DEPARTMENT OF HEALTH AND HUMAN SERVICES

Seventeenth Meeting
of the

SECRETARY'S ADVISORY COMMITTEE
ON
GENETICS, HEALTH, AND SOCIETY
(SACGHS)

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– VOLUME I –

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C O N T E N T S

C O N T E N T S *(continued)*

P R O C E E D I N G S

[8:06 a.m.]

Opening Remarks

Steven Teutsch, M.D., M.P.H.

DR. TEUTSCH: Good morning, everyone. Thanks to all of you who fought the traffic and dealt with the airlines and the weather and assorted other travails of travel yesterday. Hopefully you had a great Thanksgiving. I appreciate everyone taking the end of their weekend to get here and be with us.

This is the 17th meeting of the Secretary's Advisory Committee on Genetics, Health, and Society. Just as a matter of record, the public was made aware of this meeting through notices in the Federal Register as well as announcements on the SACGHS website and listserv. I want to welcome members of the public in attendance as well as viewers tuned in via webcast. Thanks so much for your interest in our work.

Please note that we have scheduled public comment sessions for this afternoon at 1 o'clock and again tomorrow morning at 10:15. We have several of

you already registered to make comments, but there is room for others of you to do so. If you would like to make comments, please sign up at the registration desk just outside of the meeting hall so that we can get you on the list.

We have an interesting agenda. There are four main goals for this meeting. First, we are going to be reviewing a draft report that explores the question of whether gene patenting and licensing practices are having effects on patient access to genetic tests and determining whether the report is ready to be released for public comment.

Later today, as a follow-up to some of the issues discussed in our Oversight Report, we will take an in-depth look at some of the important federal initiatives to enhance quality and innovation of genetic technologies through standards development. Tomorrow we are going to continue to discuss and refine our future study priorities and plans. Finally, we will also discuss a draft progress report for the new administration.

At our last meeting, which was in July, in

addition to preparing a progress report for the incoming Secretary, we decided to write a letter to Secretary Leavitt. We sketched out the main points of the letter during our meeting and finalized the text via Email after the meeting.

In addition to thanking the Secretary for the high priority he has given to effecting innovative policy strategies that harness public and private sector solutions and resources to address the policy challenges associated with the development of genetic technologies, we also took the opportunity to highlight several issues that we thought were in need of critical attention over the remainder of his tenure.

We urged the Secretary to move forward on one of our oversight recommendations by beginning to address the practical and legal questions surrounding the establishment of a national registry of laboratory tests, and taking steps to create incentives for laboratories to make their test menus and analytical and clinical validity data for these tests publicly available through gene tests, or at least post them on

their own websites.

In the area of pharmacogenomics, we highlighted the importance of the FDA issuing draft guidance on the co-development of pharmacogenomic drugs and diagnostics. We also reiterated the need for changes in Medicare coverage and billing policies to facilitate the integration of genetic technologies based on family history of disease and to enhance patient access to genetic counseling services.

A hard copy of that letter is in Tab 7 of your briefing books. We have also made it available to those in attendance, as well as to the public generally through our website.

With regard to the FDA co-development guidance for pharmacogenomic drugs and diagnostics, we understand that there have been a series of meetings over the fall on the guidance and that work continues on that.

With regard to the other issues we have raised regarding coverage and reimbursement, I'm told we can expect to receive a letter from the Secretary addressing some of those issues as well.

I also want to take note of the report, which you see here on the screen, that Secretary Leavitt released about two weeks ago to provide an update on HHS efforts to advance personalized health care. The report discusses many of the issues that we have been addressing as a committee. It outlines some of the important steps that have been taken to advance personalized medicine, but also offers a frank account of how much more will need to be done before personalized health care is a fully developed and fully applied system.

The report contains case studies and commissioned papers that are very relevant to a number of the issues that we are likely to take up in the years ahead. It is available on the HHS website at the URL that you see on the screen. Those of you who are on the Committee should have received copies of that as well.

We have also seen significant progress on the family history front. A demonstration of the Secretary General's Family History Tool was shown on November 25th. Marc Williams was there and can regale

us with stories of that. It is to be released in late December.

Several agencies -- CDC, HRSA, and AHRQ -- are supporting research and development through contracts and cooperative agreements to enhance the utility of family history in electronic health information to support risk assessment and prevention.

At our last meeting we not only acknowledged but we celebrated the signing of GINA, the Genetic Information Nondiscrimination Act, of 2008. The provisions of the Act do not take effect until next year. There is a great deal of focus on the implementing regulations that need to be developed. Rulemaking processes are underway throughout HHS and the Departments of Labor and Treasury and the EEOC.

We understand that a proposed rule will be issued soon by the EEOC on the employment provisions of the law. There are multiple teams working across the agencies on the health insurance provisions. The health insurance provisions take effect in May of 2009. The employer provisions start in November of 2009.

Guidance is also being developed for researchers and research oversight agencies. These are in clearance and we expect them before year's end.

I would also like to note that since our last meeting the work of the SACGHS Genetics Education and Training Task Force has proceeded under the dedicated leadership of Dr. Barbara Burns McGrath. The task force has formed three workgroups to examine the educational needs of healthcare professionals, public health providers, patients, and consumers. They are currently in a data-collecting phase and plan to begin drafting the report in February.

As part of this effort I would like to alert our ex officio representatives that they will receive a survey later this month from the task force. The survey will inquire about genetics education activities within your agencies. I hope you or your colleagues will take time to complete the survey, which should be returned by the end of January.

Also, during the course of information gathering, the task force learned that the Council on Linkages Between Academia and Public Health Practice

was revising its core competencies for public health practitioners and academicians. Since competency in genetics is not currently addressed, the task force would like SACGHS to submit a competency that emphasizes the importance of understanding genetics and genomics as they relate broadly to public health.

The proposed comments are the first item under Tab 7. The council is accepting comments until December 15th. We would like you to review the proposal over the next two days and let Cathy Fomous know if you have any suggested edits.

In particular, I want to thank Sylvia Au and Joseph Telfair for really spearheading this and making sure that this gets in here. Thanks to you both.

Tomorrow we will be delving back into our discussion of future study priorities. You will recall that in July we came to preliminary conclusions about the issue areas that we thought needed to be pursued. Our goal at this meeting will be to come to a final consensus on the issues and agree on a work plan for addressing them. As we do this, we will be mindful of the need to factor the priorities of the

new administration into our ultimate work plan.

To this end, we will also be discussing a draft report to the new administration. In July we agreed that this report should take the form of a concise summary and that it should discuss the growing importance of personalized medicine and the complex issues it raises. It should sum up our work and key recommendations over the past six years and outline the issues that will need attention going forward.

The report should also serve as a vehicle for ascertaining how we can be most helpful to the new Secretary and make clear that we are ready to adjust our priorities as needed.

We are in a time of transition in more ways than one. This will be the last SACGHS meeting for several of our ex officio members: Scott McLean, Matt Daynard, who will be joining us tomorrow, and Steve Gutman, who will be retiring from federal service at the end of the year.

Let me say we deeply appreciate your service on this Committee and your many contributions to our work. We have admired your commitment to public and

military service and your dedication to fulfilling your agencies' important missions.

Steve, I know you were involved in SACGHS's predecessor, the Secretary's Advisory Committee on Genetic Testing. All told, you are probably among the longest-serving ex officios. For that you deserve special recognition and an extra measure of our regard and appreciation.

To all of you, we wish you the best in all your new endeavors.

[Applause.]

DR. TEUTSCH: We know that FDA and DOD will be appointing new ex officios, and we will look forward to seeing those new faces and working with them.

Matt Daynard's replacement at the FTC will be Sarah Botha, an attorney in the Division of Advertising Practices. She should be here tomorrow and we will meet her then.

I also want to take this opportunity to thank Joe Boone, who I don't believe is here, and who is the associate director for science in the Division

of Laboratory Systems at CDC, for his contributions to SACGHS and SACGT over these last 10 years. Joe is also retiring at the end of the year. I have known Joe since my CDC days, so I have known him for about 30 years.

There has also been a transition at the EEOC. Peter Gray, who served as Commissioner Earp's alternate for a number of years, has moved to the Civil Rights Division of the Department of Justice. We have appreciated Peter's dedication very much and know that before he left EEOC he was working on the development of the regs implementing the employment provisions of GINA.

EEOC will now be represented at the staff level by Kerry Leibig, a senior attorney advisor in the EEOC's Office of Legal Counsel. Kerry will be joining us tomorrow as well. We welcome her to the SACGHS.

Thanks to all of you for your service and advice.

I also want to welcome Dr. Doug Olsen, a senior nurse ethicist at the National Center for

Ethics and Health Care at the VA. He is serving as the alternate ex officio today. Dr. Fox will be here tomorrow.

We have a new member of SACGHS to welcome. Darren Greninger joined the team in August and was put to immediate work. He has an undergraduate degree in biology and a law degree, and has worked as a science writer and journalist. Welcome, Darren. I'm glad to see that all the work didn't dissuade you from coming.

I also have a personal transition. This is my first day of retirement from Merck. I am leaving the private sector and will be rejoining the public health community as chief science officer at the L.A. County Health Department, so I will be here in a different capacity.

I would also like to call your attention to the fact that, like all federal advisory committees, SACGHS has a two-year charter. In September our charter was extended for another two years, so that is good news.

We also wanted to point out that SACGHS has a new Web address and a new site. You will see on the

screen the new URL, which is shown here. There is also a handout at the registration desk. Hopefully we will find people finding our materials even more accessible than they have been up until now.

Sarah, this is the time that we all know and love when we get together, the important reminder about the ethics rules, which are clearly important.

MS. CARR: Very important. As you know, you have been appointed to this Committee as a special government employee. Although you are in this special category, you are nonetheless subject to the rules of conduct that apply to regular government employees. I'm going to highlight two of those rules today: the rule about conflicts of interest and the rule about lobbying.

First, conflicts of interest. Before every meeting you provide us with information about your personal, professional, and financial interests, which is information that we use to determine whether you have any real, potential, or apparent conflicts of interest that could compromise your ability to be objective in giving advice during Committee meetings.

While we waive conflicts of interest for general matters because we believe your ability to be objective will not be affected by your interests in such matters, we also rely to a great degree on you to be attentive during our meetings to the possibility that an issue will arise that could affect or appear to affect your interests in a specific way.

In addition, we have provided each of you with a list of your financial interests and covered relationships that would pose a conflict for you if they became a focal point of Committee deliberations. If this happens, we ask you to recuse yourself from the discussion and leave the room.

Government employees are prohibited from lobbying and thus we may not lobby, not as individuals or as a Committee. If you lobby in your professional capacity or as a private citizen, it is important that you keep that activity separate from activities associated with this Committee. Just keep in mind that SACGHS is an advisory committee to the Secretary of Health and Human Services. It does not advise the Congress.

As always, I thank you for being attentive to these rules of conduct. We appreciate how conscientious you all are. Thank you.

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

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

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

The task force began under the leadership of Dr. Deb Leonard, who has continued to serve as an ad hoc member of the group and joins us today in that

capacity. Deb, thanks for your continuing service on the task force. Welcome back, as always.

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

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

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

It should be apparent that the task force has devoted countless hours to this project. I want to commend all of the members of the task force, and most specifically Jim, for his energy, dedication,

leadership, and commitment to all of this. Jim, thanks very much. Take it away.

SESSION ON GENE PATENTS AND LICENSING PRACTICES

Review of SACGHS Draft Report:

Gene Patents and Licensing Practices

and Their Impact on Patient Access to Genetic Tests

James P. Evans, M.D., Ph.D.

[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.

DR. EVANS: Again, what we need to do is now take a break. Anybody who is interested, come on over here and we will talk a little about adjusting this.

We start back at 1 o'clock with public comments. Then, 1:30 to 3:15 we will try to soldier through. Just be warned we will take the break away if we aren't done.

[Lunch recess taken at 12:22 p.m.]

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AFTERNOON SESSION

[Reconvened at 1:04 p.m.]

Public Comments

DR. TEUTSCH: Welcome back, everyone. Before we get on with our discussion on patents, we will be turning to public comment, which is one of our critical functions. As you know, we serve as a public forum for deliberations on a broad range of health and societal issues raised by the development and the use of genetic technologies.

So we truly value all the input that we hear from members of the public. This is one of the important ways in which we get that input.

As you know, we have a very full schedule. In the interest of time here, I will ask the commenters to please keep their remarks to five minutes or less. I'm going to adhere to that because we really do have a full slate. We should have copies of your full statements, which will be made part of the meeting record.

So let's begin. Is Ms. Lisa Salberg here from the Hypertrophic Cardiomyopathy Association?

[No response.]

DR. TEUTSCH: No? Well, I see that our next presenter is sitting in the back. He is a frequent attendee of these meetings and someone who we always learn a lot from. Mike Watson is representing the American College of Medical Genetics.

Welcome again, Michael. We appreciate your comments.

Comments by Michael Watson, Ph.D.

American College of Medical Genetics

DR. WATSON: Thank you. I'm going to keep my comments brief. I think most of what I have to say was pretty clear in the letter that I wrote to the Committee.

I had the luxury, that most here obviously didn't have, of listening to the webcast from my office this morning, so I will try not to repeat things that you have already talked about. Perhaps I will raise a few issues that have risen recently that I didn't hear mentioned this morning. They may have come up while I was driving down here, but who knows.

I'm from the American College of Medical

Genetics. We represent board-certified medical geneticists, both clinical and laboratory geneticists, in the United States.

As far as I know, we are the only organization that has an actual policy position that genes are naturally occurring substances and should not have been patentable initially. However, given the inability to adequately address that problem, we have focused a lot of our interest on unfair licensing issues.

Now, I do want to say in preface that I would never want to encourage anyone to infringe on a patent. Anything I say I hope you take as purely educational. I have had people inquire about the value of my home in the past in relation to patent issues, so I clearly don't want anyone to be encouraged to infringe on a patent.

I will say that, at this point in time, there is little evidence that patents have led to products. There are very few products available in genetic testing. Products used to be the way by which most licensing was done. Royalties were accrued

through the development of a particular product that made testing better and easier, or cheaper, and that laboratories thought improved on their own laboratory-developed tests.

Among those 1,500 genes on which we currently do testing, there is very little evidence that patents have led to any products, aside from a very few, at this point in time. There is limited evidence that the patents and their license have improved services, either. A few examples I would agree to, but for the most part there is very little evidence of improvement in the delivery of services.

Now, I think one of the interesting things about gene patents is that they are typically very well developed in the diagnostic sector before anybody imposes patent rights or licensing rights on particular genes. That is because they are primarily for rare diseases and there is no financial incentive to go into enforcement of those genes until the point when the test moves out of diagnostic and family-based medicine and into population-based areas.

This is what happened with Canavan disease

when it went to carrier screening. It was very shortly after two organizations, ACOG and us, recommended that carrier screening begin that the enforcement of those patents came into play. That is a very common phenomenon for the patents held in diagnostic genetic testing.

There are studies that have been done about gene patenting. Almost everybody in this room has watched these for 10 years. As far as I can tell, they largely focus on the research issues, not on clinical investigation as we know it in genetics but really on basic research, and have documented not a significant impact on research. I think the situation is very different in the clinical practice arena.

There was a recent paper in Science. Christopher Holman just a few weeks ago made a couple of arguments about gene patenting. He argued that there was very little litigation and that in and of itself was evidence that there was not a problem with patenting of genes as they related to genetic testing.

I think that is a misstatement. Our experience is that the litigation has been extremely

limited due to the extreme cost of litigation in patent-related issues. We engaged in a litigation backing Kaiser Permanente in a case involving human chorionic gonad otropin back in the mid to late '90s. At that time it was only about $1.5- to $2 million to engage in one of these cases and get all the way to the merits of the case in court.

We actually went through about $200,000 in that case and never got to the merits of the case. They gave a covenant not to sue to Kaiser, who then allowed them to do all the testing they wanted to do, without ever getting to the merits. Everybody else who had contracts and other relationships was then in the same boat they had been in.

The other argument they make is that there has been no imposition of gene patents on the new multiplex array technologies. I think this is clearly no longer the case, either. There have been a couple of recent examples. A laboratory has been told to take the dystrophin gene for Duchenne muscular dystrophy off of its CGH arrays.

What their lawyers determined was that they

would not have to take them off of the array but they would not be able to report out a deletion or duplication in the dystrophin gene itself, seriously imposing on the practice of medicine and the duty to inform when that laboratory identifies that Duchenne muscular dystrophy-related abnormality in array CGH.

Another situation has arisen recently. It is circuitous because it overlaps a couple of the examples Bob Cook-Deegan gave you this morning. He talked about newborn screening for hearing loss. He also talked about Long QT syndrome.

In the hearing loss world, one of the goals of manufacturers has been to develop an array that can identify kids in newborn screening molecularly. They come out with a functional test found to be hearing loss, and we would like a molecular test that allows us to identify the multitude of abnormalities that can lead to hearing loss.

Unfortunately, one of those is Jervell and Lange-Nielsen syndrome, also associated with Long QT syndrome. When one is doing this for a child that presents with hearing loss, you are now not allowed to

test for that particular gene in the arrays because it imposes on the Long QT patents.

I think increasing examples are arising of real patent thickets developing around gene patents that are going to require us to find some way out of the box. We really only see two options. One is to go back to the Ganske-Frist amendment and separate out the exemption for diagnostic use of gene patents from the protection of gene patents for the development of therapeutics. Clearly, that is a high-investment area where one wants to protect that investment to lead to the products we need in therapeutics. The evidence of that benefit arising on the diagnostic testing side is quite thin.

I had better not go on. There is another case. I would encourage you to look at the case of Mayo Labs v. Prometheus Labs because it is bringing us back to the Metabolife Labs v. Lab Corp. case in the very near future. It is currently at the circuit court.

DR. TEUTSCH: Thanks so much, Michael. We appreciate that. Our next speaker is changing her

role here. Debra Leonard is representing the Association of Molecular Pathology. So you are going to change hats instantly, I assume.

Comments by Debra Leonard, M.D., Ph.D.

Association of Molecular Pathology

DR. LEONARD: I am here representing the Association for Molecular Pathology. We have recently rewritten our AMP position statement on gene patents and exclusive licensing of genetic discoveries. I would like to share that with you.

Many disease-associated human genes and human pathogens have been identified in recent years, and more will be discovered in the coming decades. Clinical laboratories in both the public and private sectors translate and develop many of these discoveries into molecular diagnostic tests and seek to make these tests widely available as clinical services for the public good.

Clinical laboratories can only develop these important tests when they have access to the broadest base of genomic discoveries. The U.S. Patent and Trademark Office has historically granted broad

patents on genomic discoveries. Frequently, patent holders and their exclusive licensees are choosing to monopolize molecular testing by restricting healthcare providers from developing or performing tests covered by these patents and licenses.

AMP believes that molecular test services are medical procedures. As such, they should be widely available to promote optimal patient care, medical education, and medical research. Research, development, and practice of molecular testing is essential to medical practice, the education of physicians, researchers, and healthcare professionals, and the continued improvement of the quality of medical care.

While attaching intellectual property rights to true acts of invention, such as new therapeutics, diagnostics, or technology platforms is essential to encourage investment and reward innovation, a single gene or a sequence of the genome is a product of nature and should not be patentable.

Gene patents can serve as a disincentive to innovation in molecular testing because they deny

access to a vital baseline of genomic information that cannot be invented around. Moreover, the threat of enforcement from a patent holder and the ensuing litigation costs lead to a chilling effect, as clinical laboratories are reluctant to develop new tests which could directly benefit patients.

In addition to the concern about gene patents, exclusive licenses that confine molecular testing to a single provider are detrimental to the public interest by limiting patient access to testing, restricting medical practice and research, and impeding the advancement of medical knowledge and enhancement of the public's health through informed clinical decision-making.

Moreover, no governing standards currently exist that would prohibit the practice of granting exclusive licenses. Most patented discoveries of human genes or human pathogens can be effectively translated into molecular tests provided they are licensed on a non-exclusive basis and licenses are easily obtainable both in financial and practical terms.

Therefore, AMP recommends the following.

The patenting of single genes, sequences of a genome, or correlations between genetic variations and biological states should be discontinued, either as a result of judicial review or through an act of Congress.

Entities, including higher educational and research institutions, that currently hold gene patents should not grant exclusive licenses to these patents.

To ensure that access to innovative molecular tests remains widely available and affordable to patients, financial terms for test licenses should be reasonable and sole-source testing should be prohibited. License agreements should also be free of any terms that limit the number of tests that can be performed by a laboratory or regulate the technical performance or clinical uses of a test.

License agreement should be likewise free of terms that inappropriately limit research related to testing or the public dissemination of the resulting research findings.

AMP encourages all stakeholders to work cooperatively to develop alternative models to gene patents and exclusive licenses. Innovative, alternative models should be developed that increase patient access to health care and achieve greater benefit from our current knowledge of the human genome. Thank you.

DR. TEUTSCH: Great. Thanks so much, Debra. We appreciate all of that. I'm going to move us along because we are just pressed for time.

The next speaker is Guido Brink, who is from Agendia. Thanks for coming.

Comments by Guido Brink

Agendia

MR. BRINK: Thank you so much. I have a quick question or comment for the Committee. My name is Guido Brink. I am director of regulatory affairs and reimbursement for Agendia. I think Dr. Gutman can agree with me that, when we talk about genetic tests, the devil is in the details of the definition. What we have seen with the whole discussion around IVDMIAs is that industry has taken a lot of time and effort to

try to define IVDMIAs and to try to exclude certain deaths from the IVDMIA definition.

When I look at the definition currently stated by the Committee, it says genetic tests are, for purposes of this study, any test performed using molecular biology methods to test DNA or RNA. In our case, we have a gene expression profile. We do not assess any mutations. We do not want to assess any mutations. We assess the expression of a gene or multiple genes and put that into an algorithm to come to a conclusion on disease state.

My recommendation to the Committee, or my question, would be within this definition gene expression profiling tests would be genetic tests, although when I look at the case studies and at the investigations performed, no genomic profiles or expression profiles are investigated. It is purely mutation assays. So my question would be, or my recommendation, is looking back at what has been investigated to clearly define what has been investigated and to maybe redefine "genetic test" in this study.

DR. TEUTSCH: Great. Thank you. That is very helpful information that we can look at as we revise the draft.

The last one I have on my list is Carol Reed from Clinical Data, Incorporated. Welcome.

Comments by Carol Reed

Clinical Data, Incorporated

MS. REED: Hello. My name is Carol Reed. I'm chief medical officer of Clinical Data. Just to clarify for everyone, we are the parent company of which PGx Health is a subsidiary. I think it was reversed on the slides earlier today. We offer the FAMILION test for Long QT testing, a high-quality test of which we are very proud.

This test is actually a great example of a product that has arisen out of an exclusive patent license, and I think that has been extensively discussed already.

I would just like to make three points for the Committee. First of all, as a public, for-profit company, yes, we do license intellectual property. Our intent is to commercialize that, not to sit on it

or hide it. That is too expensive a proposition. I think we have shown our intent to do that by launching our FAMILION test in 2004.

In the time since that test was launched, other genes for Long QT syndrome have in fact been identified. We feel that one of the reasons for this is the success of our commercial test because the burden of testing for those five genes has in fact relieved research laboratories of having to sequence those more common causes of Long QT syndrome and freed their resources to identify more rare causative genes.

Secondly, I would like to address the issue of patient access. Although patents are certainly a major topic of discussion in this area, we should not ignore the issue of reimbursement and payer policy in covering these tests. In fact, I believe that patients are more directly affected in terms of their access to testing by payer reimbursement policies.

Again, to use Long QT testing as an example, we have made a significant investment in our customer service group as well as our prior authorization group, and in fact many times acquiring authorization

to pay for a test takes more time than it does to actually perform the test and return the results to patients.

We have invested significantly in people who work directly with managed care. We have succeeded in getting Medicaid coverage in 38 states and have coverage pending in the remaining 12. We are also an approved Medicare provider and now, by combining with private and government insurance, we have succeeded in gaining coverage for over 160 million lives in the United States. This is a significant advantage that we would not have invested in without patent protection for our test.

Thirdly, I think we should not underemphasize the importance of expertise in interpretation of these mutational analysis tests. It is very important to be able to draw a direct relationship between a discovered mutation and the structural relationship to the protein and to have a normal database against which to compare frequencies of mutations and other variants identified during testing. Without the investment that we made to build

the normal mutational and SNP database, we would not be able to provide interpretation of these tests.

Moving towards sequencing these tests in whole-genome scans may in fact prove to be dangerous for our patients because low-risk patients are going to have variants identified without the appropriate background against which to interpret and analyze these results. Patients may in fact be put in danger of inappropriate interventions, including the implantation of defibrillators.

Finally, I would suggest to Brian that perhaps he might include the cost of interpretation of these sorts of tests and the resources that are put into that in his cost modeling, as we begin to understand the impact of price and cost of genetic testing.

Thank you to the Committee for hearing my comments.

DR. TEUTSCH: Great. Thank you very much. These are very helpful comments for us as we deliberate.

Let me just check again. Is Ms. Salberg

here?

[No response.]

DR. TEUTSCH: If not, then we will move back to the primary topic of the day. I think our discussion will be informed by many of these perspectives from our presenters.

Folks, we have about 1.75 hours to get through all of the recommendations.

DR. EVANS: If you want a break.

DR. TEUTSCH: If you want a break. Otherwise we could be here until seven or eight.

Jim and colleagues have done a great job of leading us through a complex area this morning, but we do need to get through the recommendations. We have to get to an approval of a draft for public comment. We don't need it perfect. We need it in such a way that we can at least get it out and solicit opinions. So we will be minimizing the wordsmithing and dealing with the big issues so that we can work our way through this this afternoon.

Jim, having done a masterful job earlier, you are on again.

Discussion of Public Consultation Draft Report and Range of Potential Policy Options for Public Consideration

DR. EVANS: During the break we added a very brief preamble to that policy recommendation that we had discussed earlier saying that HHS should develop a set of principles and guidance in order to facilitate the following. Then we went through those to try to make them more action-oriented.

As we proceed, again, I would emphasize that these are draft proposals to go out. They can be amended later. They can be adjusted later as part of the whole process.

The next one would be having to do with, again, advocacy efforts by these stakeholders. "Professional associations involved in technology transfer policy and practice should embrace and promote the principles reflected in Best Practices, as well as the Nine Points to Consider," that are well known in patent circles.

"They also should work together to build on those norms and practices as they relate to gene-based

diagnostics by articulating more specific conditions under which exclusive licensing and non-exclusive licensing of uses relevant to genetic testing are appropriate.

"Professional societies should work cooperatively to forge consensus positions with respect to gene patenting and licensing policy."

So again, although this is in the general nature of an admonition, it does have more granular recommendations in the sense of articulating more specific conditions for exclusive and non-exclusive licensing. Comments?

[No response.]

DR. EVANS: Steve, you must have said something.

DR. TEUTSCH: Lunch was our friend.

[Laughter.]

DR. EVANS: Everybody has diverted their flood of comments.

Regarding transparency, this general issue of opacity, "Holders of patents on genes, genetic tests, and related technologies, including academic

institutions and companies, should make their patent licenses or information about their licenses, including such factors as the type of license, field of use, and scope on those patents, publicly available."

Mara.

DR. ASPINALL: Explain what that means? Does that mean that they may have a patent but let the patent information be available to everyone?

DR. EVANS: No, I think it is focusing primarily on the licensing issues. They should make the licenses, including such factors as the type, the field of use, and scope, publicly available. One of the real difficulties in this whole process is figuring out what the parameters are around specific licenses.

DR. ASPINALL: So this means the financial factors?

DR. EVANS: Well, no.

DR. ASPINALL: Just who it goes to and who has the license. So, beyond gene tests.

DR. EVANS: Again, field of use, scope.

Yes, the test itself.

DR. ASPINALL: I'm trying to understand the benefit of that.

DR. EVANS: The problem is patents are public records. You can find them. But it is very hard to get information on licenses. That is a problem for several reasons. One is, it is difficult to assess how various agents are acting with regard to exclusivity, non-exclusivity, et cetera.

Number two, it creates problems for developers to know who are they violating license agreements with, et cetera. In that sense, it adds cost. Trying to shed some light on the general licensing landscape would facilitate both being able to assay the field for problems that are occurring for adherence to guidelines, like best practices, but also, presumably, would help in developing tests and commercializing tests because you would know what the landscape was out there that you were dealing with.

That was it, I think. Anybody else on the task force tell me if there is.

DR. ASPINALL: For the patent holder, they

would list everyone they have licensed it to, in theory, and then it would be transparent for those who are not licensed. It would also be clear that they are not one of the licensees.

DR. EVANS: Yes. And, field of use, et cetera. Marc.

DR. WILLIAMS: The question that I have from, again, the perspective of what we can advise as a Committee is --

DR. EVANS: Where are the teeth.

DR. WILLIAMS: Yes. I think it is a desirable thing. I think that there would be a lot of value to that. But what ability does the Secretary have to be able to do this. What legal landscape is there. Are there precedents in other industries.

DR. EVANS: That is what we will get to with these subsequent recommendations. This is more, again, in the nature of general principles, as in that first one.

DR. WILLIAMS: Maybe this would require a fair amount of rewriting, but it seems to me that it would be useful for the discussion to say we are in

the "whereases" right now. I think it would be easier in terms of discussing this as a draft going out to almost frame it as such to say here are our principles of belief, whereas, whereas, whereas, and given that here is our recommendations.

If you read these as recommendations, obviously it raises questions just like I asked.

DR. EVANS: That is a point well taken. We were talking about that at lunch. Like in that first one, I think we need to revamp these a bit and say here are some basic principles that we feel are reasonable basic principles, and that, where possible and by mechanisms possible, HHS should facilitate these things.

"As a means to enhance public access to information about the licensing of patents related to gene-based diagnostics, the NIH should amend the Best Practices for the Licensing of Genomic Inventions to encourage licensors and licensees to include in their license contracts a provision that allows each party to disclose information about their licenses, including such factors as type of license, field of

use, and scope."

This actually goes beyond the general principle aspect. We can renumber these or restructure these in that sense. This is more of a directive or a recommendation that says the Best Practices, which was presumably released for a reason, should be amended in order to address those specific things which we find are perhaps lacking.

"The Secretary of HHS should seek statutory authority to enable the Food and Drug Administration and the Centers for Medicare and Medicaid Services to require patented DNA-based in vitro diagnostic tests, whether offered as a test kit or a laboratory-developed test, to display on product packaging and/or company/provider websites the issued patent and published patent numbers that the company or provider owns and controls and reasonably believes covers their product or patents licensed by the company/provider in order to market the product."

In other words, labeling. This is designed to shed some light on the general field and ensure that the information about patents and specifically

licenses is readily obtainable. Mara.

DR. ASPINALL: I have a question. I don't know where this came from. Is this consistent with how drugs and devices are done today?

DR. EVANS: I believe so.

DR. BILLINGS: Why is this necessary? What is the background and necessity for such a disclosure?

DR. EVANS: The background is that, as evidenced by the case studies, it has proven very difficult to determine, given a specific gene or given a specific test, what the license landscape is surrounding that. Again, for those same purposes of looking for adherence to things like best practices as well as for purposes of test development, et cetera, we were attempting to come to mechanisms that shed some light on this and make it approachable and easy for individuals to figure out what licenses, patents, et cetera, apply to a given test.

DR. TEUTSCH: Steve, do you want to answer the question about current labeling practices?

DR. GUTMAN: Yes. Currently, not only is labeling blind to the issue, actually our pre-market

review process, at least in devices, is blind to the issue. So we would be happy to clear or approve something that was intensely litigated, as long as it was safe and effective.

[Laughter.]

DR. GUTMAN: I assume that this recommendation is based on an understanding of that, because they are actually not suggesting we do this under existing law. They are actually suggesting statutory authority. If you wanted to make something less onerous, you might suggest that we seek either statutory or regulatory authority.

It is possible that this could be done with a rewrite of the reg rather than with a rewrite of the law. But the deal is, it isn't part of the package we offer right now.

DR. TEUTSCH: That is true of drugs as well?

DR. GUTMAN: I actually don't know. I don't recall ever having seen this information on a drug label.

DR. TEUTSCH: I don't believe so, either. Mara.

DR. ASPINALL: I guess the majority of the Committee thought it was a recommendation to leave in, but I am concerned. As a Committee, we talked about no genetic exceptionalism as part of our last report.

It concerns me that this is diagnostic exceptionalism, which to me is not healthy for the long-term environment of diagnostics or personalized medicine, putting burden on what are today traditionally and have been the lowest-priced interventions in the healthcare arena and the lowest-margin interventions in the healthcare arena, and creating a burden that is not necessary. I am not clear how it corrects access.

DR. EVANS: Two things. I don't think is the forum to decide the pros and cons of this. But I would just say that one could also envision that such transparency would enable test developers to do a more efficacious job of figuring out whether they were in violation of licenses, et cetera. I don't think it is necessarily just a burden.

DR. ASPINALL: Yes, it might be. My concern is in terms of comparability with other parts of the

industry, for new start-up companies getting access to capital and public or private access to research dollars, and others. Putting a disproportionate burden on one part of the industry versus others will not help innovation.

DR. EVANS: I think those are things that should come out in the public comments. Marc.

DR. WILLIAMS: I think the other thing to recognize relating to this is we have to be cognizant in the discussion that multiplex testing is going to be a problematic issue. You can imagine in terms of the level of burden that if you have a multiplex test you could have a patent and license list that is longer than the labeling.

DR. EVANS: But again, the argument cuts the other way. If you want to develop a multiplex test, you are in big trouble if there isn't transparency in the field and you don't know what is covered by what. The concerns about multiplex testing I think are some of the most powerful in support of this, but again, if people are okay putting this out for comment we can then weigh those various types of arguments.

DR. AMOS: If the object is to make it more transparent, then why put the burden on the company to put it on their products? If you have a multiplex of 100,000 gene segments, the packaging would be as big as the table.

You could do it on the website, but at the same time, if the object is to make it more transparent, then maybe we recommend to the HHS Secretary that some sort of central repository of that information should be made available.

DR. EVANS: Right. But somebody is going to have to put it in that central repository.

DR. AMOS: Somebody is going to have to put it in there and maintain it. That is going to be tough, too.

DR. EVANS: Again, those things can come up as we discuss them.

Filling data gaps. "In order to assess the extent to which gene patent or licensing arrangements may be affecting patient access to genetic tests, HHS should develop a voluntary reporting system to encourage researchers and medical practitioners who

order, use, or perform genetic tests to report such access problems. Given that patient access problems can occur for a number of reasons, it will be important for the reports to be verified and evaluated to be sure they can be attributed to the gene patent or licensing arrangements. For example, the reports may need to include evidence of patent enforcement actions, such as a cease-and-desist letter.

"It may be prudent to pilot-test and evaluate such a system through a demonstration program before committing to its full development."

Basically, one of the things we have been struggling with in this process is trying to corral what the perceived problems are and trying to figure out whether those perceptions are accurate. By having such a resource, there could be an ongoing forum that is centralized in order to bring to light things that people thought rose to the level of problems.

DR. ASPINALL: I'm not sure I can rephrase it in real time because I like the first sentence. Again, it presumes access problems as opposed to increased access as a result of this. So when it

starts out to say "may be affecting patient access," it could be more or less.

DR. EVANS: We could say "In order to assess whether gene patents."

DR. ASPINALL: I think that has to be more neutral.

DR. EVANS: Yes, that's fine.

COL McLEAN: I would agree. I think if you are going to focus just on finding the problems you are not going to measure the access. You are just going to measure the problems. You may have really good effects or consequences of certain patents that you didn't anticipate, and so you would miss it.

DR. EVANS: I don't envision this as tackling the whole problem. I do see it, though, as a potential part of increased transparency, trying to again fill some of these gaps that exist.

DR. TEUTSCH: If you go up to the benefits of enhanced access, in most of the systems that we are talking about here do people tend to report problems, not successes? I'm trying to figure out what that means in practical terms.

DR. ASPINALL: I guess in terms of doing the report in a broad way I wanted to encourage people to represent enhanced access.

DR. TEUTSCH: No, I think that part is good. Then we have to figure out how does one capture that. I agree; we do want to do that. What concerns me is you are talking about voluntary reporting systems. It is like safety systems. They don't tell you that, I had a great success and there was no safety problem. They only tell you about when there are issues.

I'm just trying to figure out, if we are going to do that, how do you make that operational, which needs to be, usually, a more proactive approach.

DR. PRESSMAN: If the company people who are here would be willing to disclose something about volume, it would be very helpful for an understanding in so many ways: market size, access, how many people are using it. It could be assured in this process that the data would only be presented in aggregate to help preserve confidential company information.

DR. ASPINALL: First of all, it is not all company people. Most of the patents are actually

being held by universities. Some go out to the companies, but lots do not. I think we should just describe it as patent holders.

DR. TEUTSCH: Actually, you can get this information from a good claims data system that actually would tell you what tests were being done.

DR. ASPINALL: The problem is, as we found in the other report, you can't get it because of the CPT code system.

DR. TEUTSCH: Correct. That is all part of what needs to be improved. But if you could move to a system that actually captures it, you could actually monitor that.

DR. EVANS: Perhaps that is something we should consider as another, separate policy option.

DR. ASPINALL: I guess, Steve, in answer to your question -- and I'm not sure I have the perfect wording -- the wording should be more neutral to say filling data gaps and evaluating successes. It shouldn't be focused on looking for only the problems, first of all, in terms of the wording. Then part of the challenge with the public comment period is

ensuring that people get out to tell both sides of the story.

DR. EVANS: We can work on the wording a little to try to make it a little more neutral and then allow the public comments to refine it. Yes.

DR. WILLIAMS: I was just going to say, I heard somebody say maybe a new recommendation relating to the coding issues. I would just say don't make a new recommendation. Just reference where that has come up in previous report and say, we support the previous report's recommendation that coding would fix this problem.

DR. EVANS: That is a really good idea.

Again, in the theme of filling data gaps, "Under Bayh-Dole, recipients of federal grants, cooperative agreements, and contracts are required to report to federal agencies about inventions that result from federally funded research. Such reports are submitted through an online information management system called iEdison. The reports are considered proprietary and are not publicly available.

"NIH also requires recipients of NIH

funding, upon election of title to an invention, to report utilization data annually for that invention, including whether and how many exclusive and non-exclusive licenses have been granted, if any.

"Research agencies should explore using summary data from their respective federal fund agreements as a tool to help assess the extent to which exclusive licensing practices of identified patents may play a role in inhibiting patient access to diagnostic gene-based inventions.

"NIH also should explore whether iEdison data could be used to assess whether the licensing of genomic inventions has been conducted in accordance with the NIH's best practices." Yes.

DR. ASPINALL: Strike the word "inhibiting." "May play a role in patient access," so we understand positive or negative.

DR. EVANS: We can do that.

DR. WILLIAMS: Do you have any specific research agencies in mind?

DR. EVANS: No, I was hoping you might. I think that that is something that is going to need to

be explored. Which are the most applicable and efficacious ones. We didn't want to get too granular at this point. Why; what are your thoughts?

DR. WILLIAMS: Remembering what Reed has said, the more specific we can make the recommendations to the Secretary, the more likely that they are going to go forward. If we can have some feeling about whether this would best reside with AHRQ or something of that nature, we probably should say something like that.

DR. EVANS: There wasn't any consensus on the task force about that. I think that it is something we could add in here and we could specifically ask for comments about that. That might be reasonable to solicit that type of guidance.

DR. FITZGERALD: Just on that note, the easiest thing to do is put in parentheses after "research agencies," "(e.g. AHRQ and others?)" and let people suggest and give reasons for their suggestions.

DR. EVANS: NIH, I think, is what everybody was thinking of here, which might make the most sense. So we might want to put in parentheses "for example,

NIH, AHRQ, and others as recommended."

DR. ROHRBAUGH: Jim, I would just note that iEdison is not required. It is not required that people use iEdison. They may submit by iEdison; they may submit by other means.

DR. EVANS: Would you say it is the most commonly used?

DR. ROHRBAUGH: Yes.

DR. EVANS: What we can say is "through online information such as iEdison." We can fix that. Thank you.

"More data are needed to understand the landscape of gene patenting and the licensing arrangements that are being used to commercialize the inventions. The Secretary of HHS should develop a uniform system for data collection, including database structure and standardized terminology, or enhance the existing iEdison system and encourage HHS funding recipients to submit more data about inventions that, at the time they are patented and licensed, are reasonably anticipated to be associated with clinical genetic tests.

"The data elements that would be most useful," and then this continues on to the next slide. I will back up.

"1) Whether the licensor of the inventor granted the licensee the rights to make and sell a clinical genetic test or provide a clinical service;

"2) The nature of the licensing agreement (for example, exclusive, co-exclusive, non-exclusive) and for licenses with some degree of exclusivity in the grant, information about the grant of license rights (i.e. fields of use, scope) and whether or not the license has non-financial performance incentives (diligence)."

It would be nice to get rid of some parentheses there.

"3) Patent and license timelines (dates of patent filing, publication, issuance, and license effective dates)

"4) The date of first reported sale of the genetic test or service and the periodic notations of whether the test or service remains on the market; and

"5) If possible, some measure of volume of

sales and number of tests or kits sold, even if such sales are not royalty bearing.

"Providers of the data should be consulted about the design of the database, the development of its standard terminology, and their perspectives on the burden and implications of reporting such data."

I will go back now to the first part of this rather long one. Marc.

DR. WILLIAMS: Just a clarification. Is iEdison then under HHS?

DR. EVANS: Somebody help me.

DR. ROHRBAUGH: iEdison was developed by NIH. It is an encrypted Web-based system that is optional. Many parties use it. Many universities use it. It has been adopted by many other agencies. Most of the R&D agencies in the federal government use iEdison for reporting inventions and other annual data.

DR. WILLIAMS: I guess the question I was asking is, administratively, in terms of the actionable item to revise and standardize iEdison, is that something that does reside under the Secretary's

purview. I don't know the answer to that question.

DR. EVANS: Yes, Bob. It sounds like it is.

DR. COOK-DEEGAN: That is my understanding of the history.

DR. EVANS: So, with regard to the data elements, do people have other data elements or do these seem like the types of data elements that are most useful?

DR. FITZGERALD: I have a quick question. None of this, I gather, is now put in the iEdison database; is that correct?

DR. EVANS: That is correct, I believe.

DR. COOK-DEEGAN: Some of it is.

DR. FITZGERALD: That is what I'm wondering.

DR. COOK-DEEGAN: None of us have ever seen it. At least I have never seen it. I'm pretty sure licensing data is in there.

DR. EVANS: To this extent?

DR. COOK-DEEGAN: Not to this level of detail. This part, No. 1, would be. Actually, not the genetic test part. Who the licensee is and the conditions of the license.

DR. LEONARD: From your comments, it sounds like this is not a public database.

DR. COOK-DEEGAN: That's right. It is not.

DR. LEONARD: Sarah is shaking her head no. It can't be a public database. If all this information is in there, who uses it? Do we want to make some recommendation about who should have access to this? Is it researchers by IRB approval and getting a grant? Who uses this? You put it all in there; then what?

DR. EVANS: Let's see. Is that addressed up here? The reports are proprietary, not publicly available. So they can't really be publicly available, is my understanding.

DR. LEONARD: So, who are we creating a database for?

DR. EVANS: I think for the NIH.

DR. COOK-DEEGAN: You are only asking for gathering of information. I presume there is going to be something about doing something with it and telling the world about what you have found out.

DR. EVANS: Right. I think that the idea

here would be that these types of data would be collected under the purview of HHS and would be available for as yet undefined individuals or organizations to analyze it for evidence of problems, et cetera.

DR. FERREIRA-GONZALEZ: There is a recommendation that this is created so HHS can have a periodic review of the data and report that to the public in an aggregate form?

DR. TEUTSCH: Go back to 3B, the last paragraph. There it talks about iEdison could be used to access the licensing and being able to do that assessment, which is really what you are asking about.

DR. EVANS: Right. "Should explore whether iEdison data could be used to assess whether the licensing of genomic inventions has been conducted in accordance."

DR. TEUTSCH: We will need to wordsmith it, but it looks like that analysis could be done out of that.

DR. EVANS: No other elements that people [have comments on]?

DR. AMOS: Jim, are you just trying to get to the point where there is somebody that is overseeing this and getting enough data to make it a report to the public where there is an instance of harm being done?

DR. EVANS: To try to coalesce data. To try to gather data in some centralized way by which problems could be enumerated and discovered.

DR. AMOS: In a way that proprietary information is not portrayed to the general public?

DR. EVANS: Right. In other words, there has to be some kind of firewall there. It is proprietary information. It can't just be a public --

DR. AMOS: Can't you put this all under one recommendation and just say that the HHS Secretary should develop a mechanism to do this, and then outline some of the things that you think are critical?

DR. EVANS: Yes, I think we could. It could be, for example, through iEdison, if that is the most facile way.

DR. AMOS: Without getting into exactly what

needs to be done, basically the gist of it would be to create a system for reporting back to the public where harm is being done.

DR. TEUTSCH: But as we have heard, it is not just the harms. It is to understand to what extent these uses that should have been done under the various federal granting processes are actually getting acted on and used. It is to see to what extent they are getting out and being used in a way that is consistent with the guidance that is already out there for good or not so that we don't have to have this discussion again if we don't know this information.

DR. EVANS: Especially as we go on to multiplex testing.

DR. AMOS: Basically, you want somebody to keep track of all this.

DR. EVANS: Exactly. Maybe we need to have a preamble that says it that way.

"The Secretary of HHS should establish an advisory board to provide ongoing advice about the public health impact of gene patenting and licensing

practices. The board could review new data collected on patient access problems and assess the extent to which they are caused by enforcement of intellectual property rights.

"The advisory board also could provide input on the implementation of any future policy changes, including any that might emerge as a consequence of this report."

Maybe we should somehow make that the start and change the wording so that makes sense. Good, good. We can change the order of that.

"Federal efforts to promote broad licensing and patient access:

"A) Federal agencies, including NIH, should promote wider adoption of the principles reflected in NIH Best Practices for the Licensing of Genomic Inventions and the OECD Guidelines for Licensing of Genetic Inventions, both of which encourage limited use of exclusive licensing for genetic/genomic inventions."

Now, I would anticipate that people are going to say there are no teeth to this, but I think

as we go on you will see that there are some emerging potential teeth. Comments? It is teething.

DR. WILLIAMS: I read through these but now I'm not specifically recalling. But when you say there are no teeth, there are actually huge teeth implied there in the sense that federal agencies reimburse a huge fraction of healthcare costs in this country. If there was something tied to reimbursement for tests relating to adherence to best practices --

DR. EVANS: Right. We don't go there yet.

DR. LEONARD: But it is not really the reimbursement agencies here. It is NIH giving future grants based on how they licensed whatever came out of research previously funded by NIH. That would highly motivate academic institutions.

DR. EVANS: Let me go on with this next one.

"Federal agencies, including NIH, should encourage wider use of AUTM's In the Public Interest: Nine Points to Consider in Licensing University Technology. Point Nos. 2 and 9 are particularly relevant for genetic tests. They state in part that exclusive licenses should be structured in a manner

that encourages technology development and use and in licensing arrangements institutions should 'consider including provisions that address unmet needs, such as those in neglected patient populations,' giving particular attention to improved diagnostics, among other technologies." Basically, a request to refine the Nine Points.

[No response.]

DR. EVANS: Either it is uncontroversial or everybody is completely confused.

"NIH should explore whether mechanisms such as patent pooling could facilitate the use of rapidly developing technologies for genetic tests that are dependent upon multiple licenses of patents."

This is one that works its way into every type of commission or committee that has ever looked at this. It usually hasn't gone very far, I think for some of the reasons brought up, for example, by Rochelle. But I do think that there is a lot of interest in patent pools and it is worth at least giving a nod to that or throwing that out there.

"Federal agencies should consider providing

more detailed guidance for gene-based clinical diagnostic inventions to encourage academic institutions to use terms and licensing agreements, such as due diligence clauses, to foster the availability and quality of clinical diagnostic tests and thereby reduce the likelihood that exclusivity associated with a license would lead to adverse effects on patient access.

"Taking steps likely to increase the number of insurers that reimburse for the test or improving the specificity and sensitivity of the test and enhancing knowledge of its clinical validity are examples of milestones that a licensee could be required to meet to earn or maintain license rights."

Lori might want to expand a little bit on this. The idea is that licenses are a lever which can be used and that the conditions of licenses can be manipulated, presumably, to create more benefit.

DR. ASPINALL: I understand the principle. Why, in the third line of (D) does it say "Encourage academic institutions"?

DR. EVANS: We had a lot of discussion about

the fact that it is academic institutions that issue most licenses because they own most of the patents. Now, it doesn't necessarily have to be made to look exclusively as though this is encouraging academic institutions.

DR. ASPINALL: In a way, it is the other way. We have academic institutions that don't license, and there are some that are inventors.

DR. EVANS: That makes sense. It would be silly to just narrow this down to academic institutions.

DR. ASPINALL: In reality, federal agencies may have more power.

DR. EVANS: I can't recall the exact discussion that revolved around this on the task force conference call, but that is what coming back to me. This had to do with the fact that HHS has power over universities through that mechanism.

DR. ASPINALL: I think we should clarify it either way. My key issue, especially as we are talking about transparency, is not to make an assumption that all companies are in one bucket and

all academic institutions are in another, or vice versa. We need to keep it broad. If it is meant to be NIH-granted institutions --

DR. EVANS: I think "patent holders" would be a better term.

DR. PRESSMAN: The origin? I think the origin is just Bayh-Dole and that preamble that talks about protecting the public against the non-use. That is the origin.

DR. EVANS: That is right. Would it still make sense to say "patent holders"?

DR. PRESSMAN: Sure. They are non-academic grantees.

DR. EVANS: Bayh-Dole doesn't affect them if they haven't used federal funds.

DR. ASPINALL: There are grantees that are not academic institutions. We need to keep it broad.

DR. EVANS: "Patent holders" I think would be good. Marc.

DR. WILLIAMS: One minor thing here, which is just for consistency's sake, would be to replace "quality" with "utility" just so we are consistent.

The second thing is, I would be reluctant to articulate the insurance reimbursement here, because that implies that there is actually a rational process that involves evidence for insurance reimbursement.

[Laughter.]

DR. WILLIAMS: I work in the insurance industry. I can say this, all right? The reality is that the decisions that are made are frequently not related to evidence but are related to contracts and decisions by employers in terms of what they want to cover and what they don't want to cover. So I'm not sure that that adds much to the point there.

DR. EVANS: Couldn't that be a point of leverage?

DR. WILLIAMS: For whom?

DR. EVANS: For individuals who are seeking to maintain or obtain a license. Why exclude that from this?

DR. WILLIAMS: I don't understand how it is a lever. Their business interests are to reimburse as many people as possible.

DR. EVANS: Right. But if they are

unsuccessful for various reasons, this adds more leverage, more pressure. There must be a reason for this. Why is there not third-party reimbursement.

I understand what you are saying, that their business interests are generally aligned.

DR. WILLIAMS: But I'm saying the tying of performance to insurance companies' decisions where those insurance company decisions do not rest solely on the evidence around a given test or product is really not fair.

It is just not fair. If an employer says we are not paying for genetic tests, they are not paying for genetic tests. It doesn't matter if it is a good test, bad test, or indifferent test. They just don't pay for it.

DR. PRESSMAN: If I could just make a case why it is good to maintain an option. Arguably, perhaps the public is better served this way than they are by an infinite number of non-exclusives, where perhaps no one has an incentive to go up against a recalcitrant insurer. This way, if you got four or five players under co-exclusive, maybe you actually

have an incentive. Maybe this would be good for the public.

DR. WILLIAMS: I think we are mixing apples and oranges here. I really think that that is an issue of coverage and reimbursement. It is not an issue relating to patenting.

I think you are trying to get at the fact that we want to accumulate evidence that that is a good thing and making a stronger case for clinical validity and utility is a good thing. There are a lot of people that are going to come along and say, yes, this is something we want to pay for because it is a good thing.

I don't know. I just don't understand the mechanism of this relating to an action item.

DR. EVANS: I have two responses. One is that we could put in there "for example" and then we could let things fall out as people make comments.

My other question would be that many aspects of criteria that licensing might be pegged to are not completely under control of the individuals doing the test. For example, improving specificity and

sensitivity. To some extent, that is a simple biological and technological obstacle that might not be able to be improved.

I think that to some extent the devil would be in the details of those particular parameters that the licensing is pegged to. I'm not sure that it is that different from those others.

I think we should have it in there and then have this out at the meeting where we decide. See what the public says. See what people weigh in. If it makes sense to take it out, then do it. But I think that there is at least some feeling around the table that it is worth leaving in for now. Mara.

DR. ASPINALL: I would agree.

DR. EVANS: Why don't we leave it in for now. You can make your case when we meet again.

DR. WILLIAMS: That's fine. What I want at the next meeting when we make our case is, define for me the mechanism of how that would work. I need to understand how measuring insurance reimbursement relates to licensing. Talk about the devil being in the details. I just don't understand it.

DR. EVANS: We will talk about that.

DR. FITZGERALD: Could we just say that we will address in specific the retort from the person in Utah who is going to write in about this?

DR. EVANS: I don't think we should be quite that detailed.

Now, licensing policies governing federally funded research to facilitate access. This is why NIH is focused on this.

"NIH should explore the feasibility of making compliance with the NIH Best Practices for the Licensing of Genomic Inventions as an important consideration in future grant awards."

This is where you start to get into some explicit teeth. The NIH has promulgated these guidelines or best practices, but they are sitting there. What we would be saying is, let's use them.

"The Secretary of HHS should request an executive order clarifying the authority of HHS under the Bayh-Dole Act to ensure that the goals of the statute are being fulfilled in the context of genetic diagnostic tests in the manner reflected in the NIH

Best Practices for Licensing of Genomic Inventions.

"The Secretary of HHS should request an executive order clarifying the authority of HHS under the Bayh-Dole Act to require a grantee or contractor to offer only non-exclusive licensing of DNA-based inventions for diagnostic fields of use, for example, by making the requirement a term and condition of award."

DR. ASPINALL: I don't know where to start.

DR. EVANS: Remember, before you say anything, these are a range of options that are put out there. We are not really debating the merits of implementing these at this point. We are just saying, okay, are these reasonable to go out as a range of options. They are certainly ones that have been discussed.

DR. ASPINALL: But as we get to them, and in my looking at them, I'm not sure it is fair to call them a range of options. We don't have options on the other end that say they should ensure that for most innovation and quickest access that all licenses should be exclusive.

DR. EVANS: We could do that if you want.

I think that we already have a system in which people are free to engage in exclusive licensing. Do you think it is more than just a rhetorical device to put in something saying we should make all licenses exclusive?

DR. ASPINALL: Two pieces. I'm not sure it is fair to say it is a range of options in terms of a full range. It is a range on one end of the spectrum.

DR. EVANS: It is a range. We didn't say a full range.

DR. ASPINALL: It is not the full range, which I respect. I'm not saying it has to be, but I don't think it is a full range of options from A to Z.

DR. EVANS: We didn't say it was.

DR. ASPINALL: You said "a range of options" a few times, implying that.

DR. EVANS: If the public wants to say everything should be exclusively licensed and we get an avalanche of comments like that, then I think we should consider that.

DR. ASPINALL: I'm sure we will consider

whatever the public says on either end of that.

One question I would have is, is there any comparable regulation, executive order or otherwise, where HHS would step in and say how --

DR. EVANS: Under Bayh-Dole you can. It is in Bayh-Dole that there are provisions for march-in.

DR. ASPINALL: Right. But to this extent and requiring only non-exclusive --

DR. EVANS: I think there are more dramatic examples of this. Look at the Ganske-Frist bill. Rochelle.

DR. DREYFUSS: I understood the range of options to be the range of options that flowed out of what the case studies show. What the case studies show is that exclusive licensing is sometimes a problem. The case studies don't show that non-exclusive licensing is a problem. So it seems to me that it makes a lot of sense to say that maybe we should put more teeth into the guidelines.

I think there has also been evidence that hasn't been picked up explicitly in the case studies but implicitly, where universities have a tendency to

give exclusive licenses without really thinking hard about it. These guidelines have existed for a while now. These Nine Points have existed for a while now. The better universities, who are licensing non-exclusively, don't seem to be having a problem with that.

Yet there are still some small universities that just don't seem to have the backbone to go up against the companies that want exclusive licenses. If this does nothing else, it will give these universities the option to say, we are going to lose our grants if we give in to this. I think it stiffens their spine in a way that the case studies suggest they need.

DR. ASPINALL: I guess I would say two things. One is, I will go back to not clarifying and generalizing small and large, backbone or not backbone. There are small universities that have had a lot of backbone and won or lost, and there are some very large universities that have said they don't want to go there. I don't think it is the size.

DR. DREYFUSS: No, I agree with that.

DR. ASPINALL: It is a leadership and a discussion within the university for them to make their decisions.

DR. DREYFUSS: I agree with that.

DR. ASPINALL: So I don't want to generalize it. But as you describe what is in there, I take offense to generalizing based on how they do it. HHS can certainly do it for the grantees and contractors, but I think the issue is to provide access, not necessarily on how they provide that access. I was more comfortable one step back on the last one that says access is a key issue, not telling them how to do their business.

DR. EVANS: That's fine. People are going to have different opinions on this, and that is why we are putting these out there.

Just before we move on to the next one, I would agree with what Rochelle said. I think these do flow from the lessons we learned. People are free to submit other ideas.

Another possibility that we can engage in that is on the table is we do nothing. We may in the

end feel that everything is working fine and there are no future problems and we don't have to do anything. That is in the nature of possibility.

DR. ASPINALL: That is what I was going to say. To me, the case studies said there were sometimes problems, sometimes there weren't problems.

DR. EVANS: But again, I would amplify what Rochelle said. I don't think we saw anywhere that, "Boy, exclusive licensing is the way to go." We didn't see any evidence there are lots of problems from non-exclusive licensing and that there are lots of benefits from exclusive licensing.

DR. ASPINALL: I thought in the BRCA versus HNPCC we saw that, did we not?

DR. EVANS: Not at all. Anyway, we need to move on.

DR. DREYFUSS: I think we should change it to put in a presumption of non-exclusive licensing. There might be some places where the costs of developing the tests are really, really high.

DR. EVANS: That is a very good point. I have been trying to figure out how to work that in.

Kevin.

DR. FITZGERALD: Sometimes I get the impression what you are saying is that we would like to do No. 1 and No. 2 and No. 3 and No. 4 and No. 5, and other times you are saying we would like to do A or B or C.

DR. EVANS: Right. We experimented with that in the task force. That is why I made that over-the-top admonition at the start to remember that many of these will be mutually exclusive.

DR. FITZGERALD: All I'm doing is clarifying for the public which ones are "or" and which ones are "and."

DR. EVANS: It is not even that simple because there are recommendations in No. 2 that wouldn't be compatible with something in No. 8. It is not a simple or/and in close proximity.

What people have to understand, and we are going to take great pains to illustrate this at the start, is that some of these recommendations are mutually incompatible. We recognize that. But our job, when we meet again after public comment, will be

to reconcile and make sure that they are internally consistent. Marc.

DR. WILLIAMS: I just wanted to point out for (B) and (C) here that we have in many of our recommendations asked for clarification of statute in terms of what really falls under the purview of HHS and what doesn't. I think that these are very appropriate. I don't see these as necessarily loaded because I don't think clarification of authority means that there is then a will to exert authority that is defined.

I think we do need to understand where HHS can operate within its scope and where it is really out of scope.

DR. EVANS: I agree. This has been a nebulous black box.

DR. WILLIAMS: Exactly. These are very important recommendations, from my perspective.

DR. ROHRBAUGH: Jim, I would just point out my concern is that, in (C), the Best Practices don't say "Never exclusive license." It says the exclusive license should be tailored. There may be cases where

a very narrow exclusive use, like exclusivity for a proprietary format that the company already has, would not be objectionable.

DR. EVANS: I think that is a really important point. I think Rochelle's issue of presumption might get to that. But I couldn't agree more.

DR. WILLIAMS: And for all the rare diseases.

DR. EVANS: Right. That is the classic example.

"The Secretary of HHS, in collaboration with other departments, should commission a study to evaluate and compare how federal agencies have managed government-owned DNA-based inventions with diagnostic fields of use," again to look at how these things have been used.

"The Secretary of HHS, in collaboration with other departments, should commission a study of how agencies have interpreted and applied the Bayh-Dole Act with respect to the application of the statute's march-in provisions."

This focuses on USPTO policy and trying to clarify some of the issues inherent in that. "The Secretary of HHS should recommend that the Secretary of Commerce."

So we are recommending that one secretary recommend to another, which I will freely admit is a little bit cumbersome. Let us know if you can think of [another way]. It's just that we can't say something to the Secretary of Commerce, and USPTO doesn't report to HHS. Yet this is a very important issue with regard to gene patents and licensing. I don't know if there is a more streamlined way to do that.

"A) Establish an advisory committee to provide advice about scientific and technological developments related to genetic tests and technologies that may inform its examination of patent applications and other proceedings;

"B) Gather together in a manner analogous to the Utility Guidelines non-obviousness guidelines to assist USPTO personnel in examining patent applications on nucleic acids and genetic diagnostics,

particularly those applications seeking patent protection for human DNA sequences and/or genes for diagnostic purposes analogous to the Utility Guidelines published in 2001."

I'm going to talk about (C) in a second. So, comments on (A) and (B). Yes.

MR. LeGUYADER: I'm going to comment on (B) that we probably would want to wait for Cubin to come out. I'm speaking on behalf of the Patent Office now. We probably don't have enough information to craft guidelines specifically to tell our examiners what is or isn't obviousness until Cubin comes out, which is really a seminal case.

It is about a broad claim to a gene where the Board of Appeals at the Patent Office said that it is not patentable, it is obvious, using KSR and KSR-style language straight from that decision.

So we would want to wait to see that Cubin really gets affirmed. Then we will have some really clear guidance on how to deal with the obviousness.

DR. EVANS: It might be, you are saying, that after that case is decided we really wouldn't

need something like this?

MR. LeGUYADER: No, I think (B) is a very good recommendation. I think that it would be good to say something about Cubin. The Office will want to craft new guidelines based on the guidance developed from Cubin once that is decided.

DR. EVANS: "After the decision has been rendered in Cubin we should gather together."

MR. LeGUYADER: Yes.

DR. ASPINALL: What is the timing?

MR. LeGUYADER: Oral arguments are coming up this month. I don't know what the Federal Circuit has.

DR. EVANS: Is that going to be in Polly Newman's court?

MR. LeGUYADER: I don't really know off the top of my head. Now, you have Klaussen, which is a diagnostic assay that oral arguments were heard in July and we haven't heard anything yet. It has been almost a year since oral arguments have been heard. Sometimes the CFC will sit on things for quite a while.

Then, for (C), there are really three cases. There is the Prometheus case, Arad-AR AID, and then there is also Klaussen. There are three comments in Bilski that talk about whether or not these kind of assays and diagnostics are truly patent-eligible subject matter. They talk about preemption.

There are really three cases that are currently sitting with the Federal Circuit that have not yet been decided, Klaussen being the oldest. They were probably waiting on Bilski. They were probably waiting for the guidance on Bilski. Those are the three you will want to wait for to develop guidelines. You don't want to develop the guidelines on Bilski.

DR. EVANS: Good. I think we should work those in and say after decisions have been rendered in those cases.

Let's discuss (C) for a moment. For everybody here, Bilski was a recently rendered decision that addresses, somewhat obliquely, the issue of association patents.

Remember, for example, the most famous of these for our purposes is probably the Metabolife

case, in which there was a request to grant cert to the U.S. Supreme Court to decide on whether an association of a high homocysteine level with Vitamin B12 deficiency could itself be patented. The court did not grant cert, but a dissenting opinion that was written by [Justice] Breyer said they should have because of the implications, at least in part, for medical diagnostics and for medical practice.

Bilski is a case that was just decided. People in this room could speak more eloquently about it than me. Perhaps Rochelle could. It at least begins to suggest that association patents are not going to be looked on real favorably, but there are other cases pending that might influence that.

I think that there is significant feeling about this in the medical community as a whole. We heard, for example, Mike Watson a few minutes ago talk about how association patents could have a chilling effect on the practice of medicine in general.

I'm just going to give you a quick preview. The next recommendation or draft proposed recommendation is to prohibit association patenting.

That is just the background on that for people, if that makes sense.

Are people generally okay with having these out there in the draft proposal? Especially the mentions of those pending cases.

MR. LeGUYADER: I just want to mention one thing. Your very last comment and the next slide talking about prohibiting patenting of diagnostic types of assays, that potentially would have a very chilling effect on the biotech industry. That is really a very large part of their patent portfolio, whether or not they are enforced. That needs to be considered if you are going to go out with this as a recommendation.

DR. EVANS: Yes. We are now actually getting into some of the ones that will prove most controversial and where people will have the most ardently held opinions.

But before we go on with that, it sounds like Mike and Marc.

DR. AMOS: I just think that we need to make sure that the language that we use is something that

the Secretary can actually do something with. I don't think he has the authority to change patent law or even recommend necessarily to the USPTO or to the Department of Commerce that they do that. That is a legal matter.

DR. EVANS: I think there are a couple mechanisms by which to do that. One would be a statutory remedy for that. One would be a statute that addresses association patents.

DR. AMOS: When you say "prohibiting association patents," I don't think --

DR. EVANS: We are getting there with the next one. I think developing guidelines is something that can be done. Guidelines can be developed on patentable subject matter in the wake of these cases.

MR. LeGUYADER: Absolutely. We could do everything in this slide. In fact, we are going to. We have our eyes very keenly on the Federal Circuit to see what the decisions are. We are obligated to follow the law based on those decisions. Therefore, we will have to develop guidelines and train our examiners once that law comes out.

DR. EVANS: Now we get into ones that are, again, a little more controversial, I'm sure.

"The Secretary of HHS should work within the administration to encourage support for legislative change." Here is where we are talking about seeking statutory changes. "The following are potential options to consider.

"A) Prohibit patenting of an association of a particular genotype with a disease or disorder." Again, I'm not asking whether you think that should be done or not. What we are talking about here is putting that out there for public comment as a possible option. It is certainly one that is out there in the ether. Yes.

DR. WILLIAMS: This just is an operational question for the next time we get together after we receive public comments. I think we can fairly well predict the public comments that we are going to get. We are going to get a lot on one side and a lot on the other side, which means that we are going to be in the position of having to adjudicate those.

So we really don't have a sense about

whether this is a good thing or a bad thing going into it.

DR. EVANS: Oh, I think some of us have a sense.

DR. WILLIAMS: Yes, I know that. But I suspect if we went around the table, we would have a bunch of people on one side and a bunch of people on the other side.

DR. EVANS: That's why, from the start this topic, I see as maybe the most difficult and contentious that the Secretary's Committee has addressed. When you think about some of our big topics like genetic discrimination, that was pretty much "mom and apple pie." It was pretty hard for people to get up there and say in no uncertain terms that we should engage in genetic discrimination.

I think that this is difficult. This is very difficult. Very reasonable people have different views on these things. It is going to be hard. I'm not sure how to make it easier, but we are going to have to sit down and figure out what to do.

DR. WILLIAMS: My point is that if we know

ahead of time where things sit, which is there is going to be polarization and we know that the public comments are going to be polarized, would it make more sense to pull this out until we can have --

DR. EVANS: Not at all. I think we need the public's comments.

DR. WILLIAMS: No, I don't think the public comment is going to solve anything for us. Are we going to weigh the comments for one side or the other? I think we are just going to see a bunch on both sides. I don't see how that helps us in terms of operationalizing this.

DR. EVANS: Just because we think we know what the public is going to say doesn't mean we know. I think it would be presumptuous of us to come out with a recommendation when we have not asked the public. In fact, it is not the way we can operate.

DR. WILLIAMS: I'm not saying we make a recommendation without it. I'm saying that putting something out there that says our default position is we are going to prohibit all --

DR. EVANS: But I don't know if that is our

default position. We haven't had that discussion.

DR. WILLIAMS: It looks like it. That is the issue. You say that "The following potential options are," and the options that you give there are very punitive options. They are not balanced options.

DR. EVANS: How would you remedy that?

DR. WILLIAMS: That is what I'm saying. We need to decide that before we send that out. We as a group need to decide.

DR. FITZGERALD: One possible remedy would be, like we have done in the past when we have hit these gridlock issues, is to step back and then say, "The Secretary should form a group to look into the issue," providing therefore the variety of options.

DR. EVANS: That is just punting it. We are not going to make a decision.

DR. FITZGERALD: No, we can't. We don't have the stuff to make the decision. Or, just stand up and say that there is gridlock on this. I don't know.

DR. EVANS: I think part of this is trying to get across to the public that this is an option.

It has certainly been an option. We are not the first to raise this option, by any means. As you will see in the next slide or two, there are options that are even more inflammatory. But I think that they need to be out there as options. Yes.

DR. KECKLER: Why is this section distinct. It is distinct I think not necessarily because it is controversial. The concern would be what has been raised before about these policy options, which is that they flow from the case studies as potential remedies to that.

Can the same be said of all of the options that are proposed in this section? I certainly don't feel that about the most severe ones. They might be right or wrong, but in either case they don't flow from what the task force has developed in the case studies. I think that that is what raises the concern about some elements at least of this section.

DR. EVANS: I would agree with you that the one that probably flows the least is 7A. Let's come back to that. Rochelle.

DR. DREYFUSS: I think this one does flow

very directly from what we have seen. I think one of the things that the case studies show is that patents are not the biggest motivator of doing these genetic tests. The case studies also show that whether there are patents on the basic association or not on the basic association, it is still possible to get patents on the end product, which is the thing that costs the most.

I actually do think that this possibility is raised very much by the case studies. I think it would be odd to put in all these other policy options and not give the public an opportunity to comment on this particular one. This is the one obvious answer if you think that there is any impediment to access to genetic testing.

DR. EVANS: We talked a lot in the task force conference calls about, gosh, should we have this in, should we have that in. One of the things we felt is that if there are things floating around out there that indeed -- as we will see in the next slide or two -- have actually been introduced into legislation, it would be rather remiss of us to not

include these in possible recommendations. We are supposed to look at this whole landscape. Joseph.

DR. TELFAIR: Actually, I would agree with the last statement and also with the admonishment that we really need to consider in advance if we can. We already have a device that we have used here, which is a preamble.

It seems to me that this section begs for a preamble, if for no other reason than as a clarification and a reference back. I think we have a clear understanding where this directly flows from, but by the time you get to this in the review and in public comment, you may not necessarily have that level of recollection and consideration.

For just very practical reasons, I think it is really important to just have this here. You should have options that are going to create some division, but you also want to make it a utilitarian document in the sense that you just don't want people to react to this. You want them to give you a very thoughtful set of recommendations that we could consider.

DR. EVANS: I like the idea of perhaps a preamble that couches this. Debra, I think you are next.

DR. LEONARD: Marc, I think it is wrong to presuppose what responses the SACGHS will be getting back from people. I know in my opinion this (A) would be throwing the baby out with the bath water because we are thinking only about genetic testing. This would really screw up PhRMA, and I don't think we want to do this. There are ways that you can do that without messing up PhRMA.

So you may be surprised at the responses you get back to this 8A even from people who are pro-availability of gene patents for diagnostic testing.

DR. WILLIAMS: I guess the point I'm trying to make is, the position that we are articulating here I think is clearly at one extreme. So, is the intent of this to be deliberately provocative.

DR. LEONARD: No.

DR. WILLIAMS: Let me finish. You obviously have an emotional investment in this. I'm just reflecting as someone that is reading this.

I think I would very clearly look at that and say this is no different than when the Republican National Committee sends me a survey about what I think. It is all in how the questions are asked. If the question is, here is a possible option prohibiting that, I think you at least have to say that we are putting these out as intentionally extreme positions to solicit comment. If we were to do that, then I could perhaps live with this.

DR. EVANS: As I said at the start like six times, this is a range of options. I would ardently tell you that we are not trying to be provocative. Nobody is trying to be provocative. You may find this provocative. Others may find that an exceptionally reasonable policy option.

Again, I don't think that we can ignore policy options that have been discussed that many people perceive as problems. If you look at the association patent issue, these types of things have been discussed a lot.

I would take exception to the idea that we are trying to be provocative. We are not. We are

trying to put out a range of options. I completely agree with you that we have to make it very clear to people that this is a range of options, we are not wedded to any of these, and we want to get people's comments.

DR. FERREIRA-GONZALEZ: I think that maybe we can put a preamble, as recommended earlier, that can address some of these issues. But I think we need to offer the range of options and, again, give the public the opportunity to comment on this.

DR. EVANS: Right. Mara.

DR. ASPINALL: Two comments, one on Andrea's comment and going back to the range of options. I still have a problem with that. If we wanted to truly have a broad range of options, one of them should be reinforcing the current patent system and ensuring that exclusive licenses are easily granted and can be used on a regular basis.

DR. EVANS: I think that would be reasonable.

DR. ASPINALL: Then, to me, it is a range of options. To Marc's point -- and naturally, I agree

with Marc -- the way it sounds it tacitly implies that this is the straw man that SACGHS is throwing out. I think the survey example is a good one. I actually happen to think it is provocative, but even if you didn't, it implies this is the straw man that we are starting with and this is the base that we are only putting in sand now, not concrete. I'm not ready or comfortable to do that.

DR. EVANS: Would people be okay with putting in an option just like what she said, that we should maintain the status quo in which exclusive licenses are frequently sought?

DR. ASPINALL: That is the middle of the range. The further end of the range is saying to reinforce the system as the best way to get innovative tests.

DR. EVANS: I think that is nuts, but if you really want that in there. I think that would be seen as a straw man. There are very few people who advocate that we should have nothing but exclusive licenses.

DR. ASPINALL: That gets, then, to Marc's

other point, made three times today, that I agree with. Are we here to reflect the public view and hear the public view in a way that we have 60/40 or 70/30, or are we here to listen to it and then vote with our own opinions on doing this.

DR. EVANS: Well, I would hope that we are listening to the public for a reason.

DR. ASPINALL: Right. We are listening to the public, but ultimately, if 90 percent of the public comes in with one viewpoint, are we here to represent that we heard 90 percent of the views on one side and say, I feel the 10 percent side but 90 percent of the people came to tell us they disagreed?

DR. TEUTSCH: I don't think we are here at any point to do vote counting of the public or the comments that we get. We are here to find out what we think in our collective judgment is the best way to ensure that effective technologies are available to patients. We should be looking at the range of options and listening to them. It is not a straw poll. If one person has an extraordinarily compelling point of view, we need to listen to it.

But it seems to me that is what we are here to do. Although we represent a broad range of disciplines, I hope nobody in the room feels that they are representing the company they work for or the academic institution they work for. We are here as a group of collective individuals trying to provide our best advice on a thorny set of issues.

We should make sure that the recommendations that we lay out here as potential options are the kind of things that we think are potentially viable and that we should seek comment on. Then, after we have gone through the process, we will have another rich discussion and vote. We just need to decide today what are the kinds of things that we want to lay on the table because we think that they are within the reasonable realm of possibility that we are going to solicit comments on.

DR. EVANS: I'm fine if people want to do this. I'm fine having something in here, if that is the consensus, that is more ardent about maintaining the status quo. That is great. I don't want to be seen as provocative. I want to be seen as, we are

considering all options.

DR. TEUTSCH: Kevin.

DR. FITZGERALD: In light of what you just said, Steve, and what Rochelle was saying, I think the preamble that we were talking should say, "Looking at the results gleaned from the case studies with the goal," as you just mentioned, "of making these technologies available to patients." Then you just say, "The best option for statutory change is," and then you list your possibilities.

That takes away the idea that you are putting forward something from this Committee as the best option. What you are saying is, here is our list. I don't know if this is the whole list that you would want. But one of them obviously would be to prohibit patenting of association to particular genes. There I think you would have to be clear it is an "or." You would have that preamble.

DR. ASPINALL: You would still have the status quo or something on there.

DR. FITZGERALD: That's right. Yes.

DR. ASPINALL: I'm happy with that

compromise.

DR. FERREIRA-GONZALEZ: I agree with that, too.

DR. EVANS: Mike is next.

DR. AMOS: I just want to say, I think there are profound economic implications in all this that have not been taken into consideration. Our colleague said there would be a chilling effect on the biotech industry.

I want to get back to Kevin's comment that maybe we should recommend that a more expert group look at this. With all due respect to everyone's expertise around the table, we are not economists. Perhaps that should be part of the recommendation. What are the really global aspects. To Debra's point, how will our recommendations on diagnostics affect other aspects of the healthcare industry.

I think you have done a great job of taking a look at this from a patient advocacy and laboratory perspective. But I think there are a lot of other things that need to be taken into consideration. For us to really put a stake in the ground and say that

these are the only options I think would be a mistake.

DR. EVANS: I think that is in keeping with having a range. I think that ultimately, after we receive public comment, we are going to have to face some hard decisions about whether we come out with specific recommendations or not. That will weigh into it. Did we have sufficient expertise; did we take into account sufficient breadth to make these recommendations.

DR. TEUTSCH: We need to move along.

DR. WILLIAMS: No, I understand. I must admit, though, that I feel much more like Charles feels. This really is a non sequitur because none of the case studies specifically address association patents, even though, as Rochelle says, there are aspects of associations that are within the intellectual property issues in all the case studies.

I think in some ways it just does stick out this way in the sense that if you read all of the preliminary material you wouldn't necessarily come to say this is where we should be.

DR. EVANS: Right. We can talk about this

all day. I think your point is well taken. I do think that it does relate to patentable subject matter.

DR. WILLIAMS: I think what we need to do, though, is we need to clarify, again, perhaps within the preamble or perhaps within the text of the report that goes out, why we are picking this out and how that relates to where the associations reside within the case studies.

DR. EVANS: In my mind, what legitimacy it has with residence there has to do with what is patentable subject matter, an issue which, in general, is of great interest to this Committee.

DR. WILLIAMS: I agree. It is just that, for those of us that weren't intimately involved and not living with it, you look at that and you say, where did that come from?

DR. TELFAIR: A quick comment. I would say, in respect to the preamble that is being recommended, we would like very specific comments with specific recommendations from the public so that whatever we get back is very targeted and very clear, independent

of what side it goes on.

I would just add that part of the recommendation up to this point is that an appropriate committee be formed to review these. I'm just trying to address the issue related to the breadth of the persons who are going to look at this.

DR. EVANS: In the vein of not trying to be provocative, "Modify the Patent Act as necessary to expressly withhold the right of injunctive relief from patent holders or their licensees who are impeding patient access to a genetic diagnostic test." I think this is probably best seen in the context of the subsequent ones. Then we can go back.

"The Secretary of HHS should work within the administration to encourage support for legislative change. The following are potential options:

"Create an exemption from patent infringement liability for medical practitioners who order, use, or perform diagnostic genetic tests in clinical care. Related healthcare entities should also be covered by this exemption." This is essentially expanding the Ganske-Frist Act to include

diagnostics.

The issue of research is one that comes up time and time again as one looks at the patent and licensing landscape. That is what C2 is addressing. "Create an exemption from patent infringement liability for those who order, use, or perform diagnostic genetic tests in the pursuit of research." The only reason those are underlined is to make clear their differences.

"Related healthcare and research entities should also be covered by this exemption."

Again, we are still talking about 7B and these. I think it is very important to craft a preamble that states that this is a range. We are not wedded to this. We want people's specific comments.

In the spirit of trying to adopt what Mara and Marc have said, do you feel that there are other recommendations? Are these unbalanced in your minds? Could they be balanced with other recommendations that are on a different end of a spectrum? What are people's thoughts about these?

DR. WILLIAMS: Since it was addressed to me,

I will just say that these are much less problematic from my perspective. That just may reflect ignorance on my part.

But it seems that this is not something where we are looking at necessarily opening up the competitive landscape. That would damage industry relating to things in terms of a clinical provision of a test as opposed to a test that is being used for research purposes that might gain knowledge.

I'm not even sure about C1. It makes me worry as a practitioner about what I'm actually liable for as I write that test order form. Am I actually incurring some liability? I don't know. But these are less problematic for me than the previous two.

DR. ASPINALL: I hate to go back to disagreeing with Marc, but first of all, my understanding is that C2 is the current state of events in terms of the use of patents.

DR. EVANS: No. That is a total presumption. It is not explicit by any means.

DR. ASPINALL: But if it is in the pursuit of research, at least until the patent is granted

there is no ability to enforce patents.

DR. EVANS: Once a patent is granted, many of those patent holders could, if they chose, eliminate research.

DR. ASPINALL: If it is granted. Not all the patents are granted. So for me, this goes into the same category.

I will go back. I don't mind being provocative, but I think the only way we can be provocative in throwing a straw man out there is if there is a unanimous opinion in the group that that is true to what we would like to throw out there. In and of itself, I don't mind being provocative, but I think this is an inappropriate time to do it.

DR. EVANS: I think these entirely flow from our case studies.

DR. ASPINALL: For me, that is probably the fundamental gap that I see. C1, and actually C2, really just undercuts the whole. Regardless of how you phrase it with association studies, it essentially undercuts the patent system entirely.

DR. EVANS: No more than Ganske-Frist did.

DR. ASPINALL: Except for the separation of diagnostics in a way that says that you cannot --

DR. EVANS: In a way, Ganske-Frist could be seen as being incomplete in the sense that there is an exemption for this type of thing.

DR. ASPINALL: Yes. But we talked about chilling effect and the ability to not have any reason to be innovative if we create this exemption. Clinical care is basically all patient use.

DR. EVANS: Rochelle.

DR. DREYFUSS: I think there is some confusion in the room. Every single one of these options so far has its place in the law as we now know of it. None of these things are entirely impossible under current law. For example, the association test. Justice Breyer said, I don't think that ought to be patentable, and several of the judges in the Bilski case said, I don't think under current law that is patentable.

It is not like we are throwing out something that doesn't already exist. These two certainly exist. People used to think that there was a research

exemption. It is only very recently that the Federal Circuit has hinted that maybe there isn't.

The Supreme Court has already indicated they think the Federal Circuit should rethink that, and the Federal Circuit has itself already said, not in a case but in speeches by the judges, that maybe that case where they said there was no research exemption was special and dealt only with specific things. That is not a general, run-of-the-mill case. As has been pointed out, the clinical care one is just an extension of Ganske-Frist.

So it is not like any of these things are totally new to what people have been thinking. This is all a natural progression from where various justices or judges have staked out their position on what the law is. The question is whether or not we ought to either create a statute about this.

It is also a little bit of a push to the judges to say, look at the studies that we did when you are thinking about what you want to do as a matter of common law. We have some data for you, which I think is very helpful to judges.

DR. ASPINALL: I would agree with that. I don't see these completely coming out of the blue. We can argue as to whether they came directly or indirectly from the case studies. For me, that is not the point. I would agree with Rochelle that these come out of what is there. These are extensions.

DR. EVANS: Right. But that is not what we are discussing here.

DR. ASPINALL: A few minutes ago I was going to make the decision as to whether it would even make sense to go through these in such detail. You could take the philosophy that if we add what Kevin had suggested that these are straw men and meant to be straw men, we are putting them out for comment and SACGHS is not ready to say this is our opinion now. I'm okay with that.

DR. EVANS: We are doing two things. There are possible recommendations in here that, for example, don't make sense. They just don't make sense from a legislative or rules standpoint. The other is, to think of are there things we have missed. We are a small task force. In this process of these conference

calls we tried to grapple with these things, but we certainly recognize there may be ones we have missed.

So, in the vein again of being provocative, "The Secretary of HHS should work within the administration to encourage support for legislative change. The following are potential options." Again, we will recraft the preamble to try to make this a little more clear.

Let me just read these as a unit. "Require the patents on DNA sequences be limited to the utilities specified in the patent, or prohibit patents on DNA sequences for diagnostic purposes, or prohibit patents on DNA sequences."

Now, we had a lot of discussion on the conference calls about whether, for example, D3 should be in here. Our final analysis was not only is it something people have thought of, it has been introduced as legislation in the House. This is not something we can duck. We have to at least discuss this.

I think that there are, again, differences about whether that is too blunt of an instrument or

not, but I think that it would be a glaring omission were we not to have that in there because it is already on the table.

DR. FITZGERALD: A quick question. When you say DNA sequences, is that supposed to be limited to human or opened up?

DR. EVANS: Great question. We talked a lot about that.

DR. FITZGERALD: That is why you pay me the money that you do.

DR. EVANS: That's right. That is why you get the big bucks for driving the big rigs.

[Laughter.]

DR. EVANS: Somewhere in the draft -- and we discussed this and I must admit now it eludes me where -- we were going to address that. As I was looking through the draft, I realized that perhaps we did not get that in there.

The task force's general conclusion was that we are talking about DNA and RNA nucleic acid sequences that are related to human health. I don't know what to think about this. This has been kind of

a messy issue lurking in the corner and we have about 32 minutes to resolve it.

DR. TEUTSCH: Actually, 18.

DR. EVANS: Eighteen minutes. I don't know. What do you think? Should it include SARS? Should it include human pathogens?

DR. DREYFUSS: It seems to me that what makes this different from other areas of patenting is the inability to invent around. It really, I think, has to do with natural DNA and not with man-made DNA.

DR. EVANS: I think what Kevin is getting to is, does it include non-human DNA like pathogens.

DR. DREYFUSS: That has the same problem. You can't invent around it. If you are going to deal with the pathogen you have to use its DNA. So I would include it. That would be the line I would use.

DR. EVANS: Other comments? John.

MR. LeGUYADER: First off, personally, I don't like this recommendation for the same reasons that I didn't like the previous one. It will have a chilling effect on the industry.

But if you are going to do this, I think you

should probably include pathogens or other DNAs that are associated with disease. But I think you would want to be careful also to craft this so you exclude industrially useful DNA that are used, for example, in micro-organisms to make amino acids or to make a particular protein because it is useful in detergents and so forth.

DR. EVANS: Steve's suggestion is to define it as health-related nucleic acids.

DR. FITZGERALD: A clarification on that, because I know one of the things that is going to come up again. Does that include nutrition and nutritious capacity or content of plants?

DR. EVANS: Maybe "medically relevant."

DR. FITZGERALD: That is why I say it. Try to be as precise as you can.

MR. LeGUYADER: That is a good point because plants are being used to genetically grow and make antibodies. You can use that straight as a vaccine.

DR. DREYFUSS: I guess you can create your own pathogens, but we are not trying to find ways to treat those. It is the things that are naturally

occurring that we care about as a clinical matter, things that are used the laboratory to make insulin or to do lots of other clinical activities.

DR. FITZGERALD: I guess my only concern with that is this whole area now of synthetic biology. A group of undergraduates from Slovenia just create a vaccine to Heliobacter pylori. That is not a naturally occurring sequence, but it would be a vaccine.

DR. DREYFUSS: Right. I would think that that should be patentable. Making the dividing line medical I think is a bad idea. You do want to be able to create medically relevant products through DNA genetic manipulation, and you certainly want to have patents on those things.

DR. EVANS: That just reminded me of something on the conference call that did address this. By having diagnostic purposes in there, in many ways that solves much of this problem. Diagnostic purposes then would include SARS and the genome of Heliobacter pylori.

DR. ASPINALL: But I think if you are going

to put this in, you have to put in the third one because the idea of what is diagnostic and what is therapeutic is --

DR. EVANS: The third one would be which?

DR. ASPINALL: "Prohibit patents on DNA sequencing," as opposed to just diagnostic.

DR. EVANS: I think that is the most extreme.

DR. ASPINALL: I much prefer D3 to D2. You separate one part of the industry.

DR. EVANS: That is your opinion.

DR. ASPINALL: Yes, personally. But the idea of looking at it broadly, I think having a line between a therapeutic vaccine and what is a diagnostic and what is a therapeutic [is an issue]. Somebody made the point before that we are going to be thinking forward to the future. Those lines are going to continue to blur as to how we use a drug as a tracer.

DR. EVANS: Again, those are discussions for later.

DR. AMOS: I think that once you make these rules for DNA and RNA, there is not a big leap to go

to proteins and metabolites and all these other things, too.

DR. EVANS: But we are not --

DR. AMOS: I'm just bringing it up.

DR. ASPINALL: I assumed this would include that.

DR. EVANS: Yes. It says DNA.

DR. ASPINALL: But if we use Rochelle's definition, do we assume it is the broader definition of naturally occurring substances?

DR. EVANS: It is DNA sequences.

DR. ASPINALL: So, not protein.

DR. EVANS: Not protein.

DR. ASPINALL: RNA, protein enzymes?

DR. EVANS: I think one could certainly put in nucleic acid. But I certainly think it is beyond the purview of this Committee to now start talking about proteins.

DR. ASPINALL: But, how would it philosophically be different if the next wave of technology is proteins?

DR. EVANS: It is totally different. Look

at our initial definitions at the start. We are talking about diagnostic tests that are predicated upon the analysis of nucleic acids.

DR. AMOS: For this report.

DR. EVANS: I actually do think you bring up a point. This should be "nucleic acid sequences" and not DNA because RNA is a major player in this.

DR. AMOS: Jim, I think it might be good to get some sort of legal opinion on how difficult it would be to take the legislation and language that is written on a naturally occurring DNA substance and translate that into other things.

DR. EVANS: But what is the point?

DR. AMOS: Well, everybody might get upset that protein patents are getting in the way of diagnostics.

DR. EVANS: They might, but that is not in our scope. It is not in the purview of this Committee.

DR. AMOS: I'm just saying that somebody needs to take a look at how big of a leap it would be to go from one to the other.

DR. EVANS: I think that could be something that we could talk about whether the Committee should discuss. But I don't think it is in the purview of the scope of this task force.

DR. AMOS: Except in the Oversight of Genetic Testing report. We defined a genetic test in that document --

DR. EVANS: That is different. But for very good reasons, I think.

Discussion questions. We have been hammering all this out. Here is the big question. Do you think there should be anything that should be added that is not here?

DR. ASPINALL: We talked about the preamble and showing a broader range of options.

DR. EVANS: Absolutely. Yes. That assumes that we are going to include the broader range, including status quo. I don't think we came to a definitive decision on whether there should be an option that we should encourage exclusive licenses. That seems nuts to me. Is there strong feeling we should encourage that?

[No response.]

DR. EVANS: I think status quo would be appropriate.

So, with the changes we have discussed, should we release this for public comment, with the understanding that it is a draft? We will make that clear. We will get the public comment. It is going to be quite a conversation.

DR. TEUTSCH: Just to be clear, though, we will take the comments we got today, make the revisions, and then, as you say, the task force actually will look at it once more.

DR. EVANS: Yes.

DR. TEUTSCH: Not the whole Committee but the task force will look at it before it goes out.

DR. EVANS: In December, if approved, we will send it out. February through April will be the comment period. April and May will be analysis. Clear your calendars for those delightful calls. June 11th and 12th we all meet again. At that point we will discuss preliminary findings, but it is during the summer of 2009 that we will be revising the draft

report. It will be at the October 2009 meeting that we hope to have final recommendations. That will also give some time for some of these decisions.

DR. TEUTSCH: I think it is fair to say that if we get crystalline recommendations that we can agree to in June, that would be great. But we didn't want to tie our hands too much, so we wanted to leave it open until October.

DR. EVANS: Yes, Debra.

DR. LEONARD: With the public comment invitation, how is that going to be worded? You could say, just comment on what we have written, or is it open to bring other ideas?

DR. EVANS: Yes.

DR. LEONARD: Can people say what their own experiences are?

DR. EVANS: Absolutely.

DR. LEONARD: I think that request for public comment is really critical.

DR. EVANS: Right. Yvette is pulling that out. It is not just "Confine your comments to these particular points."

DR. FERREIRA-GONZALEZ: I think we should encourage people to provide proposals. Be very specific.

DR. TEUTSCH: Page V in the report in your briefing book in the beginning is the note that goes along with it to the public.

DR. EVANS: Right. Tab 3, page V.

MR. LeGUYADER: I can say, having been through the rulemaking process from the Patent Office point of view, I can guarantee you they will comment and they will not be afraid to let you know what they think.

DR. FITZGERALD: Actually, on that note, just building onto past experience -- you can ask Andrea about this, too -- I think you are going to get a huge amount of public comments.

DR. EVANS: I completely agree. I'm sure we will.

DR. FITZGERALD: Going through that is going to take you [time].

DR. EVANS: Thank you. It will be very interesting.

DR. ASPINALL: Can I just ask a question? In the vein of the large questions that we are talking about, are there any other organizations that we want to ask this group that need to be notified?

DR. EVANS: I think that you have basically a long list of whom to target with regard to soliciting comments.

DR. ASPINALL: Maybe just to suggest that this Committee, given that this is a more legal view and a broader healthcare view than some of our other perspectives, could give recommendations on other people to ensure are on the list.

DR. EVANS: Absolutely. We want this widely disseminated for comment. Any ideas that anyone has, public or at the table, please let us know so we can target them.

DR. ASPINALL: That would be great. After the Committee reviews it, when would this go out and start the 60-day time frame?

DR. EVANS: If you want to go back to those slides. Again, February through April will be the comment period; April and May will be analysis. At

the next meeting, we will discuss preliminary findings, except Yvette is telling me we won't be done by that point.

DR. SEGER: We will be mid course.

DR. EVANS: With emphasis on the word "preliminary." Then, a revision of the draft report will be taking place in the summer, and then we hope to have final approval in October.

DR. ASPINALL: Well done. Amidst the controversy, well done.

DR. EVANS: Thank you.

DR. TEUTSCH: Jim and colleagues, a yeoman's job to get us through this. Tremendous.

[Applause.]

DR. TEUTSCH: Many thanks to all of you. I thought that was a very rich discussion and an appropriate one.

We will take a break. Since I think most of the folks are here for the next session, why don't we begin at 25 past. Then we will hear comments from NIST and other agencies about standards. Thank you all very much.

[Break.]

DR. TEUTSCH: We are going to begin the next session, but before we do, a couple of housekeeping notes. For those of you who are joining us for dinner tonight, you can meet us there at 6:30. Or if you would like to walk over from the hotel, we will meet in the lobby at 6:15.

I would also like to bring to your attention that there is a draft letter to the incoming Secretary, Secretary Daschle, that talks about the work we have done and some of the priorities that we think he should have early on in his tenure. I think it has not been officially announced that he is the incoming Secretary, but the newspapers seem to say he is. I don't even know that there has been an official announcement from the Obama camp, but that is the presumption. Then, of course, it needs to be approved.

But anyway, if you have comments on the letter, we will be discussing that tomorrow.

SESSION ON STANDARDS DEVELOPMENT INITIATIVES TO ENHANCE

OVERSIGHT AND ADVANCE INNOVATION OF GENETIC TECHNOLOGIES

Overview of Session

Steven Teutsch, M.D., M.P.H.

DR. TEUTSCH: Now we are going to turn our attention to Standards Development and Initiatives to Enhance Oversight and Advance Innovation of Genetic Technologies. I think, as many of you know who worked so diligently on the Oversight report, control and reference materials play a critical role in assuring the quality and analytic validity of genetic test results. These are the materials we use in performance assessment programs, including proficiency testing.

In the SACGHS Oversight report, we identified a number of significant gaps in the oversight of clinical lab quality and called for stronger CLIA requirements related to proficiency testing and more support for the development of reference materials and methods for assay, analyte, and platform validation, quality control, performance assessment, and standardization.

The National Institute of Standards and Technology, or NIST, and the Centers for Disease Control and Prevention, CDC, are the federal agencies most involved in addressing these quality control and reference material needs. Currently, reference materials are available for only six of the more than 1,300 clinically available genetic tests. That is pretty amazing, if you ask me.

There are many challenges to the development of these materials, including cost and time involved in producing them.

Given the importance of this area to the oversight system, we thought it would be useful to spend some time delving more deeply into how standards in lab medicine are produced and to explore the challenges and barriers that are impeding innovations in the field and in the translation of biomarker analysis into clinical practice.

We also want to begin to learn about some of the opportunities and initiatives that are under way. We want to explore the impediments to greater private sector involvement and the steps that can be taken to

incentivize commercial efforts.

In particular, I would like to thank someone who we hear from regularly, Mike Amos -- who is the ex officio member from NIST and who has been joining us since I have been on this Committee anyway -- for suggesting the idea of this session to us and, in particular, for helping organize that.

We will start with a presentation from Dr. Willie May, who is the director of NIST Chemical Science and Technology Laboratory. He will provide an overview of NIST's efforts.

Three NIST scientists, Dr. John Butler, Dr. David Bunk, and Dr. Karen Phinney, will present examples of the standards development for genomic, proteomic, and metabolomic tests.

To round out the presentation, Steve Gutman will discuss some of the measurement and standard challenges that are facing FDA, and Dr. Jeff Cossman, chief scientific officer at the Critical Path Institute, will review some of the challenges being faced by clinical labs.

Dr. Amos will discuss future trends in the

diagnosis of disease or risk projection, including next-generation diagnostic tests, based on the multiplex determination of complex biomarker signatures rather than single markers of biological activity.

While the focus of today's presentations will be on NIST's efforts, we also want to remain cognizant of CDC's work in this area through its Newborn Screening Program and the Genetic Test Reference Materials Coordination Program, or GeTRM.

We showcased these efforts in our Oversight report. Dr. Lisa Kalman from CDC is joining us today to represent GeTRM. We will have the opportunity to hear from Lisa during the discussion session about the program's current initiatives to develop reference materials for five pharmacogenomic markers and for array-based comparative genomic hybridization, which is a high-resolution analysis of chromosomal imbalances.

Finally, we are also pleased that Penny Keller is here for CMS's CLIA program.

You can find background information on this

session at Tab 4 and biosketches in Tab 2. We don't have all of the presentations in your notebooks, but I understand that the remainder will be available to us tomorrow.

Thank you very much, Dr. May, for being here. We look forward to what you have to tell us. Thanks so much.

Initiatives of the National Institute of Standards and Technology (NIST) in Clinical Diagnostics Standards Development

Willie May, Ph.D.

[PowerPoint presentation.]

DR. MAY: We don't have much time, so let's just get at it. What I would like to talk to you about this afternoon is our organization, our basic mission, and some of the new initiatives that we have. Specifically, I will talk about why NIST would be involved in bioscience and health since we are not NIH, we are not CDC, and we are not FDA. I will talk about some of our current activities in the area of bioscience and health.

I will just say now that standards for

genetic testing are a very, very small part of the portfolio but one that perhaps you can convince us to increase.

Finally, I will talk about how we are connected to the international measurement standards community.

Our organization was born, if you will, a little bit more than 100 years ago and charged with providing the measurement standards infrastructure to support manufacturing, commerce, and the makers of scientific apparatus, to work with other government agencies, and to support the academic sector. It is amazing; if you were to look now at the things we do, it is almost like this chart was given to us last year. This still remains the focus of a lot of our activities.

Now, some of the early drivers for some of our activities. We were in the midst of the Industrial Revolution, and people noticed that construction materials were not of uniform quality. Also, there were eight different values for a gallon if you drove from the East Coast to Chicago.

Standards were needed for the electrical industry. Scales were not standardized and they were often biased in favor of the seller, as you might imagine.

There were needs from chemical composition, dimensional, and metrology standards to support the railway system. In other words, lots of trains were jumping lots of tracks.

The thing that was most alarming, we being who we are, is we didn't like having to send our instruments abroad to be calibrated. So those things led to the inception of the National Bureau of Standards in 1901.

Since we are not the lead agency for health, the environment, or food safety and nutrition, and we have this arcane mission of being responsible for the nation's measurement standards, to remain a viable and productive organization we have had to change the focus of our activities continually to focus on major problems of society.

Today our organization has four major components. The NIST laboratories are the remnant of the National Bureau of Standards. We manage the

Malcolm Baldridge Quality Award. We have something called the Hollins Manufacturing Extension Partnership and the Technology Innovation Program, which used to be the Advanced Technology Program. Perhaps after the session, if anyone has any questions on any of these extramural programs, I can share those with you.

Our mission is to promote U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology in ways that enhance economic security and improve quality of life.

If you really were to look closely, this part and that part change. The words change in almost every administration. But these three bullets have not changed to any substantive effect over the last 100 years.

The NIST laboratories are responsible for maintaining the expertise and facilities for providing this measurement standards infrastructure to support the U.S. That work is carried out by what we call the laboratories, the Chemical Science and Technology Laboratory being one of 10 of these.

As you can see, we are organized pretty much like a university campus. We do what some people might call academic-type research, but that is to support the dissemination of the measurement services products that we disseminate.

Primarily, lots of work goes into the realization of the seven basic units of measurement, things like improving our realization of time. Right now the NIST Atomic Clock is accurate to one second in 30 million years. We are working on clocks now that we think will improve this by three orders of magnitude.

You might think, why would you do this? My watch works fine. Well, things like GPS and a lot of things you don't think about, like interstellar travel and so forth, are very dependent very precise realization of time and frequency measurements.

The last physical artifact that exists is the kilogram that sits in the basement of the BIPM in Paris. If you have been looking at a lot of the editorials in the popular press lately, you will find that the kilogram is said to be losing weight at about

one part in 10^8 per year. We don't really know that that is happening. All we know is that the mass of the kilogram relative to the mass of about 30 other prototypes based on that seems to be changing over time. So the relationship between them is changing, and that is a practical reason for changing.

There are also just pure scientific reasons that are leading the community to try to establish what we call the electronic kilogram. There is an approach to something called the Watt Balance. The new redefinition will be based on Plank's constant, most likely. But to lock that time, we will take this kilogram and then have a device called the Watt Balance. Different countries have different realizations of this to balance electrical force and mechanical force to try to transfer this.

Again, that realization has to agree to about one part in 10^8. Right now, we are about one to two orders or magnitude off from that. So that has to be completed by 2011 if the kilogram is to be redefined.

But we also serve a much broader community

with constantly changing measurement standards needs.

NIST has traditionally focused its research and measurement service activities on the physical science and engineering disciplines. But bioscience and health has now been identified as an area for significant emphasis and growth at NIST.

Why NIST and the biosciences. First of all, as the NIST leadership has looked at our mission, we feel that it is congruent with our mission and indeed our mandate to support U.S. industry and other stakeholders with overcoming measurement standards-related challenges in the biosciences, to provide confidence in results from measurements of complex biosystems, and to enable and facilitate realization of the maximum economic and broad societal benefits of innovation.

Now, Mike Amos and I have this discussion all the time where he says, NIST has to be involved for innovation, and I say, no, we don't, Mike. Not at all. Innovation is going to take place whether NIST exists or not. However, we maintain that by having this infrastructure to support comparable measurements

over space and time we will provide the infrastructure to allow society to gain maximum benefit out of these new innovations.

The other reason that we are doing it is, an emphasis of the administration is a better understanding of complex biological systems. I think this will continue into the next administration. The executive branch, let's say.

Other agencies come to us. This is just one quote. It's from Anna Barker, the deputy director of NCI.

There is an oversight committee that NIST has called the Committee on Advanced Technology. We have heard from two of its members that NIST should also expand its activities to support the biosciences.

Actually, we have been involved in bioscience-related activities for quite some time. Back in the 1920s a collaboration began between NIST and the American Dental Association that led to a lot of the innovations in dentistry that we take for granted now. Things like polymer composite dental fillings and the air turbine drill, found in almost

all dental offices, were developed by a number of employees of the American Dental Association who work at NIST full-time. There are about 30 people. Many people don't know they aren't NIST employees because they work there full-time.

In the 1920s we also started a program in radiation physics which focused initially on X-ray calibration and now includes standards for mammography and radionucleides for radiopharmaceuticals.

We started our program in oncodiagnostics in the 1970s with some support from NIH to provide primary references for electrolytes and metabolites. So, cholesterol, uric acid, glucose, electrolytes, calcium, sodium, and so forth. Then, later, in the 1980s, we began having serum-based standards for those. Around the turn of the century we began to focus on biomarkers for proteins, peptides, and DNA.

This is an example of some of those small molecules, primarily electrolytes and metabolites, that we have had standards for for a number of years. By standards I mean reference measurement procedures and, obviously, certified reference materials or

standard reference materials.

Then, about 10 to 15 years ago, we began to focus on more challenging biomarkers. These are some of the things that we have worked on. As you see, two of these might be considered genetic standards, but my colleagues will talk to you about some of the more in-depth details of expansion in this area.

NIST spends a little more than 10 percent of its appropriated funds on bioscience-related activities by our own self-declaration. Now, of this, around $38 million is focused on biosciences. Only about $10 million was appropriated for that. The other money has come as the result of decisions by individual laboratory directors to reprogram funds into this.

Right now, we are in the process of developing a strategic plan not only to support growth of our program in the biosciences but also to do a better job of directing some of the funds that we already have. Right now, to be quite honest, each laboratory has its own program. To get maximum impact out of the resources we have, we are going to try to

coordinate this in a much better manner.

I will just go through some of the activities and projects that we have that support health care.

So, what is the typical role of an organization like NIST. We see that all the national metrology institutes around the world have scientifically sound, metrologically-based -- not weather -- measurement science-based competencies and measurement capabilities that are vetted internationally. That underpins the delivery of a number of measurement services, one of which is certified reference materials. Standard reference materials is the NIST brand name for the certified reference materials that we produce.

Now, the Treaty of the Meter was established in 1875. It developed this collegial group of national standards institutes around the world, those that existed. Of course, that was before NIST existed. NIST or NBS, joined that in the early 1900s.

In 1999, though, there was a mutual recognition arrangement that was established that

required three things. All national standards institutes like NIST were required to declare and document the measurement capabilities that we use to deliver the services that they provided.

By signing this, you also said that you would agree to participate in very formal international comparisons so that you had some evidence to support the claims you were making and, further, you would maintain a quality system to underpin your dissemination of the services that you deliver using these techniques that you have claimed have been internationally vetted and compared. This mutual recognition arrangement now has been signed by over 200 national measurement institutes or designated institutes around the world.

This is an example of a comparison for creatinine and serum. This is the European Union laboratory, Korea, the U.K., NIST of course, and the German laboratories. This basically shows how well our capabilities for providing reference measurements for creatinine serum agree with each other

This is a more recent one that was completed

this year. This is cortisol in serum and progesterone in serum. Japan, the U.K., China, the U.S., Germany, Korea. Then, progesterone, the same laboratories, except Australia is involved, and Mexico.

In this example certainly, if there was a CRM that was developed by Mexico based on this analysis, there might be reason to question it, if you will.

The MRA is about documenting measurement capabilities that national metrology institutes maintain and looking at how well those measurement capabilities compare with each other.

Also around 1999, there was this European Union directive that said that the traceability of values of assigned to calibrators or reference materials must be assured through available reference materials of a higher order. The U.S. IVD manufacturers came to NIST and the metrology community and said, we need help with this because without that we won't be able to sell our products in the European Union.

So we convened a meeting at NIST among all

the stakeholders. One of the recommendations was the establishment of a global consortium of IVD manufacturers, professional societies, national metrology institutes, and regulatory bodies. This organization became named the Joint Committee on Traceability in Laboratory Medicine. Three principals in this were the International Committee on Weights and Measures, which represents the national metrology institute community; the International Federation for Clinical Chemistry, which represents the professional community; and the International Laboratory Accreditation Corporation, which represents the accreditation community, if you will.

The product from this is a database of higher order reference measurement procedures, certified reference materials, and laboratories that provide reference measurement services to the clinical chemistry community.

I will just show one of their work products. A work product other than this database is the comparison of standards that are in that database to see how they compare with each other. As it turns

out, the standards three years ago for cholesterol came from only two places. There were a number from NIST and a Japanese laboratory, and this just shows how they compared with each other. If one were to select randomly any of the certified reference materials in the database, they agree to within less than 1 percent of each other.

This shows also two reference measurement procedures for cholesterol that are identified in the database, and there are only two. This is how well they agree with each other.

So the world is changing, and we realize that we must change at NIST. Mike Amos is going to talk about this, so I won't say a lot about this except to say that one of the future thrusts for us is to look at tools for what we call visualization of disease signatures and our new initiative for 2010 and beyond. It will have two areas of focus. One is quantitative medical imaging and protein measurement science.

At this point we don't have standards for genetic diseases in there, but after discussing it

with you, if the general capabilities that we have won't support that, then there is an opportunity to amend our current plans.

So, thank you for your attention.

[Applause.]

DR. TEUTSCH: Are you happy to entertain questions?

DR. MAY: Sure.

Question-and-Answer Session

DR. ASPINALL: First of all, a very impressive presentation. It was great to give us the history to get to where you are going now. How do you implement new standards? In brief, how does that process work? How do you get the communication and the time frame to do that?

DR. MAY: Right now we are developing a strategic plan. We are putting together the strategic plan. We have catalogued a number of workshops, conferences, and visits to stakeholder communities. We have captured conversations that we have had when we had official visits from stakeholder communities to NIST to try to develop some sort of coherent plan for

NIST.

What we have done in the past is that individual divisions within NIST would conduct their own needs assessment. Lots of the standards that we have now were developed because of input most often from the American Association for Clinical Chemistry. So we would have workshops at AACC meetings often and try to interact with stakeholders and say, what are your top priorities. If you could give us priorities, what would the top five be, for example.

Basically, to answer your question very quickly, we get input from lots of sources. We distill that, try to look at the highest priorities, and then match that with the capabilities that we have. If there is something that is a high priority but we don't have the skill set to address that problem within the next two or three years, then we tend not to address that because it wouldn't do us any good to have an answer 10 years later when probably the priorities have changed.

DR. ASPINALL: Do you use those same societies to disseminate the information after you

have created new standards?

DR. MAY: We disseminate information probably poorly. We have our website. The standards are in our standard reference materials catalogue. Right now, NIST has about 1,400 standard reference materials. About 1,000 of those have values assigned for chemical or biological analytes.

Our old customers know to go through that SRM catalogue to look for what they need. But what we have not done as effectively as we should is provide avenues for new customers and people who don't know about that. That is one of the reasons we are down here today.

DR. TEUTSCH: Julio and then Andrea.

DR. LICINIO: Wonderful presentation. I had a question on the cortisol and progesterone measurements that you had, which was, I think, a fantastic thing to do because it is true that you have the same sample and you get different measures. It can be very confusing.

One of the things we discussed here before is that one of the issues in the area is that genetic

labs sometimes can get disparate results. Would you be willing to do the same type of thing with genetic companies and see what the divergence rate is?

DR. MAY: I guess we could do that. Normally we look to the CAP and other accreditation bodies to do this. This was a comparison among national standards laboratories. These are the laboratories that are supposed to be providing traceability to the companies within their region.

Now, obviously, that is not a perfect thing because right now more than half of the standard reference materials that we sell at NIST are sold internationally, not within the United States. So people are free to get their reference materials from wherever they want.

But this basically is information to the national metrology institute as to how they stack up relative to others. You might ask, how do we know the true answer here? These are not spiked samples. We don't use spiked samples. We use naturally occurring samples. We have a lot of, let's say, intellectual debates, if you will. We have each of the

participants go through their methodology. We shoot holes in it. Then we try to discern from those arguments which laboratories will be used to assign the reference value.

It is not just if you happen to luckily get an answer. We look at the material. For example, LGC's information wasn't used to define this. As it turns out, they were right on. But in their description of their methodology there were some issues. The same thing here. There were only three laboratories that we agreed to consensus had a sound approach.

So everybody develops the approach in their laboratories. This is not using one published method but methods of the highest metrological order as defined by that individual institution. Then we try to get from that to discern what we think the truth is. Then we compare things against that.

DR. FERREIRA-GONZALEZ: Part of my question has already been answered. But, you bring that information back to NIST and assign a value. Before you commercialize that, do you engage your end users

again to see if that value has changed? Do you periodically send surveys out to some of these laboratories to recheck the values?

DR. MAY: It is within our system to do a stability check on all of our reference materials. Some of them might take a year or two years. We might make a measurement now and might make another set of measurements in our laboratories a year or a year and a half later to assure ourselves that the matrix is stable. So it is not until we have addressed all of the issues.

Every certification campaign is different because it depends on what the material is and how stable we think it is. Then we do other measurements to try to assure ourselves that in fact the values are correct and that the material is stable. We do all of that before the customer ever gets the material.

DR. FERREIRA-GONZALEZ: Different analytes for materials will have different times from conception to distribution. What is about a mean time from actual formal distribution of some of these?

DR. MAY: I guess, back when I did useful

work in the laboratory I could give you that answer.

[Laughter.]

DR. MAY: It varies so much. For clinical material, I would probably say two years. For a genetic standard, how long would that be, John? A year? I would say a year minimum, probably a maximum of two to three years from the time that we actually began working on the project.

Now, from the time we get input from the stakeholder community, that could be three to four years. Getting the input and deciding that this is going to be our priority, that might take a year's time, because we get lots and lots of input from lots and lots of people. Part of that is deciding internally if this is going to be one of our priorities and making sure that we have the resources to have a successful campaign for development of the reference material.

DR. TEUTSCH: Great. Thank you so much, Dr. May. We are going to take the next three presentations in a row and then get questions after that. Let me turn it over to Dr. Butler, who is going

to talk to us about nucleic acid tests.

Nucleic Acid Tests

John Butler, Ph.D.

[PowerPoint presentation.]

DR. BUTLER: Thank you for the opportunity to address the Committee today. You will notice the slides that you have will be different from mine. I will have a few new ones. Some of them will be hidden, so I won't show all of them, in the interest of time.

What I want to show are some of the things we have done in the past and what we are trying to do now with the new Applied Genetics Group that has been formed within the Biochemical Science Division at NIST and within the Chemical Science and Technology Laboratory, and then some of our thoughts for the future.

In terms of the past, most of our experience has come with doing forensic DNA testing, developing reference materials and methods, genotyping assays, and new technologies for improving forensic DNA testing. This is something that has been well noted

in the press in terms of the need for good standards and quality measurements.

In terms of the present, two months ago, on October 1st, we formed a new Applied Genetics Group, which is, again, bringing the expertise we have with developing reference materials for forensic purposes and now applying that to clinical genetics and also agricultural biotechnology efforts, like genetically modified organism detection.

We have some done some work with genetic genealogy and DNA ancestry, trying to help with improving their nomenclature and how testing is compatible within things.

I will finish with just a few thoughts on some planned genetic testing and some of the things we would like to work with. For example, the CDC's GeTRM program. We want to collaborate with them on things.

In terms of our initial efforts and interest in getting into forensic DNA, Congress passed the DNA Identification Act in 1994, which gave the FBI authority to establish a national DNA index system, or national database for DNA testing.

As part of that, there was a DNA advisory board that was formed. One member of that was from NIST. From that came quality assurance standards which now govern how all forensic testing is done in the United States. These standards have also been adopted for testing around the world as well.

Standard 9.5 within the section on analytical testing says specifically that the laboratory shall check its DNA procedures whenever a change is made against an appropriate and available NIST standard reference material or a standard traceable to a NIST standard. This is what has driven most of our efforts in forensic DNA testing, trying to provide information that can help with the underpinnings of quality measurements for forensic laboratories.

This is a new slide here that I just added showing that at the highest level, the community level, there are quality assurance standards to make sure that there is also, of course, inter-laboratory studies to make sure that everybody can talk to each other in terms of their data.

Within the laboratory, there is the American Society of Crime Lab Directors Laboratory Accreditation Board. They have accreditation of laboratories. Audits are performed, usually annually, of laboratories to make sure that they are compliant with the specifications there.

Each individual forensic DNA analyst must perform two proficiency tests per year on any type of testing that they are doing, plus they are required to have continuing education to keep up with new technologies.

The next level is the instrument or the method level, where we have validation of analytical procedures. This is where the NIST reference materials come in. You have a traceable reference material to make sure that your instrument or your method is working properly.

Next is at the protocol level, where you have standard operating procedures to make sure that the instruments are used consistently from analyst to analyst and so on. Each data set has its own standard materials that are run, positive and negative

controls, and so on. Allelic ladders are a mixture of DNA samples to show all the possible alleles that would be seen.

Individual samples have internal size standards that are run with them. Then we have interpretation of results that are confirmed by a second analyst. Finally, of course, when you go to court, you have defense attorneys and defense experts that can examine your data as part of discovery requests. That provides another check and balance on how forensic DNA results are done.

So, all the way from the community level to what is presented in court there are checks and balances with things. The reference materials that NIST provides are only a small piece of the validation of the analytical performance of something.

Over the years, there have been a number of different technologies that have been used. For each of these different technologies we try to have a NIST reference material available to help with this. The first is, of course, the restriction fragment link polymorphism, developed in the late '80s. That was

the initial DNA fingerprinting or DNA typing that was developed.

Then there became polymerase chain reaction-based tests. The next series of reference materials was SRM 2391, which has been available since the mid 1990s. Then we have had ones for DNA sequencing and mitochondrial DNA and, most recently, for Y chromosome testing.

The technology in some cases is no longer used and therefore reference materials get phased out. Then there are growth areas in terms of new markers and new information that can be added to the same samples and certified on the same samples.

This is just to illustrate what we do on the genetic tests. On the top right, you see a picture of the DNA samples themselves. There are 12 different samples that are provided for this particular test. Then there is a certificate of analysis that provides genetic data for each of those samples.

In this case, they were characterized for 22 autosomal, short-10 and repeat markers that are used in forensic testing around the world. We have just

recently added 26 new STR markers. It is basically a value added to the same reference material. So the DNAs haven't changed. We have just added more certified information to them.

We have also tried to encourage the slowing down of the consumption of these because they are expensive to make and certify. We tried to help laboratories make traceable materials instead of just using straight off the shelf the reference materials themselves.

These are the basic steps in forensic DNA testing. You collect the sample, you extract the DNA and quantify how much DNA is present, perform a multiplex PCR application. Then you look at the short tandem repeat markers and interpret those results, and then put those results in a database where they would be checked against the frequencies of alleles to determine how common that particular profile is. That is what would be presented in court if they match.

So the reference materials only focus on the actual typing results that are produced. There are many other aspects of the process that could have

reference materials, but right now we are just focusing on the separation of the DNA itself.

We are looking at short tandem repeats. That is what is used in forensics where we have primers that target a repeat region. The number of repeats is then converted. The overall size of the PCR product is measured and then the number of repeats is what is actually considered in the final analysis and what is reported. In this case, 11 GATA repeats is what is recorded in the database for that DNA profile.

That measurement is made against an allelic ladder, which is a mixture of alleles. You can see in this case, just showing two samples, one that is a 16/17 and one that is a 15/16. Both those samples are compared against an allelic ladder that a commercial manufacturer produces. They check that allelic ladder against the NIST reference material.

There are different sites that are used throughout the human genome for forensic testing. In 1997 the FBI defined 13 core loci. There is also a sex-typing marker that is used called amylogenin that

is present on X and Y. Then there is some overlap with Europe. So our reference materials are also used in Europe, though they use slightly different genetic markers for their testing there.

Now, within the U.S. we have over 6.5 million profiles on the database. A laboratory cannot put their results on the database unless they have run a NIST SRM to make sure that their results are accurate and so on.

Again, a little bit more on the STRs. We are measuring the base pair size, converting that back to a repeat number, and that is what is being stored.

This is also used for paternity testing. Our reference materials are used to help with making sure that paternity testing is done properly. The American Association of Blood Banks, AABB, is who oversees how paternity testing is done.

This is what a full DNA profile looks like, just to illustrate the process. An internal size standard is run with every sample. Then we have the individual samples compared to an allelic ladder to actually get the genotypes for each individual site.

The measurement is performed by the allele size.

Another thing that is important to point out, of course, is that different genetic tests may use different PCR primers and therefore, because of binding site mutations, may produce different results because of allele dropout or null alleles. This is just to illustrate one example with a NIST SRM 2391b.

The Genomic DNA 8 actually has a dropout at this marker on chromosome 16 with a new kit that just came out from Applied Biosystems. You lose Allele 11. This becomes important as laboratories are trying to verify if their procedure is working properly. So we go through and do a lot of work to calibrate and sequence the regions and define why a particular new assay or kit doesn't work properly.

We are funded primarily by the National Institute of Justice to do this work, as well as internal NIST funds. We have reference materials, as I mentioned. We have standard information. We have conducted a lot of interlaboratory studies. On the technology side, we are constantly developing new assays and new software. We have training materials.

You can go on our website, which is the STRBASE website, and download PowerPoints and other workshop information to help people learn more about this.

Just to get to where we are now, you will hear about some work going on in the Analytical Chemistry Division in just a moment. We are within the Biochemical Science Division. It is all underneath CSTL. We just, as recently as two months ago, formed an Applied Genetics Group, which is one of six groups doing work with genetic testing. These are the people that are involved there. Marcia Holden and Ross Haynes are new additions to our group, the former forensic group. We are really expanding in this area.

Our mission is to advance technology and traceability then with quality genetic measurements, continuing to help the forensic testing community but also clinical genetics, the ag bio tech, and then also DNA biometrics. There is a tremendous interest in this area and speeding up the process of DNA testing and making sure that is done accurately by the intelligence community, and so on.

This is some of our group expertise and

funding sources. We have primarily, again, expertise in reference material characterization, construction of new assays, a lot of work with sequencing, SNPs, STRs, and so on. Our primary funding is coming from NIJ, but we are also getting internal funding from NIST. We plan to strengthen our portfolio in the clinical genetics area.

DR. TEUTSCH: Dr. Butler, I hate to interrupt you, but we will need to wrap this up so we give everybody a chance.

DR. BUTLER: That's fine. These are our reference materials that are available right now. There are some slides from Mark Salit here on some of the RNA work that he has been doing.

We have been trying to help with nomenclature to help the genetic genealogy community to make sure that they are getting consistent results across laboratories.

This is one of the new ones. We are working on Huntington's disease, trying to have alleles that appropriately define each of the characteristics you would expect to see with Huntington's disease.

We have to decide, and we welcome input, in terms of what types of materials should we certify. We can certify for a sequence, a specific genotype, and of course, the quantity of DNA that is present.

We want to continue making information available to the public, as we have with our forensic stuff, and make that available for clinical diagnostics as well. Feel free to contact me if you have questions, and thanks again for your attention.

[Applause.]

DR. TEUTSCH: Thank you. I hate to rush you through all of that, but I want to give everybody else a fair chance.

Let's move on to Dr. Bunk, who is going to talk to us about proteomic tests. Welcome.

Proteomic Tests

David Bunk, Ph.D.

[PowerPoint presentation.]

DR. BUNK: Thank you very much. Thanks for the invitation to come speak to you this afternoon. Now for something slightly different, some protein work that we are doing at NIST. This is a new effort

in terms of helping to standardize and improve the measurement quality of proteomic clinical research.

Proteomics has not yet moved its way into the clinical diagnostic lab. I'm sure it will be entering soon enough. Right now proteomics is mostly used for medical research and medical diagnostic research. But the important thing here is that the measurements still need to be standardized. There still need to be high-quality measurements in order to make sure that the medical research is moving forward in the right directions and not leading down the wrong paths.

Just a quick definition in case we are not familiar with what proteomics is. Proteomics is the identification and quantification of all proteins of whatever sample you are talking about, whether it is the human proteome or specific tissue proteomes.

The interesting thing about proteomics, where it differs from genomics or metabolomics, is that very little research in proteomics actually measures intact proteins. You can divide proteomics into two distinct approaches: the top-down

proteomics, where intact proteins are measured, but the vast majority of proteomic research is done using an approach called bottom-up proteomics, in which proteins are degraded down into peptides and peptides are measured. Then we are relating that information back to try to figure out what is going on at the protein level.

That is important when we talk about how we standardize the measurement techniques because we need to know what is going on. If things are not being done at the protein level, then we don't necessarily need reference materials at the protein level. We can actually do a lot of work by having peptide-based reference materials.

Clinical proteomics is a subcommunity of all proteomics. Really, from my understanding, the goal of clinical proteomics is to discover new diagnostic biomarkers. It is both looking at the change in the structure of the concentration and interactions with different proteins in order to improve clinical diagnostics.

If we look at the clinical biomarker

pipeline, the first phase of biomarker work is the discovery phase, where we identify candidate biomarkers. That moves into the verification of these candidate protein biomarkers and finally into clinical validation. Currently, proteomics is being used in the discovery phase and the verification phase. The clinical validation is large-scale, large cohort studies in which most of the work is done using traditional techniques like amino assays.

But there is some belief that proteomic measurement technology will be used in clinical validation in the near future, and some of these technologies are being developed in order to do that. But currently, proteomics is focused on the discovery phase and the candidate verification.

The distinction here is, in the discovery phase we are only talking about a small number of samples, maybe one healthy and one disease state samples. As we move into verification, we want to try to reduce the number of candidate biomarkers down to a manageable number, and so we use a larger amount of clinical samples. Of course, with clinical

validation, we are talking about thousands of patients in order to make sure that we have a true biomarker that has either diagnostic or prognostic utility.

Proteomics is still in its infancy, to a certain degree. There are a lot of problems in proteomic measurements. That is one of the reasons why NIST is involved. We want to bring a higher level measurement quality to proteomics.

Basically, I think one of the fundamental problems in proteomics now is that there are no quality metrics. There are no performance criteria. At least, there have not been in the last few years. There have been a number of studies published. The Human Proteomics Organization has published a number of studies where they are looking at interlaboratory comparisons of proteomic investigations. Unfortunately, many of the results are not very positive. There has been very little comparability in proteomics investigation from laboratory to laboratory. Obviously, if you want to develop technologies for doing clinical diagnostics, the field of proteomics had to be improved in order to get more

reliability and more comparability of the measurements.

The other issue is, it is very difficult to assess truth in proteomics. No one knows what the human proteome is. It is very difficult right now to assess agreements if you don't have standards. That is one of the reasons why we are here at NIST.

Unfortunately, all of this has led to the potential of diminishing opportunities for future research funding. On that note, a few years back we partnered with the National Cancer Institute on one of their initiatives and really discussed this.

One of the fundamental approaches we take in developing reference materials and reference measurement procedures for clinical diagnostics is partnering. We at NIST are not clinical chemists. I am not a clinical chemist. What we do know at NIST is the basic fundamentals of measurements.

So what we have to do is partner with professional organizations like the AACC, the IFCC, and the National Cancer Institute in this case, to bring their expertise into our efforts in

standardization. We apply our measurement skills, our knowledge of the fundamentals of measurement, and we bring in their application knowledge to solve the problems that are relevant to them.

The National Cancer Institute, about three years ago, developed a program to assess proteomic technologies because, basically, their advisors were telling them that they are not going to be funding much future research for proteomics because there was no payoff. So NCI decided they needed to initiate a program to evaluate the technologies.

It is a very interesting program because it is not about biomarker discovery. It is about validating the technology used in clinical proteomics.

The role that NIST plays in this program is that we are advising them in some of their interlaboratory study designs and developing the materials that are being used in interlaboratory studies. We are working with them to really help assess the technology ourselves. In the meantime, we are learning a lot about proteomics. So we are gaining the knowledge from the community by working

with these partners, and that is an important aspect.

Through this initiative we are working on interlaboratory studies but we are also developing the information we need to develop our own reference material program to support proteomics.

Let me go back to the biomarker pipeline once again to draw some distinctions here. Biomarker discovery is mostly a qualitative or relative quantitative measurement. This work is mostly done these days in tissues, so we are looking at the sources of disease, like cancer would be in tumors.

The verification stage is doing more of an absolute quantification of signature peptides from whatever the candidate biomarkers are. That is being done in mostly plasma because this is leading toward a more diagnostic platform. The instruments being used are much more qualitative.

Realizing that proteomics is playing a role in both of these fields, discovery and verification, NIST is developing reference materials to support both efforts because if you are not supporting the entire pipeline you are still going to run into problems. We

need to have reference materials and standard operating procedures and validation tools for the entire pipeline.

Let me just mention some terminology we use in terms of reference materials, which is horizontal versus vertical standards, or vertical reference materials.

When we are talking about a very complicated measurement technique or measurement pipeline like in proteomics, where there is sample collection, sample processing, instrumental analysis, and data analysis, there are a lot of places where problems can come in. We approach that we take at NIST is to develop horizontal standards, which are standards which support measurement quality in individual steps along the way.

The other thing we also develop is vertical standards, which are very much application-specific standards.

A horizontal standard might be a standard that can be used to validate your data analysis, whereas a vertical standard would be a more complex,

application-specific standard like cholesterol in serum, where it is geared towards a much more specific measurement problem. The standard is carried through the entire measurement process.

In proteomics, that is the approach we are taking. We are developing horizontal standards and vertical standards in order to support the measurements.

In most cases, for a new measurement area it would be impossible to develop just vertical standards. The applications where proteomics is being used are very significant, so we would have to develop vertical standards for every specific application.

In clinical diagnostics, we have reference materials for cholesterol measurements, glucose measurements, creatinine measurements, and so on and so forth. That approach for proteomics just wouldn't work because there are too many areas in which it is used. So a horizontal standard is a way that we apply our resources to improve the measurement as best we can.

Currently, we have two reference materials

in production. The horizontal standard is a mixture of synthetic peptides, so it is not application-specific. It is designed to improve quality in mass spectrometry instrumentation. So all fields of proteomics that involve mass spectrometry could benefit from this reference material since this is a common point in their pipeline, making that a horizontal standard.

The other reference material we are currently developing is a yeast proteome reference material. This is a vertical standard, so this is designed for proteomic investigators to take a complex protein mixture through their entire proteomic pipeline and validate the procedures that are being used here.

We also have plans to develop more complex proteomics reference materials that are plasma-based for quantitative measurements.

In addition to those two new reference materials and the additional one that I mentioned of complex-matrix horizontal standards and vertical standards, we are also looking at developing higher-

order measurement tools for assessing performance of affinity reagents in proteomic arrays, multiplex arrays, as well as developing and validating novel affinity capture reagents. So we are looking at both improving technologies, developing standard operating procedures for people doing proteomics, as well as delivering services through reference materials, which people can use to validate their technologies and their techniques in proteomics.

We hope that by having all these different areas we can support the measurements that are going on in the clinical community and improve the outcome of clinical proteomic research.

Thank you.

DR. TEUTSCH: Thank you, Dr. Bunk.

[Applause.]

DR. TEUTSCH: Now, metabolomics. Dr. Phinney, welcome.

Metabolomic Tests

Karen Phinney, Ph.D.

[PowerPoint presentation.]

DR. PHINNEY: Thank you. I'm very happy to

be here today. I appreciate the invitation. For those of you who are unfamiliar with metabolomics, this is something that has been going on in clinical chemistry for a long time. We have been measuring small molecules like glucose and cholesterol as part of diagnosing disease. To a great extent, this is just a fancy name for something that has been going on for a long time.

Metabolomics really represents the endpoint of genomics and proteomics. It is what you really get when you look at a sample of serum, plasma, or urine. Those samples reflect the exact processes going on at that period of time.

There are some advantages to looking at the metabolome. It does represent an exact picture of the situation in the body at that point in time, and it is affected by things like diet, stress, exercise, disease, health, you name it. So instead of looking at the genome, where you look at what might happen, you actually look at the phenotype or what really did happen. To a great extent, this could be the ultimate in really doing disease diagnosis.

There are some other things to know about the metabolome. It is simpler than looking at either the genome or proteome. Even though in the metabolome you are still talking about thousands of potential metabolites, that is still a far simpler situation than thinking of hundreds of thousands of different proteins or even tens of thousands of different genes.

So, what is the goal of metabolomics. Why are we throwing around this fancy terminology. As I mentioned, we have been using metabolites as diagnostic markers for a long time, but we have tended to do them one at a time. We might look at glucose to diagnose diabetes and we look at cholesterol to look at risk of heart disease. But we haven't put all those pieces together. So what is unique about metabolomics is that it involves looking at panels or signatures of different analytes and their levels under different circumstances in the case of health or disease.

Ideally, you can use those patterns or those signatures to try and segment people into different groups and, ideally, use that as a way of doing

disease diagnosis.

If you look at the picture that is there on the left, that is an NMR pattern or NMR analysis of a particular sample. You can see there are lots of different peaks there. You can see, looking at the different color of spectra, that there are some differences in how those appear.

The goal of metabolomics is to try to look at those different patterns and to be able to say something about different levels of particular metabolites representing some signature. So, does it represent a healthy person or a diseased person.

Ideally, we would like to get to the situation that you see on the right, where you can put people in different boxes and say in this particular population we see this signature or these different metabolites at these particular levels and in a healthy person we see a different pattern. If you can do that with some reliability, you could use that as a diagnostic tool.

Now, one of the reasons to do this is also to try and identify places where we could intervene in

a disease state. If we know that in a particular disease certain metabolites were elevated or decreased, we could then try to intervene in that particular metabolic pathway through pharmaceuticals or some other therapy. So metabolomics does represent one potential mechanism to identify new therapies, and there is certainly a lot of activity in this area in the pharmaceutical industry.

The drug industry is also interested in looking at this as a mechanism to identify toxicity. If you can identify particular markers that indicate liver toxicity, for example, and you can measure those in a multiplexed way, you might be able to predict ahead of time whether a particular pharmaceutical is going to have adverse effects.

That would certainly be very valuable. We know these days we hear a lot in the news about things that make it onto the market only to be withdrawn later. Certainly, that is why the pharmaceutical industry has such an interest in this area.

Finally, as you saw in one of the first slides there, all these things are related. The

metabolome can be traced all the way back to the genome. If you look at patterns of metabolites, you might be able to say something about gene function that assumes something about the metabolome, the proteome, and the genome all at the same time. That is quite a lot of information to try to capture, but under ideal circumstances you might be able to do that.

So, what are some of the issues. Where does standardization come in. If you think about trying to measure thousands of metabolites simultaneously, you are talking about very large and complex data sets. As David mentioned, there are always issues in terms of instrumentation, sample collection, and sample handling. So, how can you get to a point where you can say with some certainty that the pattern of metabolites that you see is really representative of a particular condition.

There are a number of these issues: sampling, instrument variations, platform variations, and software, just in dealing with these very large data sets.

Once you get your data, how do you pick out which things actually mean something. There are thousands of metabolites but maybe only three are relevant to the particular condition that you are studying. This comes down to software and it comes down to making assumptions about the data that you have. Clearly, in those situations there is room for error and there is room for differences in interpretation.

Finally, before we can get to a clinical diagnostic setting, we need to actually validate that the patterns of metabolites we think are useful in diagnosis really are. Certainly, that comes back to looking at large populations of people and making sure that you really can say with some certainty that you are making an accurate diagnosis based on this metabolite signature.

About two years ago, I guess, NIH came to us. They have been funding a number of investigators for metabolomics technology development. But along with that effort they realized the importance of some standardization and some common way for people to

evaluate the technology that they were developing, some common mechanism for them to use. So they approached NIST about developing reference material for metabolomics.

We have been involved in that effort over about the past two years, and this material will be introduced I think probably early in 2009. So we are coming close to at least the end of the first stage of this process.

This reference material is actually a plasma pool. The reason that we did that is we didn't want to represent any particular part of a population. We wanted this to be indicative of a mix of male and female, different age groups, and healthy individuals, and we wanted it to also have some of the ethnic characteristics of the U.S. population. So the samples that were pooled to prepared this material came from African Americans, Asians, Caucasians, and, again, both male and female individuals.

One of the reasons that we did that was that when we have to prepare this material again in, say, 10 years, we wanted to be able to prepare it in a very

similar way. That is why we set these criteria in designing the material.

We have a lot of experience in measuring individual metabolites. As Dr. May mentioned, we have a number of different reference materials for individual metabolites in serum, the traditional analytes like cholesterol, glucose, and creatinine. We have measured those same analytes in this particular reference material, so we will have certified values for probably 40 different metabolites, everything from fatty acids to glucose, to hormones.

But we also realized that people want something more than that. They would like to know what other metabolites are present. So the effort that we are focusing on right now is more of a qualitative effort to see what techniques do we have available, either at NIST or through collaborators, where we can identify additional metabolites and also provide that information.

Clearly, there is the potential to use this material in a variety of different ways. Depending

upon your particular study, if you are looking at glucose metabolism or if you are looking at kidney disease, your interests may be different. So in order to make this material relevant to as many different people as possible, we are trying to provide as much information as we can.

Now, clearly, this is a starting point in terms of providing standards for this particular area. It is an evolving field, and we certainly recognize that. We do see the potential for additional reference materials and different standards here, and also tools in the area of bioinformatics. One of the big questions here is how do you handle these large data sets. How do you insure their reliability. How do you compare data from different instrument platforms or different laboratories. I think these are all questions that will be coming up as this field moves forward. It is still very early on.

We also realize that there may be a need for reference materials to focus on more specific populations. It might be a group of individuals with heart disease or it might be male versus female. The

list could go on and on. Certainly, we look to the field to help us in prioritizing those efforts.

There are some fledgling standardization efforts in this field, particularly in the area of data reporting. So we are also working with those organizations to offer our insight into metrology and to learn from them in the areas where NIST can contribute in terms of standardization.

With that, I will close. I know we are going to have time for some discussion here at the end. I appreciate your time.

[Applause.]

DR. TEUTSCH: Great. Thank you very much. I think what we will do is continue on. Then we can take questions at the very end.

Steve, let me welcome you. Again, thank you for all your service to FDA and to the Committee in so many ways, and not only this Committee but our predecessor. Thanks so much. You will be talking to us a bit about the regulatory agency perspective.

Regulatory Agency Perspective

Steve Gutman, M.D., M.B.A.

[PowerPoint presentation.]

DR. GUTMAN: I can't think of a better swan song than to stumble across this topic, so I thank you.

FDA has a longstanding interest in standards. In fact, the original regulations in FDA for our primetime submission, the 510(k), which is what we use for me-too devices, call for the use of standards in equivalency decisions.

In the early '80s FDA initiated development of standardized, traceable methods and expected thresholds for both glucose and hemoglobin, took them to the public, and I guess they weren't ready for primetime yet because we couldn't make the sale.

So what we resorted to -- and in fact the regs were subsequently changed to accommodate for the nascent life of standards in the '80s -- is we changed the regs to call for special controls.

Our program is largely based on two operative terms for me-too devices: showing that they are substantially equivalent to a predicate and, for novel, high-risk devices, showing that they are de

novo, safe, and effective. Neither of these regulatory submissions actually calls for or requires identification of either standards, traceability, or performance against standards. I would argue that that is a weakness in our regulatory toolbox.

That has, of course, not been a deterrent to our renegade workgroup. We continue to rail for standards. FDA was a founding member of the CLSI. We are an active member of the ISO Technical Committee 212, an active member of the IBD Subgroup of the Global Harmonization Task Force, and an early proponent of the CDC's Standardization Program. So the lack of standards does not demonstrate a lack of enthusiasm on the part of our workgroup.

In fact, if you bother to look at our webpage, you can see that when we write guidance we frequently reference standards. When we develop special controls, we frequently reference standards. In fact, if you look at our decision summaries, the more "with it" companies will in fact reference standards.

We also have an interest in the material

standards that NIST is developing. We always attempt to identify usable standards, whether they are NIST, whether they are CDC, whether they are WHO, or whether they come from other legitimate sources. We have experience with the use of material standards in both pre- and post-market programs.

In terms of the formal process, there is a formal recognition process, at least for methods standards. About two dozen members of my office participate actively. We have recognized a number of CLSI standards and a smaller number of ISO standards. They are all, again, found on our webpage.

There is a formal process that these standards, once recognized, can be used in the context of pre-market review. There is a particular entity called the abbreviated 510(k), where companies can actually conform to standards. That increases the certainty and decreases the negotiation between FDA and the sponsor submitting that particular standard.

In point of fact, there is usually partial rather than complete conformance. The CLSI standards are an interesting hybrid, some more geared towards

laboratory practice and manufacturing practice. It would be fair to say the abbreviated 510(k) is not a perfect program.

I would also point out that informal use of standards is very frequent. Often pedigreed materials, sometimes from CDC, sometimes from WHO, sometimes from other sources, may actually carry a floundering company over the threshold in terms of pre-market review. While our pre-market review has, I think, weak regulatory tools, the quality system regs that are part of our post-market compliance program do in fact have very beguiling portions of the regs that might speak to. if FDA were aggressive in the pursuit of those regs, the use of standards. So there are interesting tools to look at in the future if there was a call for better standardization products.

There certainly are incentives to do this. The IVD directive in Europe very explicitly calls for the use of standards. Our transparent posting of decision summaries provides a reward for use of standard materials or methods because it becomes a matter of public information. I would argue the

STAR*D initiative and other efforts to provide clinical standardization will only be as good as the ability to have an underpinning of analytical standardization as well.

That being said, there is a long journey ahead. The truth is the status quo for routine assays -- PSA, troponin, d-dimer are three of my favorites -- is absolute noncongruence. If you look at proficiency testing surveys, you will be astounded by the laboratory and company differences. You can get a heart attack simply moving from one ER to another.

The status quo for new assays is worse because there is no proficiency testing. There is no QC material. It is gratifying to see that NIST is starting to move forward, but there is a mountain of new assays, some of them protected by IP, that might make it very difficult to create cross-lab standards.

This has all been further complicated by the fact that in the year 2009 we actually get it in terms of the complexity of sample procurement and the whimsy of pre-analytical systems in terms of impacting the results any particular system might generate.

At the end of the rainbow, there is a pot of gold. I think Mike may talk about this in more detail. There is a shift towards evidence-based medicine, even laboratory medicine.

Thank God, because there is an escalation in healthcare costs that laboratory medicine could help or could hinder which is not sustainable. In fact, consumers are increasingly interested in quality. That being said, there is no free lunch. All of this will take a lot of work.

Fortunately, there is free literature about standards, literature written, usually by dark poets, often poets who died young like Dylan or Plath. I will let her have the final word.

"Cold worlds shake from the oar.

"The spirit of blackness is in us, it is in the fishes.

"A snag is lifting a valedictory, pale hand;

"Stars open among the lilies,

"Are you not blinded by such expressionless sirens?

"This is the silence of astounded souls."

This is the path forward for standards. Thank you.

[Applause.]

DR. TEUTSCH: That last slide is going to give us a lot to think about.

I'm not sure where to go. I guess we will go to Dr. Cossman.

DR. COSSMAN: That is a tough act to follow.

DR. TEUTSCH: Thank you for being here and talking about a little bit about the clinical perspective from the Critical Path Institute.

Clinical Perspective

Jeff Cossman, M.D.

[PowerPoint presentation.]

DR. COSSMAN: Thank you very much. Steve Gutman is a tough act to follow. But, Steve, I just want to say thank you for all your service at FDA. It has been a real pleasure working with you, and I look forward to whatever you are doing in the future and maybe having a chance to work with you that way, too.

I'm here to talk to you today about something that we are doing at the Critical Path

Institute which may impact standardization of diagnostics in genetics. Let me explain as we go along here what this concept is.

In the development of diagnostics, we can expect delays not just because FDA regulates it but delays in many of the regulatory paths of diagnostics. Many times we see surprises. A diagnostic manufacturer may submit an application to FDA and it may be returned saying, you need to do this again, the data is not prepared in a way that we need, we don't understand it, and you need to redo this for a variety of reasons.

Or there may be surprises on the part of FDA, receiving data that they say is inconsistent or shoddy or not the way that they needed it in the first place.

In order to reduce surprises from either side, we have started to create a standards method that might help both the diagnostic manufacturers and the FDA communicate with each other.

What is needed for this change. This is something that has been a pattern that we have used

through Critical Path Institute. We are a nonprofit agency that is not part of the FDA, not part of industry, and in fact is not part of the government at all. It is a neutral party that helps in communication between the FDA, industry, patient advocacy groups, and researchers in order to communicate among them around science; to improve the methods that are used to develop drugs and diagnostics and bring them to the public and to the consumers.

We have a number of consortia at the Critical Path Institute, or C-Path, which involve multiple companies signing agreements and working with FDA, and in some cases EMEA in Europe, to create best-of-class methods. These can be in safety; efficacy; in the case of Warfarin, dosing; and in the case of Alzheimer's disease and Parkinson's disease, a coalition against major disease in which the largest pharmaceutical companies in the world sign an agreement to work and share data.

What we are talking about here in all of these cases is a way of verifying the quality and accuracy of biomarkers; sharing information across

these groups; finding out what is the best-of-class method for predicting safety or efficacy in a particular condition and sharing that information; agreeing on a consensus on what is the best-of-class method; and having FDA accept this method so that when a company comes with a new submission they will know that the FDA already understands these biomarkers and has, in a sense, preaccepted them as part of their application for a new drug.

Now, what we have seen in running these consortia, because C-Path creates and leads these consortia, is a common theme of diagnostics that are needed. What we felt was there may be a role here for establishing an entity that could provide a means for standardizing the testing of diagnostics before they are submitted to the FDA.

We see many bottlenecks along the way. There are problems in the development of the data that goes to the FDA and the creation, as you have heard, of standard samples. Ten companies may have an assay against, say, troponin or d-dimers, but they are not testing them against the same standard analyte sample.

So the data that is coming in to FDA may not necessarily be comparable. So if you are looking for a me-too device or a 510(k), we can't always prove that the test is equivalent because it hasn't been tested on the same clinical material.

What we are trying to do is reduce the number of surprises that FDA is giving to industry, telling them to redo the study, or the other way around, surprises to FDA from industry. We want to look at ways to improve the efficiency of the requirement for the highest standard of approval at FDA, which is the PMA, and how companies can improve their efficiency in getting to that very high bar.

Finally, there are bottlenecks, as you have just heard, in lack of evidence for payers. How does a payer know whether the test performs as required. An insurance company or CMS is going to pay for a test. What evidence does it have that that test is valuable and actually does the performance that it claims that it does.

So, how do we improve. We improve by the ways that we have already done in the other consortia

that we are involved in, and that is to find the best-of-class methods, to look for real proof and real evidence of reliability, and also for a standard submission process. In other words, multiple companies submitting data now submit them in different formats, different kinds of data, different ways of analyzing the data, different clinical samples. Why don't we standardize that and make life easier for those reviewers at FDA who are looking at diagnostic device applications.

So what we thought was, what we don't have for diagnostics is an underwriter's lab. This would be not a proficiency testing agency like CAP but, instead, further upstream in the pipeline. Diagnostic manufacturers develop tests, submit those for beta testing, say at universities, and that data goes into the submission to FDA.

Why not have a standardized format, a single agency whose sole focus is only on evaluating these diagnostic tests before they are submitted to FDA. They can be an independent body and put a seal of approval on it saying, yes, this test did perform as

claimed. We ran it exactly the way it says in the manufacturer's instructions. We ran it on standardized samples. We can attest that, with no incentive as to whether this test is approved or not, it did perform as claimed.

Why not do this in diagnostics. It is done in many other industries: in semiconductors, in food safety, for drugs. This is not a new idea. It is just a new idea for this particular industry.

To quote a famous poet, Steve Gutman, we see that the FDA is interested in this. You have just heard him say the FDA is interested in finding standards for diagnostics. In this case he is talking about targeted therapy. Our original plan was to focus specifically on targeted therapy in cancer, but for this standards laboratory we have heard from industry that they would like to see this service applied and be available for any kind of clinical laboratory diagnostic.

So what Steve told us, as you can see in the middle paragraph, this could be "a template for the validation of diagnostics in targeted cancer therapy,"

but any kind of therapy. This could be a template and a way to evaluate diagnostics before they go to FDA.

The concept here is to have two levels of evaluation of a diagnostic. One is simply performance. Does it tell you the correct level of whatever the analyte is.

Second would be a much more complex one, and that would be where you have outcomes information attached to the clinical samples so that you could determine the relative value of this diagnostic in predicting a clinical value such as response to therapy and association with a particular clinical condition.

That information would be put into a report, certified as to the accuracy of the test, and then that data could be used voluntarily by the manufacturer in their submission for FDA approval.

So, what needs does this type of testing meet. One of the goals here is something that this session is all about: having a standard repository of samples that could be used and normalized, and to create methods so that they could be reused as

consumed. Then tests could be analyzed on the same samples repeatedly and competing tests could be compared if manufacturers wished to.

It would be a neutral site. It could determine whether or not a new test equals the predicate, or is equivalent to it. For lab-developed tests such as genetics, which may not end up being submitted to the FDA as an in vitro diagnostic, it could be used to evaluate those as well so that providers, consumers, payers, and investors would know whether or not the genetic test or other laboratory-developed test performed as claimed. In other words, did it detect the SNP. Did it do what it was said to do.

What does this do. It improves reporting to FDA, hopefully improving for the diagnostic manufacturer their chances of having their data accepted. Second, it does provide a format for comparing competing products. If companies wished to, they could have their assays run in a bake-off. You could have multiple companies competing with the same assay, all tested at a neutral site on the same

analytes.

All of this information, whether it is competing or whether it is single case-by-case information, provides evidence to the community that needs to know whether or not a test performs as is claimed.

Now, we have talked about this. We are now starting to develop this laboratory. We have seed funding. It is starting in the State of Arizona. The state has provided an economic development package. We have a couple of people who are helping to start this here today with us: Mary Ellen Demars and Ralph Martel. We are looking to take on our first demonstration case, whether it is in genetics or in cancer. We are not sure yet. We are looking for ideas that would fit very specific criteria for first demonstration cases.

Because people have heard about this, we have been asked a number of questions. One, is this just another regulatory hurdle, which is exactly what I would think this is. I used to run a clinical laboratory. If I had heard about this and didn't

quite understand it, I would think the last thing I need is somebody else coming into my laboratory to inspect it and regulate it and find something else wrong.

This is not what this is about. This is not a regulatory body. It has no regulatory authority. It is completely voluntary. The whole idea is to be helpful to the manufacturer or the developer of the diagnostic.

How does this United States Diagnostic Standards Lab, USDS, relate to federal agencies and other agencies that are involved. We are looking at ways of becoming synergistic and complementary. We have had detailed discussions with NIST and Mike Amos as to how they could develop standards for the platforms for this particular testing, as well as with many of the other agencies across federal government.

What happens if the test result comes out and it is not acceptable or not useful to the manufacturer? They don't have to use it. They own that data. It is their data. They can keep it. It is not published. They can do whatever they want with

it. If they don't want to use it, they don't have to use it. They will pay for it. They will be running a fee for service and they can have the data, but if they don't want to use it, they don't have to.

How is IP protected? Everything that is run is confidential within this standards laboratory. If there is any kind of intellectual property or special methods that are being run, those will not be revealed unless the manufacturer wants it to.

How will reference standards be maintained? You have heard methods that are used for that. We know that we need to do that on a case-by-case basis as we enter into this space.

That is the story. I thank you very much for listening and for your attention. Thank you.

DR. TEUTSCH: Great. Thank you.

[Applause.]

DR. TEUTSCH: Why don't we take a couple questions at this point before we move to our final presentation. Marc.

Question-and-Answer Session

DR. WILLIAMS: This is for Jeff and relates to the last slide. We have certainly seen in other circumstances where "voluntary" things have become ersatz regulatory issues. Look at the NCQA, the Joint Commission, and others. In some sense, if you tie this to data that will be used by payers and other reimbursers, the people that control the purse strings, they may say, we are not going to reimburse any tests that haven't gone through this process. Then you have a de facto regulatory system.

While I think this is really important and this is definitely the direction that things need to be going, I would ask you to respond to that issue.

DR. COSSMAN: I don't know if everybody heard the question. Maybe I can paraphrase it. This could end up becoming too successful in the sense that even though it is not a regulatory body and there is no federal mandate that you have to go through this, it still may be something that everybody wants because the reimbursers, the payers, may require this certification or this process before they pay. It would then become a de facto regulatory body.

That is a real problem. I can't tell you I have a glib answer how to solve something like that. What we would like to do is start very small with single bites and look at one area and see the pattern that emerges in terms of the reflex of the payers.

First of all, we have to start small because there is no way that you could start with all diagnostics all at once. You are looking at the entire agency so far. We are 2.5 FTEs.

[Laughter.]

DR. COSSMAN: So it is going to be hard to handle all of diagnostics right when we open the door. We are looking for one. One of the criteria would be that exact issue. We have heard that same question from others, that we would be swamped and wouldn't have the bandwidth to be able to manage this and it would become a second FDA. We don't want to be a second FDA. We have no interest in doing that. If that becomes a non-starter, then this won't happen.

But we think that this is so valuable to do, from what we have been hearing from people, that we need to find a solution to that. I'm open to people

who have ideas and are creative and innovative here. We need to be problem-solving. But we don't want to create more of a problem than already exists.

DR. TEUTSCH: Andrea.

DR. FERREIRA-GONZALEZ: To take the next step on that question of becoming a de facto regulator, how do you envision not going that route? What I see is that people start using it and third-party payers get hold of this information. Then you can require an academic laboratory or any other laboratory to send the data to this place in order to be reimbursed by any of the third-party payers.

DR. COSSMAN: I think it is a similar issue. How do we not become a regulatory body. That is in terms of payers. Is that what you are asking? If payers would require it, then you would become a de facto regulatory body. I think it is a similar point.

We don't have the solution for that. What we are saying is we would start small, with a single example, move out from there, and see what emerges in terms of the pattern from payers. We are just starting our discussions with payers to see how they

would react to this.

In fact, the very first one I talked to -- and I won't say what company, but it is a very large insurance company -- said, we at the insurance company don't have the bandwidth to be able to determine which test someone ran. We just pay a CPT code. We don't know if they ran the test that worked well or the test that worked medium well or the test that doesn't work at all. We don't have an inspection method to be able to determine that. So right now, they wouldn't even be able to use this information. Even that hasn't happened yet.

DR. FERREIRA-GONZALEZ: They don't have the means today of identifying this, but they can ask that. If you are going to be submitting claims to particular third-party payers, then you submit information that you have been cleared.

DR. COSSMAN: They could.

DR. FERREIRA-GONZALEZ: We already have regulatory bodies to look at the quality of the testing. It seems to me that it could be, in the future, another hurdle to this.

DR. COSSMAN: Exactly. If this looks like it is an insoluble problem and is another hurdle, that is a deal-stopper. What we want to do is be innovative and creative here and find solutions for getting through this so that we can find ways around it. I don't have the answer here today, but if people have ideas, we are open to suggestions. I would be happy to talk to people in the insurance industry and CMS and see if there are ways that we can do this so that it works in a way that doesn't open up a floodgate of problems but rather is problem-solving.

DR. TEUTSCH: Great. I know we would like to have some more discussion. Thank you very much, Dr. Cossman. We appreciate that and your initiative in addressing this important topic.

Our final speaker is Mike Amos, who we all know. He will talk a little bit about the future directions in clinical diagnostic standards development.

Mike, we are going to hold you to your 10 minutes so we do have time for some discussion at the end. Take it away.

Future Directions in Clinical Diagnostic Standards Development

Michael Amos, Ph.D.

[PowerPoint presentation.]

DR. AMOS: Not a problem, not a problem. Thanks for your attention. I hope you appreciate the level of detail and precision that my NIST colleagues go to to provide standards for the various applications. I think John's table that talked about the various levels of who uses them and then Dave's table talking about the horizontal versus vertical standards gave you an idea about how we think about things.

I should probably bring my other hat up here because my boss, who is Dr. May, told me to put this disclaimer on here. I'm going to talk about things that we have learned over the last couple of years through many talks with many different people about what they consider the future of diagnostics and where things are going. At the same time, these are not official NIST programs or ideas but just food for

thought for you.

What I want to talk about today are some of the harsh realities that are really going to drive health care change in the future, some lessons learned and what I think will happen, the fact that laboratory medicine will drive a lot of this change, some measurement challenges and the role measurement technologies and standards will play, and a potential plan to enable the change.

Where we are is kind of scary when you consider that about 83 percent of our total health care costs go to cover chronic diseases, whereas the rest of it is only about 17 percent. This constitutes almost $1.7 trillion out of the $2 trillion that we spent in 2005. Forty-three percent of that is spent on hospitalizations. The scary part is the most expensive to treat are among the fastest-growing reasons for hospitalizations, according to AHRQ.

Millions of people suffer from diseases that there is little known about the genetic basis. We have a growing number of problems with kids taking drugs for chronic diseases. More and more kids are

being diagnosed with chronic diseases for which they are being treated. Diabetes is running rampant and growing at a rate of about, I think, 5 percent a year for type 1 diabetes. Kids under the age of five are now taking drugs for type 2 diabetes.

The problem is that things are not going that well in medical research. The innovation gap is really widening. There is more money going into research with not great returns on investment. There are more and more manufacturer-reported adverse events to the FDA all the time. It has grown dramatically since 1990, with billions of dollars of drugs coming off the market because of toxicity.

The future is not that great for diagnostics, really, if you base it on what has happened since 1995. This is, as best as we can tell -- and Steve's group helped me put this together -- the complete list of single protein biomarkers that have been approved by the FDA. There may be one or two recent ones. But I went through the FDA website again before I did this, and I couldn't find any more.

So things are not really looking that great

in the future. Our grandchildren are going to be spending more money than they earn on health care. Like Steve said, these trends are not sustainable and a new development paradigm is really needed.

So, what have we learned. We have learned that the human body is very complex. It is really not just made up of all those individual components. Really, disease is caused by perturbations in very, very complex biological networks. It is not simple pathways anymore. Forget what you learned in high school. There is no such thing as a metabolic pathway. It is one of these globby things.

So, what have we learned. Disease is a result of perturbations in these pathways. Genomics has been helpful, and it will continue to be helpful but it is limited. Only a very small number of single protein biomarkers are good indicators or predictors of a limited number of diseases, and more complete understanding of human physiology is needed in order to identify good biomarkers.

What is going to happen. Medicine will focus on keeping people well. It has to. The only

way we are going to really catch up in health care is by keeping people out of the hospital. That is possible. The way to do it is the fact that laboratory medicine will probably lead the way. -Omics will dominate. Complex disease signatures that are comprised of hundreds or thousands of data points will really be the biomarkers of the future.

Drug companies will develop their markets around interventional therapeutics and treatments like cholesterol and statins. They will use the same model. It will be based around these complex disease signatures. Disease signatures are measurable alterations in complex biochemical networks.

So, what happens. You get abnormalities in all this stuff, and you can do multiplex measurements and computer integration to develop disease signatures. There are a bunch of these things. We have no idea what these disease signatures are going to look like. Probably, it is going to be some sort of risk score, a number from one to 100, whether somebody is going to get this disease or not, but we really don't know what that is going to be. We hope

that it is going to enable scientists and physicians to make better decisions.

Discovery decisions will increase the drug pipeline and all those things. Better clinical decisions help people, not just the drug and diagnostic companies.

Really, in between wellness and symptoms are these transitional states. That is where the focus is going to have to be. We are really looking at markers that occur years before disease symptoms occur. They often occur long before people realize they are sick.

They are unique biochemical markers. They can distinguish health from sickness. They are going to be person-specific. The rules of clinical trials are going to have to change because each person will end up serving as their own control.

There are typically going to be parameters in blood. Those probably are the true biomarkers that we are all looking for and that could be detected with proper technology.

A disease signature is like a radar signature. A good radar operator can identify a blip

on a radar screen that is a bad guy versus a good guy. What we want to be able to do is develop similar technologies in the future for diagnostics.

One potential concept is being espoused by Dr. Lee Hood, who talks about organ-specific blood protein fingerprints as a potential way to do this. He calls it systems medicine. It integrates measurements and computers. It is basically taking a drop of blood, putting it on some analytical platform, putting it in an instrument, and then getting some data out to enable the complete visualization of what is going on in your body. That is the dream.

Why is this critical and what is going to happen. Today the healthcare markets are based on the number of sick people. Every drug company bases their market numbers and projections on the number of people they can treat. That is based on the number of people that they project will come down with a disease based on historical data.

The metrics of morbidity and mortality show the outcome is that people suffer and die of chronic diseases. It is not changing. We will see $4

trillion in healthcare costs projected by the year 2015. Like Janet Woodcock said, that is probably not sustainable.

The healthcare markets could be based on the number of people with preventable diseases. If that were the case, the metric would be the number of people positive for a valid predictive biomarker. The outcome would be that more people would die of trauma and in their sleep from old age, rather than spend 70 percent of healthcare dollars in the last two years of their life in terminal care.

Potential savings are, just for diabetes, probably at least $50 billion. Diabetes is more expensive to treat than cancer. We all know that.

What is going to happen is visualization of disease signatures. What kind of standards will be needed for this type of thing. We are really talking about the complete spectrum, but we will have to take a very logical and structured approach to it and take into account all the things you heard today from my colleagues: horizontal versus vertical standards, and what are the highest priorities of things that we

should go after.

That is really what Willie talked about. We felt, and the community felt, that protein measurement science is probably one of the biggest challenges.

These are some of the things that we are going to have to do. But two fronts are really to promote discovery of disease signatures and then, on the back end, clinical analysis of these disease signatures.

I love my boss, but I have to disagree with you. We will always have this conversation, Willie. I think, coming from industry, if I had had a set of standards that I could anchor my tests against where I didn't have to guess and empirically try to figure out what my assays were really doing, then I could have sped up things a lot in my assay development.

I think the things that Dave is trying to do with proteomics and anchoring what I call the platform standards of mass spec to make sure that your mass spec works properly, are going to really drive the future.

You have transition states and systems

medicine. That is one approach. Developing disease signatures to usher in the age of individual therapeutics and improve quality of life and help in economic security, which is, as Willie showed, part of our mission.

What is preventing us from getting there. Basically, it is the capabilities of doing these things, among many other things, but these are pretty much the major issues. It is really doing these types of measurements and the ability to analyze these types of things.

Here is a potential opportunity and a potential way of stimulating the advent of new technology. I think we are woefully deficient in our ability to measure proteins, and that is a real issue. I think we are at about the same place we were at the beginning of the Human Genome Project.

One way to stimulate interest is to have a mission to the Moon. So here is an idea. Maybe we can put a stake in the ground and say we can identify disease signatures for the most important diseases by the year 2020. The number is obviously subject to

debate, but these are the kinds of things that we would have to do and hopefully will enable some new approaches and a better way of looking at diseases and keeping people healthy.

What do we hope to learn? We have some pretty lofty goals here, but I think without new technology it is not going to happen.

One thing I can say is, when I came to NIST I was pretty ignorant of all this. I hope that the presentations today really helped you get an appreciation for what my colleagues do. I am amongst egghead scientists who focus on the nitty-gritty, nuts and bolts of measurement, and I think that that is why we are here. I appreciate your attention.

DR. TEUTSCH: Thanks, Mike.

[Applause.]

DR. TEUTSCH: Thanks to all of our speakers. We have obviously had a tour from the importance of getting measurement accurately to what the future world might look like.

We have just a few minutes, and I think we should take this opportunity to ask questions of any

of our speakers who are still here or to have a discussion among ourselves. Let me open the floor for a couple of questions.

Discussion

DR. TEUTSCH: Let me ask you, do you have any additional comments that you would like to make from the CDC perspective?

DR. KALMAN: We think that having reference material is really key to assuring the quality of these tests not only for the day-to-day QC of the tests but also for proficiency testing, which is a big deal. It was quite a large part of the Oversight report that this group did a few months back.

We did a count. I think there are about six different diseases for which there are higher-order reference materials either from NIST or FDA or something like that. We count six. On the Gene Test website, there are over 1,300 genetic tests currently available. That is a really small fraction of the current tests that are available.

So the CDC, through the GeTRM program, is trying to address this gap by just simply organizing a

volunteer effort among the people in the genetic community. We are just characterizing publicly available cell lines and DNA from the Coriell repository so that we have a larger supply of materials so that we can feel confident in knowing the genotype of these and so labs can use them for quality control and also the proficiency testing needs.

Right now the projects that we are working on are pretty much all being driven by requests from CAP for proficiency testing materials. We are starting a real large project for pharmacogenetic materials. We are going to do over 100 DNA samples for five pharmacogenetic loci. We are going to get other data from other labs as well on other loci. We are going to try to do a project for array CGH.

We were trying to do a project for Duchenne muscular dystrophy, which is something that CAP asked me to work on, but all the labs are stopping their testing because of the patent issue. So I don't know what is going to happen.

DR. TEUTSCH: Coming full circle. Andrea.

DR. FERREIRA-GONZALEZ: I want to thank Lisa for a tremendous effort and the role that she has played at CDC in getting the GeTRM program started and being one of the strongest advocates for this. I think she needs a round of applause from all of us.

[Applause.]

DR. FERREIRA-GONZALEZ: That said, like you said, there is a lot more work that needs to be done. But I think it is interesting that you have already identified through the collaboration with professional organizations or end users of different laboratories what are the current needs of the laboratory not only in proficiency testing but also reference materials that we can use to analytically validate the assays and continue quality control.

I was wondering, what is the level of cooperation between the GeTRM program and the NIST genomic program. I think a lot of the work that you have done in identifying some of the needs can be translated and the deployment of the work NIST can take over.

DR. KALMAN: I do talk to NIST on a regular

basis. Our program has a yearly advisory committee meeting. We always have a few people from NIST at our meeting, so I talk to them. Also, in the area of molecular oncology there are a few people from NIST that I have been talking to.

So, yes, I try to keep the communication lines open. But if you want to talk some more, that would be great.

DR. BUTLER: Margaret Klein went to the meeting that you had last month. We are looking forward to working more with you in the future as we get more into future genetic tests.

DR. TEUTSCH: Marc.

DR. WILLIAMS: I was going to ask Andrea's question. But then as Mike spoke, I said, if that is the vision of where things are going, then in some sense is investing a lot in genomic validated samples really worth it if we are really going there.

I guess the question that I have -- and probably you or Dr. May would be the best ones to address it -- would be, what is your real vision about where you are going to need to invest your limited

funds in terms of standards in the biomedical realm? Is it going to focus on genomics? Is it going to focus on proteomics or metabolomics? Are you going to try and do it all?

DR. MAY: I think, in the short term, Mike's vision is 2020. We have a lot of living to do between now and then.

Certainly, in the short term, the focus of the NIST's new activities is going to be on medical imaging and protein measurement science, for sure. Beyond that, we might do some other things.

If you are looking at the near future, I think for the next two to five years the emphasis is going to be on improving our capabilities to support medical imaging and developing more core competencies in protein measurement science.

That would address lots of things. It would address this disease signature issue that Mike talked about, as well as the issue of follow-on biologies.

So we are trying to increase our core competencies and put more tools in the toolkit to address a number of things. Now, in the longer term,

we are still going to continue our work in genetics. We are not going to stop those things. But if you look for areas that across all of NIST we are going to expand in, it would be those two.

Now, putting on my director of the Chemical Science and Technology Laboratory hat, certainly in the Biochemical Science Division there is going to be a greater emphasis on genetic testing and DNA-based diagnostics. As John mentioned to you, we have just done some reorganization within our Biochemical Science Division to address just that issue.

DR. WILLIAMS: In follow-up to that, our Oversight report identified, as Andrea pointed out, that this PT issue and having samples is a huge issue. We have 5,000, plus or minus, genetic tests that are out there and a small fraction of those actually have PT materials that are available and in use.

From what I'm hearing you say, I think it may be unrealistic to expect that NIST is going to be the savior riding in on the stallion at this point.

DR. MAY: That is true. But certainly, if that is a major issue that your Committee has

identified, sending a note to me to that effect, perhaps with a copy to the acting NIST director, would not be a bad idea.

DR. AMOS: Marc, just let me say one thing. It is clear that genomics is going to be an integral part of the disease signature. I think that the discovering technologies of the future are really going to focus on the ability to understand the environmental effect on the genome. So you have to have good genomic data to do that. There are all sorts of issues with the sequencing things that are going forward.

I think my colleagues have decided that genome-wide association studies are something that we don't want to do. We are looking at next-generation sequencing. I will put it that way.

DR. TEUTSCH: Mara, you get the last word.

DR. ASPINALL: I think I also, once again, agree with where Marc is going. So this has truly been a red-letter day.

DR. TEUTSCH: It is a great place to end the meeting.

DR. WILLIAMS: She is going to hit me up for a drink later.

[Laughter.]

DR. ASPINALL: The question really, Steve, was to you. I think this was a great session, with the ability to hear the different perspectives of what is happening today and getting the various approaches to that. What role do you see SACGHS taking? This is great information, but I know that tomorrow we are going to jump into priorities going forward. Where do you see this going?

I love the idea of taking some action and sending some letters to NIST. As Marc said, this is, to me, entirely consistent with the recommendations not just in the last report but in the last two that talk about gaps and the need for essentially standard-setting or ensuring quality across the system. Now we have an opportunity that doesn't require potentially major changes in legislation by Congress or otherwise but just a prioritization. I would vote for taking some action to at least enforce that.

Closing Remarks

Steven Teutsch, M.D., M.P.H.

DR. TEUTSCH: Letters we can certainly write. I think that we did get a lot of reinforcement for some of the things that we have said in the Oversight report and the importance of measurement going forward.

I think there are some follow-up things we can clearly do, because we need to monitor the implementation of that, and take some steps there.

I think in terms of our prioritization of what we need to do, we can have some of that discussion tomorrow. In terms of both short-term and longer-term actions, it has come up in various places in the prioritization process. So we should talk about that. It is not what I will do, it is what we will do.

So I think that we should think about what can be done. Certainly, letters of support are important, but we have a lot in that Oversight report as well as the PGX report that we don't want to have sit on paper. We need to move forward.

DR. MAY: A quick comment and an invitation.

NIST is going to have a new director in the next six months or so. Bioscience and health has been identified as a priority. I'm fairly sure the new director will honor that.

Having said that bioscience and health has been identified as a priority, right now we are looking at protein measurement science and medical imaging as being major thrusts. That doesn't mean we aren't going to do other things. So I would certainly extend an invitation for you to have your next meeting at our campus, if you would like. We have nice meeting facilities. It is not as convenient to the airports as down here, but the Metro does run out there in the hinterlands.

So I would invite you to perhaps meet there. I don't know whether we will have a new director, but certainly we can have you speak with the leadership and perhaps you can help to influence some of our future directions.

DR. TEUTSCH: Great. Thanks again to all our speakers.

I want to remind all of you who may not be

aware of it, in follow-up to the discussion we just had, the Second International Workshop on Clinical Cytogenetic Arrays is actually going to be a couple of weeks from now, December 15th and 16th at the Natcher Center on the NIH campus.

The goal of that workshop is to continue discussions on standardization of quality control in cytogenetic array and clinical application design, resolution interpretation, and a central database for clinical and research purposes. There is a website for those of you who might be interested in getting more information.

In bringing this session to a close, first of all, in addition to thanking all our speakers for the presentations this afternoon, I want to again express my gratitude to Jim and to the staff and everyone who worked so hard on the patents. We came a long way. We have a long way to go to get to agreement on what we are planning to recommend, but it will be great to get that out for comment. So, thanks, Jim, for your leadership on all of that.

There is a bus, for those of you headed back

to the hotel, leaving from the Third Street side. I think when you go out it is to the left.

We will reconvene tomorrow at 8 o'clock a.m., and Paul Wise will lead us through a discussion of our priorities going forward.

Thanks to everybody. Thanks for a good meeting.

[Whereupon, at 5:35 p.m., the meeting was adjourned to reconvene the following day.]

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CERTIFICATION

This is to certify that the attached proceedings

BEFORE THE: **Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS)**

HELD: **December 1-2, 2008**

were convened as herein appears, and that this is the official transcript thereof for the file of the Department or Commission.

SONIA GONZALEZ, Court Reporter