we may want to consider looking in the future.

DR. TELFAIR: Then, can I just recommend that that actually become the focus more and that is considered when we talk about more actionable steps and what to do? It seems to me that that would actually help focus a little bit more whatever recommendations that we make in terms of something very concrete to do.

DR. EVANS: I think we can focus this some. We will do that during the break and then come back with some wording. One more comment.

DR. WILLIAMS: Again, thinking about actionability, speaking as someone who is really naive in terms of how these agencies work together, would there be a

role for the Secretary to convene something that would involve the Patent Office, Commerce, and different people at the governmental level who have a stakeholder's interest in this as well, to say here are the issues that have been teed up by our advisory committee. We think it impacts you. Can we get together and discuss your perspective on this. I don't know if that would be reasonable or not.