U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

# SECRETARY'S ADVISORY COMMITTEE ON GENETICS, HEALTH, AND SOCIETY

Eleventh Meeting

Monday,
November 13, 2006

Fort McHenry Room
Inn and Conference Center
University of Maryland
3501 University Boulevard East
Adelphi, Maryland

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C O N T E N T S

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P R O C E E D I N G S (8:40 a.m.)

DR. TUCKSON: Good morning.

PARTICIPANTS: Good morning.

DR. TUCKSON: Thank you. My gosh, some energy or something. Painful. We have a terrific agenda, power packed and an awful lot. So I hope the coffee is good and that you're stoked up.

Welcome to the 11th meeting of the Secretary's Advisory Committee on Genetics, Health, and Society. The public was made aware of this meeting through the notices in the Federal Register, and also announcements on the SACGHS website and listserv. I want to welcome members of the public in attendance, as well as any viewers who are tuning in through the webcast. We really do thank you for your interest in our work.

Before I begin, I want to make a few introductions. First, we are joined this morning by a special guest and an important member of Secretary Leavitt's staff, Sheila Walcoff. She was council to the Secretary for science and public health programs. Sheila will be saying a few words about the Secretary's personalized health initiative in a few moments.

Thank you very much for taking the time to join us.

Dr. Greg Downing. Is Greg here yet? I just saw you, Greg. I was just talking to Greg. He's the project director of personalized health care initiative and is also here.

Welcome to you both and thank you very much for taking time from your busy schedules to be here. We'll come back to you, Sheila, in a few minutes, but I want to thank you, Greg, for all the efforts that you have done on behalf of this committee. It has been very, very much appreciated.

I also want to thank Debra Leonard and Emily Winn-Deen back to the committee. Debra and Emily rotated off the committee after our last meeting, but we immediately, smartly commissioned them back to serve on our task forces on gene patents and pharmacogenomics.

Debra and Emily, thank you for your continued dedication to advancing the work of our committee on these important topics, and thank you for being here today to participate in the task force recommendations. Where are you? Oh, there they are. You guys are just hiding everywhere. I can't find anyone this morning.

I want to welcome three new ex officios. I've worked on this very hard, so I'm going to do this right. But I want to welcome Gurvaneet Randhawa, and Gurvaneet will correct that, except she's not there, but we are happy when Gurvaneet gets here, who has been with us before. Dr. Randhawa has focused on clinical applications of genetics and genomics and the advancement of evidence-based decisionmaking in the use of genomic technologies. This you will hear in a moment is going to be key to much of what we're going to be doing coming forward.

I also want to welcome Anand Parekh.

Anand, say it again.

DR. PAREKH: That was close, Reed. It's Anand Parekh. Pretty good, though.

DR. TUCKSON: We also practiced that he was going to say that that was close.

(Laughter.)

DR. TUCKSON: Thank you so much. The emphasis, by the way, is on the first syllable, and that's the way you can do it. Even knowing that, I messed it up.

He's the senior medical advisor in the Office of Public Health and Science, where he advises the Assistant Secretary for Health on a variety of medical and public health policy issues.

Thank you very much for being here.

Michael Amos -- I think I got that right -- is representing the Department of Commerce, and

you are the biosciences advisor to the director of the Chemical Science and Technology Laboratory at the National Institute of Standards and Technology. Mike, thank you very much.

Bio-sketches for these three outstanding people you will find in your table folders.

I also want to acknowledge new staff member Yvette Seger. I'm sorry, Yvette. To have to work that hard, because the staff here works terrifically hard. Yvette joined the team in August and has been working closely with Hunt Willard and our large population study task force in developing our final report on large population studies. Yvette came to us from Faster Cures, a biomedical research advocacy organization, where she served as research associate. She was also a science and technology policy graduate fellow at the National Academies. Her dissertation research at Cold Spring Harbor Laboratory received her Ph.D. in genetics from SUNY Stony Brook in 2004.

You may recall that in June I met with Dr. Elias Zerhouni, who is Director of NIH and our conduit to the Secretary of Health. I briefed Dr. Zerhouni about the progress of our work, and we discussed the committee's accomplishments and the ways in which SACGHS might enhance our impact and public visibility. I will tell you that meeting with Elias is always a pleasure. He is extremely well aware of what we are doing. He is up on all of the details, and what he really thought that we ought to be thinking more about is how we disseminate the results of our deliberations and of our products. He had a few ideas, in particular thinking that we ought to transform some of our reports and recommendations into manuscripts for journals. We have taken this advice to heart, and we are now working on an article about our recommendations on coverage and reimbursement for genetic tests, and we're talking to some of the people at journals like the Journal of Health Affairs and others. So we're working hard on that, and we want to have you start to think about places in your domain where you have influence or where you think it would be important for us to get our reports and recommendations out. So I'll be very, very eager to see that, and our terrific staff team would be happy to help facilitate that. So bring those ideas forward.

Our community has a very broad mandate and charter. Within that broad scope, our agenda is guided by a strategic plan that we developed as a committee through a systematic priority-setting process in March of '04. As you know, every meeting I would pull out this chart, and I'm going to do it now, because I think it is critical that you keep in front of you what it is that we said we wanted to achieve, and we have to keep checking ourselves to see whether or not we are meeting our expectations for our work.

Importantly also, I think, it's important that we take time to be thinking about whether we want to modify what's up there, what our agenda is. So I want to be pretty rigorous about reviewing with you, but quickly, about what it is that we are doing and where we are in our strategic plan. Again, I remind you, 2004 was a while ago, and so at some point we're going to need to revisit the strategic plan.

First, public concerns about genetic discrimination have been our highest priority issue. You know that we've written three letters to the Secretary championing federal genetic non-discrimination legislation. We commissioned a legal analysis of the adequacy of current law, compiled a significant set of public comments on the issue, almost like a phone book size, and to document public concerns about the issue in a more compelling way we produced a DVD, a 10-minute summary of our public testimonies. We'll be getting an update on the status of Congressional activity in this area tomorrow afternoon.

Number two, we produced a report and nine recommendations on coverage and reimbursement for genetic tests and services, and we've had a very good meeting with CMS as we have looked at the recommendations that apply to them, and they have those recommendations that they are evaluating as we speak.

Number three, we've developed a resolution about the importance of genetics education and training of health professionals and how that should be enhanced. We've written several letters to the Secretary on direct-to-consumer marketing of genetic tests and have prompted several collaborative

efforts among relevant agencies. At our last meeting in June we heard updates from the agency's working groups that were formed to address our concerns about direct-to-consumer marketing, and I am very pleased that the working groups have continued to make progress and that in July their efforts culminated in the publication by the Federal Trade Commission on this consumer alert on direct-to-consumer marketing of genetic tests that was produced in cooperation between FDA and CDC. This is just a fantastic example of the agencies working together to solve a problem, and you as a committee should feel good for highlighting it, but our ex officios ought to feel real terrific in making it happen. The alert is aimed at raising consumer awareness of the facts about "at home" genetic tests. It cautions consumers that "at home" genetic tests have not been evaluated by the FDA and urges them to be wary of the claims made by companies marketing such tests. If they're considering using an in-home test, the alert warns them to protect their privacy before doing business with an online company and to, of course, consult a health care provider.

We were enormously pleased by this action and impressed by the collaboration of it all, and I just want to take a moment to applaud Matt Daynard of the FTC and Steve Goodman and his team at FDA, Muin Khoury at CDC and Linda Bradley. The director of CDC, Dr. Julie Gerberding, was clearly very pleased as well, and her letter, which is in Tab 3 of your briefing books, affirms the importance of these efforts.

Earlier this year we wrote to the Secretary to commend his leadership in advancing the health information infrastructure and to urge his attention to the development of standards, common vocabularies and security measures to support the incorporation, interoperability and security of genetic data. I'll say more about the Secretary's efforts in this area in a moment.

Work on a large population studies report will be a major focus of this meeting. The draft report we saw last time went out for public comment this summer, and the task force made extensive revisions based upon feedback that we've received. We'll have an update from task force chairman Hunt Willard on the public comments that came in and how they helped to shape the development of the report. The goal for that session -- and let me be clear and slow down for a minute -- the goal for that session will be to come to closure on the report so it can be sent to the Secretary in final form.

One thing we're going to be doing in this meeting, again, in introducing every topic area, you're going to be very clear about what it is you're supposed to do today, so that when you ask the great smart questions or put the great input that you do, it's designed to get us to a goal. So the goal on this one is close the report and send it to the Secretary in final form. So we're going to move this today.

Gene patents and licensing. At our last meeting we decided to move forward with a study on the impact of gene patents and licensing practices on patient access to genetic technologies. The committee established a task force to refine the scope and study plan we discussed, and they have a detailed scope, work plan and timetable for us to review today.

Work will also continue on the priority issue of pharmacogenomics. Since our last meeting, the task force has refined the draft report and recommendations, and we will begin an important and very focused discussion about it in just a few minutes.

We'll also be looking closely at the issue of oversight of genetic tests. We will be updated on developments at FDA and CMS, and then we'll have a discussion about whether SACGHS should take on a more analytical role in this area. For those who are new to the committee, we'll be bringing you up to speed about our history. Our committee evolved out of an earlier committee that was very focused on this issue of oversight of genetic tests. We've sort of been able to turn our attention to other issues, and now developments are such that we are bringing that back for a decision about whether or not we need to be more involved or not in this oversight of genetic tests. So this is going to be an extremely important

discussion for us in a few minutes.

The cross-cutting issues of access, public awareness and genetic exceptionalism are integrated into all of our other work. So that's where we are with our priority issues. So I ask you to keep that in mind, and always we want to revisit it.

In your briefing books in the left-hand pocket is an annual survey that we're supposed to fill out about your perspectives about our effectiveness and whether we're meeting our goals and priorities. So if you've not done so, then you're supposed to do that and turn it in before we leave.

The thing is, if you don't think we are making the progress we're supposed to make, then you've got to say that, but we've got to then figure out what it is that we're not doing to meet the objectives that we have. But one thing at least we are is focused on what our objectives are supposed to be.

The work we've done in priority areas provides a strong foundation for us to assist HHS in other ways, and I want to talk now about new work that Secretary Leavitt would like us to undertake in the near future.

I have to say something about Secretary Leavitt. I am extremely excited about his leadership. He has been, in a way that we have not experienced before, attentive in an unusual way to the work of this committee, and he's been very receptive to talking to me as your chairman about this, and he has made his key staff available to us. We have an opportunity that we've never had before, which is to really get input and guidance from the Secretary about his agenda and how he wants to see us help to move that agenda forward. So I really want us to spend a minute now, as we pay attention to that agenda, and understand that what he's really focused on is improving the quality and cost of health care and making that quality and cost transparent to consumers. The President of the United States advanced this agenda not long ago in an executive order that requires agencies administering health care insurance programs to use health information technology as a way of sharing information on the price and quality of services. Some of his other high priorities, of course, include implementing Part D of the Medicare program, that every senior citizen has access to affordable prescription drugs. He's been working hard and I've been in a number of meetings with him on planning and preparing for the potential of an influenza pandemic, and promoting the development of electronic medical records and health information technology.

He is deeply committed to the development of personalized health care through the advancement of medical science and the transformation of the health care system, taking a systems approach. Over the next 10 years he wants to see health care system development that can support new frontiers in medicine, where our ability to exchange information, including genetic testing information, will be applied for clinical decisionmaking. Electronic health records are part of that transformation, part of what will enable health care to become more preventive, predictive, and certainly more personalized.

The Secretary also recognizes that genomics is playing a larger role in medicine and that we need to begin now to address how to incorporate this new information.

Last month I met with, as I mentioned, both Sheila and Greg to discuss our work and how we might be helpful in advancing the Secretary's agenda. The work we are doing to address the challenges of integrating genetics and genomics into health care and public health, particularly in the area of pharmacogenomics, is already well on the Secretary's radar.

Another federal advisory committee that is part of this effort is something that's called the American Health Information Community, or AHIC. This is a public/private partnership that is aimed at getting the best thinkers across health care and those who pay for health care to try to put together a coordinated way of combining performance assessment, consumer decision support, health information technology, and data that allows people to make better choices and decisions, having physicians and health care professionals have access to information so that they can make better choices and decisions,

and to do this in a way that protects privacy and security within the confines of an interoperable health care delivery system. So this is right down the middle of the plate for us.

So the last meeting, AHIC formed a working group on personalized health care and are thinking through some of the technological challenges. So it will be very important for us to stay tuned to some of that work.

Finally, the Secretary asked me to make you aware of a request for information that HHS published in the Federal Register November 1. A copy of that document was sent to you last week and another is in your table folders. The Secretary's office and America's Health Information Community are seeking input from the public and private sectors on plans for developing and using health information technology and genetic and molecular medicine for evidence-based clinical practice, health outcome evaluation, and research. HHS is seeking information on a wide range of topics, and we'll be hearing about that in a minute. I encourage you to respond to the RFI and to share the RFI with interested colleagues. Feedback is due by the 1st of next year.

So with that, and again because I think this is a moment of trying to now bring together this health information technology, this ability to have information about personalized genetics combined with enhanced consumer decisionmaking, combined with health providers and hospitals having access to information, all of that coming together now in a new and interesting way, I want to turn to Sheila and see if she can bring us up to date a little bit more on what is going on here and how, from the point of view of the Secretary's office, this committee might be more helpful.

Thank you for joining us.

MS. WALCOFF: Thank you, Reed, for the opportunity to join you and the SACGHS members here today in your important work. As you mentioned, the work of this committee is highly relevant to the Secretary, in particular one of his top-ten initiatives, and that is accelerating personalized health care.

Under the leadership of Secretary Mike Leavitt, the initiative he's undertaken will improve the safety, quality and effectiveness of health care by leveraging advances in genomics and health information technology. The convergence of these will be a powerful force in educating consumers and providers and enabling better clinical outcomes. His focus is primarily on how to improve health in a more patient-centric way.

However, to fully realize the potential of personalized health care, we recognize that we will need input from many important stakeholders, including the science community, the provider and patient community, and the health information technology community.

At your prior meetings you discussed many of the areas of importance related to science and public policy, and we eagerly await the work of this committee. I've briefed the Secretary extensively on the work you have been doing, and I can tell you that he is eager to see the product that you're producing over the next several months, and he appreciates what you've done previously.

Let me share a few other points that I think might add to what Reed has already mentioned in terms of what we're working on in the Secretary's office and across HHS. As Reed mentioned, the Secretary has been highly focused on using information technology to advance health care. At the October 31 meeting of the AHIC, it was recommended that a formal working group be established to address the information technology aspects of personalized health care. Some of the recommendations that you can expect to see from this group include standards on how to incorporate genetic information and genomic test information into a personal electronic health record. Other issues that this working group may address include integrating databases and including genetic and medical test information as part of the analysis for clinical decision support.

In conclusion, I'd like to say that we recognize the many thoughtful hours this committee has

devoted to working on these very important issues, and that list that you had up earlier really highlights the focus areas that we have been discussing in the Secretary's office over the last several months. We have a countdown clock. The Secretary feels a great sense of urgency in trying to do as much as he can to accelerate this area during his tenure at HHS, and I have it sitting right on my desk, and I believe we have less than 800 days. We want to focus on what we can accomplish in the near term but, importantly, make sure that we are on the track, and this committee is the perfect forum to continue that work beyond his tenure on this really important public health area.

On behalf of the Secretary and Dr. Greg Downing, I'd like to thank you for having me here today. We'd like to discuss these issues in greater detail at your next meeting, and I hope you will allow us to come and give you a more fuller briefing on where we are in terms of this initiative. I look forward to seeing you again then.

DR. TUCKSON: That's terrific. Again, I want to really acknowledge Greg as well, and I don't know how long Greg will be here. I know the Secretary has asked Sheila to go back downtown, so she's going to have to leave in just a minute. But Greg, I know you've been really attending, so however long you're going to be here, we really want to use you. But I know you'll be following up.

I know we've got a busy agenda, and I want to move us forward, but I just want to make sure if there are any questions you may have of Sheila or Greg, since we have them here. Again, I want to keep center for you that the 800 days -- when they tell me they have a countdown, that's not a countdown to figure out how quick they can go home. The countdown is they're going to make some changes, and I will tell you from where I sit, and you all may have seen what the impact of this is from where you sit, this activity that they are engaged in, both the AHIC, the President's order, the personalized health care agenda, the interoperability of health data and information, the transparency of information about quality and performance being fed into physicians, hospitals and consumers, this stuff is transforming the way in which health care is delivered. It is a sea change. You know that IBM commercial? "This changes everything." This is one of those "this changes everything."

So I just want you to be thinking a lot, especially when this pharmacogenomic stuff, but our work around educating the public, around anything to do with data systems, and the large pops, all of that is connected in here. So you really do want to be making sure that we are in that 800-day agenda.

MS. WALCOFF: Well, thank you very much, and I also want to recognize Dr. Greg Downing. He really is the director of our personalized health care initiative and has done an enormous amount of work in a very, very short period of time and is an incredible force supporting the Secretary in this initiative, and as you said, it's important for us to keep in mind all of the activities that are going on in this area. Close coordination, transparency of activity and the participation, the meaningful participation of these stakeholder groups is going to be essential for us to achieve the objectives that we all share, and I thank you very much for supporting us in that.

DR. TUCKSON: Terrific. They have nailed this pretty well, but I'm just looking to make sure there is no question.

With that, then, Sheila, thank you. I know you've got to get back down the way. Greg, as long as you can stay, you're more than welcome.

MS. WALCOFF: Thank you.

DR. TUCKSON: Thank you so much.

We have a couple of things before we move to our pharmacogenomic session. Didn't we plan this agenda well?

Public comment sessions are scheduled for both days. Individuals who would like to provide testimony and have not already signed up should do so at the registration desk.

Two housekeeping matters related to important topics, lunch and dinner. To save time at lunch, I want to encourage committee members to order a boxed lunch. So please fill out the form in front of you, or else Abbe Smith will be very upset with you.

We will also be having a group dinner tonight. If you can attend, please let Abbe know at our first break.

Now for the technical commercial from our sponsor, Sarah Carr, and all the technical rules about the ethics.

MS. CARR: Well, I won't go over all of them. I just wanted to highlight a couple, and I do this at every meeting, so I know you probably know what I'm going to say by heart. But it's important, so it does bear repeating.

As you know, you've been appointed to the committee as a special government employee in order to serve the Secretary and the public. This is a special category, but you are nonetheless subject to the same rule that apply to regular government employees. These rules are outlined in a large document that you received when you were appointed, and I'm just going to highlight, as I said, two of those rules, first about conflicts of interest. Before every meeting, you provide us with information about your personal, professional and financial interests, and this 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 our 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've 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.

As government employees, you are also prohibited from lobbying and thus 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 the activities associated with this committee. Just keep in mind that we are advisory to the Secretary of Health and Human Services and we don't advise the Congress.

As always, I thank you for being attentive to these rules, and we appreciate your conscientiousness very, very much. Thank you.

DR. TUCKSON: Now to the meeting. As you know, we are in the process of developing a report to the Secretary on pharmacogenomics and the opportunities and challenges associated with its integration into health care and public health. At our last meeting in June, we discussed some preliminary straw man recommendations. Following that meeting, the Lewin Group prepared a draft report, and staff revised the initial recommendations based on the committee's input. The task force met in September to further develop the report and recommendations. Our colleague, Kevin FitzGerald, who has assumed the chairmanship of the task force following the great work and leadership of Emily Winn-Deen, will present the results of this work, and we will have an in-depth discussion of the issues identified in the report and the revised recommendations.

We're going to spend about four hours on this important topic. By the end of the session, we need to have reached consensus on whether the draft report is ready to be released for public comment or whether further work by the task force is needed. A copy of the draft report is in your Tab 4 of your briefing book.

So with that, again, you're going to listen to these things, you're going to go through it

systematically, and at the end of the day you're going to make a choice, after four hours or less, about whether or not the report is ready to be released or whether it has to go back to the task force, and whether it's released for public comment or whether it comes back to the task force.

With that, Kevin.

DR. FITZGERALD: Really, I'm just a spokesperson for Suzanne.

Thank you, Reed. As you heard this morning, I will have the privilege of giving you an update on where we are with our report on pharmacogenomics, and I would like to ask your patience while I begin by giving you a little more background -- Reed has already given you some -- before we dive into the report. First of all, just to say much appreciation for the task force committee. People have worked very hard, given marvelous insight and input into this report, and as usual there are some names missing from that list of people to thank, because regardless of how many times I tell them to put their names on there, Suzanne and Sarah and Yvette and Amita refuse. So there you go, but we don't want to forget them and all the incredible work that they have done in getting to where we are today.

Why are we here? Well, again, as we just heard, the great impetus to pursue personalized medicine and how pharmacogenomics will be a part of this, especially in delivering the right drug at the right dosage to the right patient at the right time. There are a variety of drivers behind this impetus. We have broken these down into research and development, health care system, public interest and public policy, and this comes right out of the Secretary's Personalized Health Care Initiative, as we've heard, which is one of the major initiatives for the Secretary.

The reason behind this, again, is because pharmacogenomics has significant promise.

By the way, I'm sorry. Yes, you do all have these slides in front of you. It's the handout from today, and we are currently on number 5. So you don't have to twist your necks around and pretend to be owls or whatever. Just read off the paper.

But for our Internet audience out there who don't have the handouts, in addition to the many promises that pharmacogenomics offers as far as improved productivity, increased safety and more efficient use of drugs, there are obviously many challenges that must be addressed in order to get pharmacogenomics integrated into the clinical and public health care practice.

What's our role in all this? Again, as we've already indicated, identifying the opportunities and the challenges that are ahead of us, and advising the Secretary on how the federal government can help to advance the opportunities in this field and to address the challenges; in other words, to develop this report and these recommendations specifically for the Secretary.

A little history. As you heard, we had the informational sessions. Well, you haven't heard this yet. We had the informational sessions a year and a half ago, in June. Then there was the approval of a report outline a year ago in October, the compilation of the federal pharmacogenomics activities, which you can find in Appendix A. We will mention that again. They are extensive. I think it's important to be aware of what's going on because this will be part of the challenge of integration. Then development of the draft recommendations that we put forth in June. We took your feedback and your responses on those and tried to rework the report integrating those responses and trying to move ahead so we could develop a report and recommendations for the Secretary.

So following the June meeting, the staff revised the draft recommendations based on our discussion, and in spite of the guidance of the new task force chair we were able to move ahead. The Lewin Group, if you need to identify the Lewin Group, look for the people in the room who look the most harried and dependent on caffeine. That would be that group over there in the corner, because we really put them through their paces these past several months, and they did tremendously well. So they developed the draft report. We brought that to our meeting in September and worked that over and

dragged the horse to the middle of the stream so that we could get them off the horse and put them on a high-speed speedboat and send them down the river. They took our recommendations from that time and put them in the draft report that you see before you today.

So what are we here to do today? As we've heard, we want to ensure that all the major opportunities and challenges associated with pharmacogenomics have been identified. We want to ensure that the draft recommendations address these high-priority issues, and we want to ensure that the draft recommendations are the appropriate solutions for addressing the issues. So as Reed mentioned, we want to reach consensus on whether or not the draft report and recommendations are ready for public review. Of course, the most important goal is not up there on the slide, but that is to keep Reed happy. So that is why we're going to work very efficiently through these few hours that we have to achieve our consensus on where we are.

We want to get to this point so that the next planned steps might be pursued, however we decide to go at them today. Those steps would be, of course, to revise the report and recommendations based upon today's input, and then the Lewin Group will go out and look for input from 15 federal and non-federal expert stakeholders on various pharmacogenomics issues. This is scheduled to be done this winter. Then, of course, we will seek general public comment, which would be sort of late winter and into the spring. We would love to finalize the report and recommendations next summer and to release the final report in fall 2007 so that we don't take too many days off the Secretary's 800, or as few as possible.

The way the report has been structured for today is that we took three overarching themes: research and development; who are the gatekeepers that are facilitating or inhibiting the development of pharmacogenomics, appropriately or inappropriately; toward the implementation of pharmacogenomics to improve outcomes in clinical practice. Now, as far as the research and development piece, this involves, obviously, basic and translational research, clinical research, and also the infrastructure enabling research and development, and then the ELSI issues involved in research and development.

In this section, we had five recommendations which break down into 14 subparts, and we will go through those piece by piece to identify if we have covered the terrain well and have articulated what the recommendations should be.

We will then move on to the next section. Again, these are the gatekeepers, industry, FDA, CMS and other third-party payers, and clinical practice guideline developers. In this, there's one set of recommendations, Recommendation 6, that has three subparts. It may appear to be a smaller section, but it was a section that was identified by the task force as critical to pharmacogenomics moving forward and requiring our direct addressing of these groups.

Then finally we will look at the implementation of pharmacogenomics, and that will involve education and guidance, information technology, economic implications, again the ELSI issues, and coordination of all the HHS pharmacogenomics activities. As you can see, there are a variety of recommendations here, also with about 14 subparts.

So we'd like to walk through the three overarching sections one at a time, go through the issues that we've identified in each section to make sure we've hit the major ones, and we're not obviously going to be able to do everything, but we want to hit the big ones, then consider the recommendations we have drafted and consider if they're going to be adequate to the task of identifying the issues, and then finally, since no institution can do everything all at once, the thought was that perhaps we should attempt to identify what the recommendations of highest priority should be so that we might be able to give, if we want to -- this is not written in stone, but we thought it might be useful to give back to the Secretary some of the recommendations which we would consider to be particularly high priority.

In trying to pursue this, we went to the task force and asked them which recommendations they came up with that they considered to be high priority versus the low. It's a simple high/low kind of delineation, and the task force identified 12 high-priority recommendations of the 31 subparts, and we have identified those by the little bouncing star on the right.

Now, as we know, stars may appear to be permanent, but they are not. They evolve, too. So these stars are not set in the sky. We can move them around. We can remove them. We can place new stars somewhere. It's our chance to play God. We can do that with this report. So I invite you to not feel like these things are set in stone. What we want is your feedback that we can give to the public and get their feedback on what we have come up with.

Okay. So there's one thing that we learned in Jesuit education. It's repetition, repetition, repetition. That's how we learn. So again, why are we going to do this? The issues are does the report cover the major issues, either any issues that have not been but should be raised in the report, what issues are of the highest priority?

Recommendations. Do the recommendations as they are currently worded sufficiently address a high-priority issue? Are there any recommendations that have not been but should be included? Are there any recommendations that should be deleted because they are low priority, they will not have enough of an impact on the problem, or they are not implementable at this time?

Then the prioritization. To what extent will addressing this issue via this recommendation advance the goals of pharmacogenomics, and is the federal government in a position to act upon this issue or recommendation?

I think now that you've heard this several times, everything is pretty clear in our heads, so we can start to get into the first section, which is research and development. Again, this breaks down into the four subgroups that I have mentioned before, and we want to look at the issues at this time. We'll get to the recommendations after we have gone through the issues.

Here are the issues. Basic and translational research. We have identified issues that say that more basic research is needed to advance understanding of the biochemical pathways associated with drug metabolism and drug action; the genes involved in these pathways and genes related to the safety and effectiveness of drug treatments. In addition, more translational research is needed to apply this knowledge to the development of clinically useful pharmacogenomics technologies. Finally, translational research studies, if designed carefully, can themselves be a source of data for downstream studies of the clinical validity and clinical utility of pharmacogenomic tests. These are three issues that we have identified.

When one looks at the co-development of pharmacogenomics drugs and diagnostics, other issues arise: the possibility of resistance by industry to co-developed drugs and diagnostics. Why? Concern for market segmentation, uncertainty about FDA regulations of co-developed products, the requirement for new collaborations between drug and diagnostic industries, and coordination of development processes. This can result in expedited FDA approval, fewer label changes and greater likelihood for provider uptake.

What about the application of pharmacogenomics to abandoned drugs? Many drugs have been called "abandoned" because they have failed to detect a significant treatment effect in a broad enough population group. A post hoc analysis of clinical drug trial data for which genotype information is available can enable the rescue of abandoned drugs for use by smaller population of high responders. In this area again, it's going to be important to look at what the incentives are for pursuing identification of new indications for existing drugs, because these incentives are mixed. We have this little breakdown here. This is not in the report as structured here, but this is what we put together.

If you look at the patent status, for instance, you could see that an industry might have more incentive if the drug or device is still under patent, less incentive if it isn't. If the adverse drug reactions are severe, there might be more incentive to pursue this, less if they are mild. There's certainly more incentive to pursue this if there's no availability of alternate treatments. On the other hand, if there is, there would be less incentive to pursue this application.

When we get to the orphan category, we have other issues that we have to look at. There are differences in thresholds for drugs in diagnostics. Right now, the orphan drug threshold is it has to be less than or equal to 200,000, while the diagnostic threshold is less than or equal to 4,000. This could favor development of pharmacogenomic drugs, but not their accompanying diagnostics. So the question here is it is unclear whether the FDA would consider a pharmacogenomics-based drug and orphan product if it confers large benefit to an orphan-sized population but a modest benefit to a large population, and this could be seen similarly for a diagnostic.

Then when we're trying to put the two together, how does one balance these differences in the 200,000 and the 4,000?

Clinical validity and clinical utility. Most pharmacogenomics research has yet to be translated into clinical practice. Adoption will hinge on evidence of clinical validity and clinical utility, and yet little evidence of this validity and this utility currently exists.

As far as infrastructure is concerned, pharmacogenomics research could benefit from integration of research and clinical databases, repositories and records. However, there are issues in this integration because data collection storage, modeling and transfer within and among pharmacogenomics databases have a lot of challenges, in infrastructure and in support, because there's variation in data formats, EHRs are in early stages, and there are different funding streams, stakeholders, administrative protocols, and organizational cultures.

As far as the ELSI issues involved in research and development, we have the privacy and confidentiality concerns relating to research records. Data access and utility may be lost in exchange for gains in data protection. As things are structured now, it is often seen as a tradeoff. One has to balance the protections of privacy and confidentiality against access and utility. Does that have to be the case? Are there new and creative ways around this problem, or is this a balance that we're going to just have to strike?

Secondly, pharmacogenomic test results may reveal secondary information. What do we do if they do? There are discrepancies between human subjects research regulations, the Common Rule versus FDA regulations. Not requiring pharmacogenomics testing as a condition for drug treatment could increase drug company liability risk. How do we address those issues?

On a more social perspective, indeed pharmacogenomics promises to advance the development of personalized medicine by identifying individual differences in drug response. However, that very identification could continue to stratify subgroups, and stratify them along categories that are problematic such as race. The example currently in the literature and in the media is the BiDil application. Or you could associate molecular subgroups with race, and that could reinforce the idea or the concept of race as a biological construct, and that could limit the availability of pharmacogenomic-based drugs to certain subpopulations. How do we continue to deal with that issue?

So those are the issues that we raised for this section. What I'd like to do now is ask these three questions: Are these the major issues? Are there major issues that we have missed? If these are the major issues and these are good, are there some that aren't of high priority and that we don't need to include in here, and which ones are of the highest priority for the federal government to address? What I can do is take some time now to get your feedback before we launch -- remember, we're going to launch

into the recommendations after this, and we can then see if our recommendations do indeed address the issues that we have raised.

So first of all, I'd like to ask if anybody has any responses or reactions to the issues as they have been laid out in the report. Cynthia?

MS. BERRY: I don't know if this rises to the level of a major issue, and Reed will probably know more about this than I, but I do know that there's been some discussion about comparative effectiveness and having AHRQ and HHS and other entities helped by comparing drugs against one another to do the research so that across-the-board payers and providers would have access to information about which drugs would work best. That, I think, is gaining some interest and momentum, and I'm just wondering if it should be addressed even if in just a small way in this report, because it sounds on its face incompatible with the notion of personalized medicine, but I think there can be ways to reconcile the two, and I'm just wondering if maybe some passing reference to it at least would be worthwhile.

Reed, you might want to expand on it, because I don't know enough and I haven't been participating in that group. But I know that there are several sectors of the health care industry calling for this, and I think HHS is aware of it.

DR. TUCKSON: I don't know if I know a lot more than you. I mean, the key issue here, obviously, as you have underscored, is that people really do want to have information about whether this new thing, whatever the new thing is, does it work better than the old thing. If it does, is it more cost effective when you look at the total management of the condition, from diagnostics through the therapeutic implications, to the testing cost and implications, to the safety, to the convenience. So I think it is right down the middle of the plate, Cindy, because what this is ultimately saying for these new personalized pharmacogenomic products is how do these things fit into the overall health care landscape in terms of throwing out old stuff and replacing it with new stuff, or is this synergistic or additive or combinatorial or whatever. But if you don't have that information in a health care industry like this, with 48 million uninsured people who can't get at anything, it will be very difficult for the new thing to ever break through.

DR. ROLLINS: I also would like to comment on the initiation of some type of comparative analysis in terms of diagnostic tests. I know that CMS has commissioned AHRQ to look at various tests for genetic cancer disorders, and one of the things that we've also asked them to take a look at is the effectiveness in terms of not only effectiveness but also the accuracy of the test, looking at measures of accuracy, including such things as sensitivity, specificity, receiver-operator characteristics, as well as likelihood ratios. So in that instance, yes, there are comparative tests which might be applicable in terms of determining whether or not one particular test is more appropriate than another.

DR. FITZGERALD: Francis?

DR. COLLINS: One of the practical issues with implementing pharmacogenomics in the regular standard of care medicine is the need for rapid turnaround and results, and clearly many circumstances where one would like to adjust the plan about what drug to prescribe or what dose to prescribe are not well served if it takes a week or more for the test to be returned. So the prescriber can make that decision. In fact, I think this could be potentially quite a major issue.

Until such time as everybody has their entire genome already pre-sequenced and sitting in their medical record, where it simply becomes a matter of a computer search to get the genotype, we are going to be, I think, very much at the mercy of what kind of technologies provide the kind of point of care, rapid turnaround results.

I didn't specifically see that flag as a research and development priority, but clearly that could well turn out to be rate-limiting. If we have wonderful data showing, for instance, that in the presence of

a particular, fairly acute medical illness a particular pharmacogenomic test would be valuable in terms of illuminating what drug to give and at what dose, but you can't get that result quickly enough to actually influence that decision, then people will continue doing what they've been doing all along. So this notion of coming up with a means of accelerating turnaround time for these kinds of genotyping experiences when it comes to pharmacogenomics it seems to me has probably not gotten as much attention as it should, because until now most genetic tests are done in central laboratories where samples are shipped, and if it takes a while for the results to come back, in many instances that has not been so critical, but here it could be. So I just wanted to flag that as another potential research need.

DR. FITZGERALD: Thank you.

Andrea?

DR. FERREIRA-GONZALEZ: Yes, I just want to bring up another issue to the committee. I sit on one IRB panel within our institution. Our institution has four IRB panels that are looking at some of this review. One of the things that caught my attention going through our current draft report is that it's very important as we move forward for our translation and research and the clinical research that when testing is going to be done, to go back to the patient or to put patients in different categories because you have a certain genotype or you will act upon a specific result from the laboratory, that these tests need to be performed in a CLIA-certified laboratory. There's current regulation, because even research laboratories are under CLIA. If you're going to report back the results, I'm not sure if all the IRBs throughout the country are really aware of this issue.

So either through communications at the Office of Human Subjects Protection or some other venue, make all IRBs aware of this particular federal regulation.

DR. FITZGERALD: Scott?

DR. McLEAN: To follow on after Dr. Collins' point about the practical implications of how to get the tests done at the right time, there is the prospect of doing presymptomatic testing so that you have those results in hand at the time that you need them for an acute illness or for an acute need. The military has a little experience in the area of doing G6PD testing beforehand in case you need anti-malarials that may or may not cause problems, depending on what your test results are, and the same sort of approach to illness might be leveraged with certain presymptomatic testing for pharmacogenomic applications.

DR. FITZGERALD: Scott, would you see that short of falling under the same issue as Francis?

DR. McLEAN: Yes, in terms of practicality, but it does raise a lot of ethical questions when you go down that road, but it will come up. If you're in a practice and you want to prescribe a particular medication but you know that you're going to run into problems based on the genetic profile of your patient, then you can know ahead of time that you're going to need to select a particular drug with better benefits.

DR. FITZGERALD: Okay, great.

What I'd like to do is just get a sense of the committee, where we are on these things. Again, as I said, nobody can do everything. We can't put everything in the report and all that. So what I heard so far is we have three issues that we can certainly put in. Now, let's start with Cynthia, because she had the first one.

Could you restate it and state it as you see it specifically relevant to the research and development section? Because this is the section it will be going into rather than, say, the application section, which we'll get to later, but if you want to bring it up again, it might also be applicable there.

MS. BERRY: Well, that's why I wasn't sure. I had a couple of issues written down, and I was trying to categorize them, and I thought this could potentially be in either the research section or perhaps coverage. I don't know how you'd characterize it. It certainly doesn't matter to me where we put it. I just

know that it's out there, and maybe when we have someone from AHRQ, perhaps others could inform us a little bit better and we can bring it up at a later time.

DR. FITZGERALD: Okay. I'm just guessing that that one might go better in the third section. So we're going to hold that.

Francis, definitely looking in R&D, how would you specifically phrase that?

DR. COLLINS: The need for additional research in rapid turnaround cost-effective point of care genotyping for pharmacogenomics.

DR. FITZGERALD: Okay, great. Got it.

Andrea?

DR. FERREIRA-GONZALEZ: I think just a sentence or two, and I'm not sure how you dealt with this issue, where the Secretary could work with OHRP to remind IRBs throughout the country that they need to have CLIA-certified laboratories performing testing when results go back to the patients, either through putting patients in specific different arms or different dosages. Every time a result of this testing goes back to the patient, it needs to be from a CLIA-certified laboratory.

DR. FITZGERALD: Okay, we got that. I think what we may have to do is, when we get the report more fleshed out, we'll have a good idea where that could slide in.

DR. ROLLINS: In terms of adding on and coming up with specific wording, and whether or not you put it in this section or another section, it might be something like, "In addition to looking at the clinical utility and clinical validity of the test, measures also evaluating accuracy should also be taken into consideration."

DR. FITZGERALD: All right. Is that good with what Francis said in also incorporating --

DR. ROLLINS: I think so.

DR. FITZGERALD: Good. Great. Excellent.

Yes, go ahead, Debra.

DR. LEONARD: One of the areas of research that I've noted as I'm trying to implement pharmacogenomics in a health care system setting is cost effectiveness research. What is the cost effectiveness of spending the money to do a test on 100 percent of patients where you know 10 percent of them will have a variant, versus what is that saving you in adverse outcomes? This type of research is really needed to support the clinical implementation of pharmacogenetic testing.

DR. FITZGERALD: Currently, we have that in the third section of the report.

DR. LEONARD: So there are research parts in the third? That's what I'm not sure about, where it goes.

DR. FITZGERALD: What do you mean by "research"? Right. So there's certainly the identification of a need for that kind of information as one tries to apply what the basic science and translational data is going to be to the clinic. But if you think it's important to have a statement about that in the R&D section, that's --

DR. LEONARD: Well, there are public health faculty who would like to be doing this research but don't have the funding opportunities to support their efforts.

DR. FITZGERALD: Okay, that's good.

Michael?

DR. AMOS: In reading the report, there seem to be some assumptions that I want to make sure I understand. The assumptions are, as Dr. Rollins was saying, that the tests are accurate, and I want to make everybody understand that there are only a handful of clinical diagnostic tests that currently have standard reference materials available, out of the 1,500 or 2,000 tests that are done all the time.

The other part of this is that in order to make the dream a reality of pharmacogenomics, and to

get to some of the basic pieces that you need here as far as gene expression for everyone, genetics for everyone, to really make this happen, the technology simply is just not there right now. In order, as Dr. Collins said, to have a gene sequence for everyone, it still costs about a million, roughly a million dollars per person. That has to get down to $1,000 or less.

The accuracy of the gene expression measurements, the clinical microarrays and things like that, NIST has a major program in trying to figure out how to make those tests work better. Just the signal transduction problem is a big issue.

So there is a great deal of hope in this, but the technologies just don't exist to really make that happen.

DR. FITZGERALD: Emily, go ahead.

DR. WINN-DEEN: I just wanted to address that comment. I think the technologies to do rapid genetic testing are coming along, and there's actually an RFP out from CDC right now to develop rapid point of care testing for avian influenza based on genetic analysis. I think what you'll see coming out of that RFP is funding for a number of different technology platforms which could then be leveraged across, because you're still doing genetic testing, whether you're doing human genetics or infectious disease genetics, into the pharmacogenetics area. So I think one of the things we should do is make sure we're closing the loop between those kinds of activities within CDC in an area which might be perceived as quite different from this and understand that that same technology platform that CDC is funding and helping to move forward in terms of getting to rapid point of care molecular testing can also be applied in pharmacogenetics. So it's sort of double bang for your buck.

DR. AMOS: Yes, there are a lot of those. I mean, DHS has got tons of money going into rapid genetic testing with bio-threat agents that could be leveraged against what you're doing as well. But the other part of this is integrating all that data into some form that can actually be used and studied and learned from to implement new biomarker discovery. Dr. Gutman will tell you that if you look at the FDA website, there have been no new protein biomarkers approved by the FDA over the last 10 years. So the system for discovery is a bit broken right now, and I think you have an opportunity here to change that.

DR. FITZGERALD: The two of you, in the report as it stands now there are a couple of different places where we emphasize the need for -- I'll call it education or public access to information, and this could certainly be in there. We certainly want to discuss the hopes and the goals of pharmacogenomics, but also make it realistic and let people know where it is we stand now. So that I think is already in there. We can be more specific in that regard.

But I also gather there's the issue of the cooperation and the interaction of these different groups that are already involved in it. We also try to address that in the report in some places. We can, again, be more specific in the report as to the issues you raise.

But then there was a third thing I was hearing, and actually it may have been more specific. I think maybe, Emily, you were talking about it in particular, a step that needs to be taken that is very concrete. Could you just outline that again?

DR. WINN-DEEN: I think it was really a reiteration of Francis' point, that it's wonderful to discover biomarkers, to validate biomarkers, but if you can't deliver the results back to the patient in a timely way for a physician to take action, then you've missed the implementation part of it.

DR. FITZGERALD: So that falls under that. Okay, good. Thank you.

If it's all right, and we do want to keep moving, let's get on to the recommendations, because I think that's really where we're going to have the rubber meet the road here.

What we have now, again, we are looking at the wording of the recommendations. Do they

sufficiently address what they are intended to address? Are we missing any? Are there some that are there that don't need to be there because they're not a high priority, because they won't have enough impact on the problem, or they're just not implementable at this time?

So how will these recommendations advance the goals of pharmacogenomics, and is the federal government in a position to act upon this recommendation? Here's our first one, Recommendation 1A. If you wish, in your executive summaries, starting on page 5, you have the entire recommendations spelled out. On some of the slides we've truncated it a little bit, obviously due to space limitations. So if you want to follow along, on page 5 of your executive summary you have the recommendations beginning. We'll start with the basic and translational research ones, and this is 1A, that the "NIH should invest more resources into basic research on the biochemical pathways associated with drug metabolism and drug action, the genes involved in these pathways, and gene functions related to the safety and effectiveness of drug treatments." I think that's exactly how we have it worded in the executive summary, so these two are the same.

Any comments on this particular recommendation? Debra?

DR. LEONARD: It's really the genes and gene variations, because we very often know the genes but we may not know the gene variations. So somehow the gene variability from person to person is key to this recommendation, I would think.

DR. FITZGERALD: Okay. So you would want to put in "the genes involved in these pathways and gene variability and function"? Or would you just --

DR. LEONARD: You could say "and gene variations and functions related to the safety and effectiveness."

DR. FITZGERALD: Great. Thank you.

Everybody else is comfortable? Great.

Next, 1B. "NIH should support more translational research focused on the development of clinically useful pharmacogenomic technologies." These are sort of maybe boilerplate in one sense, but these were things that certainly came out of the report.

Oh, there's more. I'm sorry. There is more there in the executive summary, if you want to look at that.

DR. AMOS: Is it appropriate to comment on the philosophy used to do these sorts of things? I mean, up to this point, a reductionist has been used, one protein and one gene at a time. There's some broader work being done, but up to this point I think some of these -- like I said, there have been no new biomarkers. So I think it may be important for us to comment on the philosophy used up to this point, because no new biomarkers in 10 years is pretty significant to me. Are we taking the right approach, or should we be taking a more systems approach, looking at the systems medicine or systems biology approach to some of these things? Because right now, things aren't moving as quickly as we'd hope.

DR. FITZGERALD: We can certainly raise that issue, and I think that's a good thing to bring up in the research and development section, to say this is how we've gotten where we are, and in that process this has raised the question that you raise, do we need to be more open than we are currently to a more systems approach. We can do that. Does that for you translate into a specific recommendation, or is it okay just to put that in the -- I mean, to be clear and to put that in the issue?

DR. AMOS: I'd open it up to the committee to discuss.

DR. FITZGERALD: Okay. Anybody?

Yes, Debra.

DR. LEONARD: I'm concerned about the statement that there haven't been any new biomarkers in 10 years, because I'm aware of new biomarkers being introduced into the clinical testing

arena yearly. So I'm not sure where that statement is coming from.

DR. AMOS: If you look at the FDA website and look at the new PMAs in diagnostics, I'm talking about protein biomarkers. There have been some new genetic biomarkers approved.

DR. LEONARD: What about the triponin?

Francis, maybe you can comment as well. I don't want to be hanging out here on my own at the end of the limb.

DR. COLLINS: I'm a little confused by this discussion as well, because I think we're not talking about the whole universe of biomarkers here, we're talking about pharmacogenomics, and to the extent that we have identified promising but perhaps not fully clinically validated examples of genetic variations that are associated with drug response -- I mean, take all of the P450 opportunities, all of the VKRC1s, all of the things that we know about things like TPMT, I would not say at all that we're in a circumstance where there hasn't been a lot of progress. I think what's missing is that next step of full-fledged clinical validity established in prospective trials. But I don't think we need a systems biology approach to identify the potential candidates to put into those trials. I think the main rate-limiting step now is the trials themselves.

DR. LONG: To follow up on that, maybe Recommendation 1A and 1C should come before 1B.

DR. FITZGERALD: You want 1C to come before 1B. Is that right?

DR. LONG: Or said another way, if 1B comes after you put 1A and 1C together, that's the next step, taking those who were involved in the basic discovery and linking those who are doing the trials, the studies of the people who are actually being treated with drugs, so that they can collect that information and draw the conclusions, take that next step, as was just said.

DR. FITZGERALD: Now, Rochelle, just a quick question. I think we broke these out, not that they're not related, but to try to emphasize each particular piece. Are you saying it would be more effective to put 1C together with 1A?

DR. LONG: No, no, no.

DR. FITZGERALD: Just change the order, 1A, 1C, 1B.

DR. LONG: Yes.

DR. FITZGERALD: Okay.

DR. LONG: I have a comment I want to make on 1C when you get there, and that will probably make it more clear.

DR. FITZGERALD: Right. Again, the order, as Suzanne reminded me, is based on how they are discussed in the report, but we can certainly look at changing, even in the report, to just create a better flow.

DR. LEONARD: Kevin, perhaps 1B could be expanded to include Francis' point, and Emily's. The pharmacogenetics technologies that are being developed have to be able to provide answers in a clinically timely manner with appropriate turnaround times. So that's part of a technologies development.

DR. FITZGERALD: We could say there, and Francis, tell me if this is okay, "on the timely development of clinically useful pharmacogenomics." Is that enough, or do we need to be more --

DR. COLLINS: I think you need something more explicit about the need to encourage technologies that give you rapid turnaround, cost-effective, point of care genotyping for pharmacogenomics, but that could fit into that particular recommendation just fine. It just needs to be fleshed out a little bit.

DR. FITZGERALD: Thank you.

Now, we've already talked a little about 1C, but let's -- go ahead, Rochelle.

DR. LONG: I was going to make a specific recommendation. There is a tool that NIH does have, a mechanism for clinical trial designers to actually list their ongoing trials, and that's ClinicalTrials.gov, and there have been numerous editorials in the New England Journal of Medicine. Everybody who does federally funded work must list there. Those who do industry-supported trials who want to be published in the New England Journal have to be listed there, and I think you could encourage its further use to enable collaborations where pharmacogenetic components could be added onto or even designed into clinical trials at the outset.

So, for example, the registry could list whether materials have been collected, whether DNA has been collected, whether it's been consented for pharmacogenetic studies. I view that as part and parcel of discovering -- how did you phrase it? -- the clinically validated knowledge that later on you want to implement into tests that are available rapidly at the point of care, but you've got to know what you're doing first, and you have to utilize the trials and studies that are already ongoing by adding that pharmacogenetic component, and a mechanism exists to do that if that registry were upgraded a bit, and those who run the registry are interested in doing it. They just need the recommendation or perhaps government encouragement to do it. It's a matter of collecting the right fields and the right encouraging and enabling research.

DR. FITZGERALD: That would be great. It's wonderful. The more specific we can get, if we can get concrete, that's wonderful. I have the sense that I think that could work.

DR. FERREIRA-GONZALEZ: Is that registry you design in your own institution the research and then you post it in that registry?

DR. LONG: ClinicalTrials.gov is run out of the National Library of Medicine. It is a project in itself, and anybody can post information to it. They make available the fields to do it. Then a trial designer must voluntarily submit that information.

DR. FERREIRA-GONZALEZ: For publication purposes. Is that tied to publications in a peer-reviewed journal?

DR. LONG: The journal editors got together and said we so much want to promote this kind of sharing of information that if you want to get into our top-drawer journal, you'd better be using that government registry.

DR. FERREIRA-GONZALEZ: But I think what we're trying to say here is that before you engage in these clinical trials, meet with certain people who do outcomes research or actually clinical trials that will actually develop these in a systematic way, that gather the right information that then can be used further down the road for applications for the FDA.

DR. LONG: I was thinking that the trials, in the context that I was presenting things, I thought the trials would be a source of discovery, discovering the information by doing the genetic evaluation, by looking at their genotypes, by looking at the medications that they're taking. You would discover the links that you later want to evaluate through the right kinds of outcomes or evidence-based studies, whether that should be implemented into clinical practice. But I consider this back at the basic discovery of those connections, that knowledge in the first place, and that's what I'm seeing under the basic and translational research recommendations here.

DR. FERREIRA-GONZALEZ: I thought that we were also looking to increase some of the values of these earlier clinical trials that will have --

DR. LONG: We're in total agreement there, increasing the value of research that's already getting done.

DR. FERREIRA-GONZALEZ: Exactly.

DR. FITZGERALD: Okay. Good.

Yes, Barbara?

DR. McGRATH: Under C, I was wondering if it might be useful to add in, under the list of clinical trial outcome research, also cost effectiveness there, to highlight that, since it's such a key point in this area.

The other thing I wondered about is although there's a separate section on ELSI, to maybe bring that into this section where you're talking about translational research, to highlight that as not just a separate type of research but that's embedded in translational research, the ELSI issues. So add in "cost effectiveness studies and ELSI issues" or "ELSI concerns" in C.

DR. FITZGERALD: Oh, I see. Okay. "Cost effectiveness and ELSI."

Now, with the ClinicalTrials.gov website, obviously that information doesn't get put in there, too. Or could that?

DR. LONG: "That information" meaning --

DR. FITZGERALD: Cost effectiveness, ELSI issues.

DR. LONG: I would say no. Think of it as a registry that simply presents to the world, we, a group of researchers or a company are planning to do a trial or we are doing a trial, this is what we are studying, this is who you would contact, these are the enrollment criteria, this is what's being collected. So it enables researchers to make connections. It doesn't dictate what kind of research is done. It's not a funding mechanism. It's a directory.

DR. FITZGERALD: We can still put that in, but we'll make sure that some of that breaks out and goes in one direction and others is there for people to --

DR. FERREIRA-GONZALEZ: I think it's different. What we're trying to say here is that we want to encourage researchers to coordinate with clinical trials outcome researchers while they're doing their study design. What you're talking about is just listing what other people are doing so they can actually communicate with each other, hopefully not even repeat some of these studies.

DR. FITZGERALD: Right. That works.

DR. RANDHAWA: Perhaps I came in late, but this discussion is getting into Recommendation 3, which deals with clinical validity and utility. So the effectiveness, cost effectiveness, ELSI issues are certainly part of that also. So I wasn't sure are we meshing and combining all the recommendations, or are we going to keep them in different places?

DR. FITZGERALD: No. We're trying to be as discrete as possible. On the other hand, we're trying to make sure we do the proper amount of emphasis on the various issues. That's why we're going through this now. If we need to jump back and forth a little bit, we can do that in this section. Now, we'll also probably revisit some of these issues in other sections as they regard application, but that's okay too. So we'll do that.

Look at 1D. "Research that could lead to the development of a pharmacogenomics test requiring FDA review should be planned with the goal of meeting FDA quality of evidence standards so that the results can be used in support of a premarket review application. NIH should encourage investigators to consult FDA when their research reaches a pivotal stage, and NIH could encourage the conduct of methodologically sound and statistically rigorous studies by giving higher priority scores to studies that are designed to satisfy FDA quality of evidence standards."

Again, this is a recommendation in an attempt to tie things together, which we thought was an important thing to do.

Is everybody all right with that? Wonderful.

DR. LONG: That's just a little bit awkward in that NIH doesn't actually give priority scores. NIH assembles review panels that do peer review. I would say funding decisions should give weight to

satisfying FDA quality of evidence standards.

DR. COLLINS: I think if we just drop the word "scores" --

DR. LONG: "Priority scores."

DR. COLLINS: Because it sounds like NIH is going to overrule the study section.

DR. FITZGERALD: We like anything that makes them shorter. That's good.

Andrea?

DR. FERREIRA-GONZALEZ: Do you think here that maybe something education to research, doing translational research and how to conduct some of these statistical studies?

DR. FITZGERALD: We have some other educational ones.

DR. FERREIRA-GONZALEZ: Through workshops or some other venue?

DR. LONG: I hear you. Let me try to figure out the best efficient way to do that and get it inserted at the right time.

DR. COLLINS: I think that does come up in the later recommendations.

DR. FITZGERALD: It does, later on. We do get to education of the researchers.

Michael, you had something?

DR. AMOS: I just want to get back to Mr. Rollins' point before about the testing accuracy. Is that captured in any of these four subcategories? Because I really think that the standardization of the testing and the accuracy of the testing really need to be evaluated. Like I said before, there are only a handful of diagnostic tests with actual standard reference materials.

DR. FITZGERALD: Well, when we get to Recommendation 3, we talk about validity and utility, and we could certainly add in accuracy at that point. That might fit I think the concerns on that. Is that okay?

Joe?

DR. TELFAIR: It's a question, which is more a point of clarification to ask to the NIH. I guess I have always been under the assumption, in looking at the way studies are reviewed, that priorities are already given to those that are methodologically sound and statistically rigorous already. I mean, I thought that was already in existence, and I'm wondering if that's true, then maybe the wording should be something along the lines of if it's going to be integration, that it should continue to enforce or continue to remind people. I mean, if it's already there, it seems a bit unnecessary to say they should do something they're already doing.

DR. LONG: I think you're correct that instructions to review panels are to give the higher scores to the statistically rigorous well-designed studies. You're right. I believe, and I didn't craft this original recommendation, that there was some intent here that the FDA saw specific and unique needs, and sometimes they felt that the weight should go into funding the types of studies they need to see done. Am I accurate? So I think that's the little FDA angle that made this one different. But you're right, I think review groups already give the best scores for merit to the most well-designed studies.

DR. FITZGERALD: Again, we can reword this to make this more clear, but I think the implication is that what's in the first paragraph is what's considered to be methodologically sound. How do we put it that way? And statistically rigorous. That's not necessarily thought to be as strong at the moment.

DR. MANSFIELD: Hi. It's Liz Mansfield. I'm from the FDA. I would just encourage you not to put the cart before the horse here, that studies are typically reviewed and funded prior to having been done, and the way that this is written, it appears that they would only seek FDA advice after they had reached a certain point. So I'm not sure how review boards could say that something was meeting FDA specifics if the studies had never even started yet.

DR. FITZGERALD: Right. Well, in the second paragraph we have "NIH should encourage investigators to consult FDA when their research reaches a pivotal stage." Is that what you're --

DR. MANSFIELD: Right, but then the next section says you would encourage funding to studies that are designed to satisfy FDA quality of evidence standards, and I think those may be somewhat in conflict with each other. As far as I understand, you tend to get funding before you reach pivotal stages.

PARTICIPANT: So drop the last paragraph there?

DR. MANSFIELD: Perhaps. I agree that you're on the right track. I just think that it will be hard to say that this will meet FDA quality standards before the funding has been given.

DR. FITZGERALD: Emily?

DR. WINN-DEEN: I think what we were trying to get to is the next level of study beyond the tantalizing early results study. So now you're going to design a study that really is a validation study, and having been into FDA once or twice and been told that one of the things that FDA would like to see is some good published studies done independent from the manufacturer indicating that that marker has clinical utility and validity, I think what we were trying to get to is to encourage people doing those studies separate from whatever company might sponsor a device, to do those in a rigorous way so that FDA could consider that as a reasonable piece of literature.

DR. MANSFIELD: Yes, I think that's entirely reasonable. Maybe just a little clarification here, then.

DR. FITZGERALD: Okay. So when you read this, you were hearing that the third paragraph sort of stood out on its own, and I think that's what we're getting from both Joe and you. So that third paragraph is leading people away from the first two somehow. Okay. Great.

In 2A, this is development of pharmacogenomics products. "Health and Human Services should provide FDA with the necessary resources to develop guidance documents about best practices for the co-development of pharmacogenomics drugs and diagnostics. This guidance should promote collaboration between the drug and diagnostic industries and clarify the review process for co-developed products where the drug is subject to FDA review but the laboratory-developed companion diagnostic test may not be."

Oh, in your executive summary this is 2D. It got moved up, if the list is actually somehow some kind of prioritization, which it isn't. But in any case, it's now 2A. Okay?

DR. LEONARD: Kevin, can I ask a question here?

DR. FITZGERALD: Sure.

DR. LEONARD: I thought FDA had a draft guidance on the co-development. Hasn't this been done?

DR. MANSFIELD: It's actually a white paper right now, headed towards draft guidance status.

DR. LEONARD: So if this is underway, do you need to have a recommendation on this?

DR. FITZGERALD: I thought the sense of the task force was that this could only help move this process forward, that there was a desire to make sure that this was emphasized.

DR. MANSFIELD: Yes, there is a desire to get the draft guidance out, but it has been previously released as a white paper and not a draft guidance.

DR. FITZGERALD: Good.

This is 2B. "FDA should identify research opportunities relating to the co-development of pharmacogenomics products. FDA could encourage and facilitate the conduct of this research through its Critical Path Initiative."

Then 2C. "HHS should advance the further development of abandoned drugs by facilitating

access to information about such drugs. Incentives will be needed to encourage the voluntary submission of proprietary data by pharmaceutical companies." Again, trying to address some of that gap problem that we had identified in the issues earlier. All right? Great.

Then what is now 2D.

Sorry, Gurvaneet. Back on 2C?

DR. RANDHAWA: Yes. It's not clear here where that data will be housed. It says "to encourage manufacturers to submit proprietary data." To whom? Where would that data be housed?

DR. FITZGERALD: Right. It doesn't say that there either, right?

DR. LONG: It's housed at FDA right now, right? Voluntary genomic data.

DR. FITZGERALD: Do you have a specific place that you want it to be housed, or is FDA okay? Because that's where it is housed now, right?

DR. RANDHAWA: Well, if the intent is to try and have the database available to others to take the technology further, I'm not sure that that's going to be feasible. So I wasn't quite sure what the intent was after the manufacturers release it. If it still stays in FDA and it's not accessible to others, would it meet the purposes?

DR. FITZGERALD: I see.

DR. LONG: Can you ask for development of incentives to encourage the eventual release? Because right now there are no plans to release any of that, right?

DR. MANSFIELD: The voluntary genomic data submissions? No. I suppose any company that's submitting could release it if they wanted to.

DR. FITZGERALD: Identify yourself, please.

DR. RUDMAN: Allen Rudman, FDA, CDER. FDA has a voluntary genomic data submission process, but the information that comes into it is confidential. So that helps FDA. It doesn't necessarily help the rest of the industry or academia. So I think what we're talking about here is a process for making it public.

DR. FITZGERALD: Right.

DR. RUDMAN: So then how we go about that, that could be publications or something else, but that's what really needs to be determined.

DR. MANSFIELD: As far as incentives, I think you would want to make some concrete suggestions of what those incentives might be.

DR. FITZGERALD: Now, you want those in this report or we can just put that forward to the Secretary and allow the Secretary to make those determinations?

DR. MANSFIELD: That's up to you.

DR. LEONARD: Can I ask a question here? If it's in a blended drug, would the drug company have done a submission to the FDA? If they'd gone through trials, are we talking about something that would even be submitted to the FDA here? I don't think so.

DR. MANSFIELD: Drugs can be abandoned at many stages, and they may have been submitted to FDA.

DR. LEONARD: But they may not have.

DR. MANSFIELD: But they may have been abandoned prior to that in developmental stages, clinical stages. Yes.

DR. LEONARD: So we may not be capturing all the abandoned drugs if we're talking about data that's submitted to the FDA. So I think we need to incentivize the drug companies to further develop or move forward abandoned drugs using pharmacogenetic technologies, and I don't know what those incentives would be. You'd have to ask drug companies what would incentivize them to move drugs

forward for a smaller market than what they were originally anticipating.

DR. FITZGERALD: I'm not sure that we need here to -- because there are a variety of reasons that one could abandon a drug in the development process. Not all drugs are abandoned because of a population problem, they just can't get enough people or they don't get enough effectiveness. Do we need to capture all "abandoned drugs," or are we trying to incentivize the ones that, in fact, might fit this profile of being able to target a smaller subpopulation?

DR. EVANS: I think we should be careful about making recommendations that aren't feasible or that we have no inkling of how we could ever incentivize for it. Unless we have some inkling about how one could incentivize drug companies to make such information public, I'm concerned that we dilute our recommendations if we just say, oh, you should do this, that you should incentivize it without any idea of --

DR. FITZGERALD: Right. In the fact-finding stage that's next, we could certainly ask what those concrete incentives would be. We could certainly ask industry what they would consider incentives.

DR. FERREIRA-GONZALEZ: Is there a concern now that we need to keep this here and not just take it out?

DR. LONG: I think that second paragraph is really valuable, because I think the individuals that I know at the FDA have all worked hard with industry for the voluntary submission of genomics data, and to reinforce that voluntary submission of proprietary data to an agency that can gain in its knowledge as it makes decisions about drug approvals, this is not for abandoned drugs, this is for things that are in development now. That's a wonderful thing.

Coming from the NIH side of the fence, I would love to promote that it ultimately be made public, but I have to be realistic. How many companies are going to voluntarily submit data to the FDA that they think they're going to be forced to make public? That's going to have a very chilling effect on the voluntary status of the submission system.

So I understand the competing nature of the issues here. What you have written is good in that second paragraph. I guess the confusion is it applies to more than just abandoned drugs. It applies to things in development now.

DR. FITZGERALD: It certainly could, right.

DR. LONG: It does, it does.

DR. FITZGERALD: It does. But the question is can we narrow the scope?

DR. LONG: I think your fact-finding suggestion so the group can make careful recommendations in concert with the system that already exists is a good idea.

DR. FITZGERALD: Okay.

DR. LONG: You may want to fact-find more before you do it, or you'll drill down too deep and have unintended consequences, disrupting something good. Would you agree?

DR. FITZGERALD: Well, I think we can certainly, in looking for incentives, discover that. That would help elucidate that.

Yes, Michael?

DR. AMOS: If the committee is saying that this is something that's absolutely needed to move pharmacogenomics along and you can't identify any real way of doing it with the existing data, should you also consider another recommendation for implementing that if this is not the only way to do it?

DR. FITZGERALD: That's a good point. So you're saying if this turns out to be one of those things that's not implementable, then what do we do? Right?

DR. AMOS: Right.

DR. FITZGERALD: Okay. That's definitely a conditional statement. So since we don't know yet whether the "if" is true, I don't think we can quite get to the "then." But that's certainly something we'll have to look at. If incentives do not exist and it's not implementable, I think we'd have to then address that particular situation. Okay, that's a good point.

DR. EVANS: So what's the resolution, then?

DR. FITZGERALD: So what we're doing is saying the resolution, in a sense, can I think stand at the moment, but we need to go and find what those incentives might be so that we can be a little bit more specific in recommending to the Secretary this is what we have discovered from industry or from our fact-finding; not to say that you have to do it this way, but we would at least be able to make some specific concrete recommendations along those lines, such as what we do in some of these other recommendations where we say such and such is already underway. We could say these are things that have already been identified as possible incentives.

Debra?

DR. LEONARD: But these seem to be two different recommendations that are bundled together here. One is abandoned drugs and encouraging industry to move abandoned drugs forward if they're abandoned because of an adverse drug reaction in a small population but it shows effectiveness in those who don't have the adverse reaction, or other things that pharmacogenetic testing could help with to identify the populations that will be helped by these abandoned drugs. Then the incentives part really applies to all drugs. I mean, you want the pharmacogenetic information for any drug, not just abandoned ones. So it seems like there are two things here that are being mixed together inappropriately.

DR. FITZGERALD: Okay. I think what we were trying to do was to narrow this down, but we could broaden it if the committee thinks this is better. "HHS should advance the further development of drugs by facilitating access to information about incentives that would be needed to encourage voluntary submission." We could just drop "abandoned." We don't need to have that in there.

Emily?

DR. WINN-DEEN: Well, I think the original discussion about this was this whole concept of drug rescue. Either there are perfectly good drugs out there where if you could eliminate the few individuals who have bad reactions to them would be great for the majority of people for whom they are effective. I think we were trying to take a very narrow, defined subset where we thought pharma might not be as sensitive about it. Okay, your drug was abandoned or it was pulled off the market anyway, so you're making no money off of this. Is there some way that pharmacogenetics could help bring that back for the benefit of patients? So I don't think this was ever intended to be a broad recommendation that every drug and every pharma company had to collect this information and reveal it to the public. It was really in its initial discussion I think focused on this small subset of things that are off the market now for one reason or another, so the stakes are pretty low from the pharma company point of view because it's making no money for them right now, and this might be a way to resurrect something.

DR. LONG: I hear what you're saying. You're saying this is the data that wouldn't have been submitted ordinarily, while other data would have been.

DR. FITZGERALD: The idea was to pick a battleground --

DR. LEONARD: I understand what Emily is saying, which is what I was saying about this first part of this slide 39. By facilitating access to information about such drugs, I think facilitating information to whom, to do what with? It just is very vague. I mean, basically what you want to do is encourage the pharmaceutical companies to move these drugs forward by using pharmacogenetics. Do they have to give proprietary information to anybody?

DR. WINN-DEEN: My experience with most pharma companies is that once it's done, it's

done from their point of view. So the chance for them to resurrect it is not as good. It's an emotional thing within the company. It's much more likely that some other company would take it on and buy the rights to that drug and then do these studies and try and show that although the drug was not safe for the general population, if you do this test, that it then could be used effectively.

DR. LEONARD: So is this recommendation capturing what needs to be done? I don't think it is.

DR. FITZGERALD: One minute, before we get too deeply enmeshed in one. I'm going to pull a Reed and we're going to flag this for just a moment, and we'll come back to this if we have time at the end, but we're definitely going to say this is a problematic recommendation. If we don't get back to it today, we'll certainly try to rework it in such a way as to make it more clear what the intent of the recommendation is and how it addresses the issue, because we're running a little behind.

DR. TUCKSON: I think what we can do, by the way, just to help out our chairperson, is if you could just jot on a little piece of paper what you think it ought to say, just try to give him the solution to the problem and then hand that in and he can look at it at the break.

DR. FITZGERALD: That's great. We can do that.

So going on to 2D, this was one that was flagged as a high priority by the task force, that "FDA should amend the Humanitarian Device Exemption Regulation so that incentives for the development of orphan drugs are extended to pharmacogenomic tests that are intended to be used in conjunction with the orphan drugs."

DR. MANSFIELD: FDA again. First of all, I want to make sure that everybody understands the Humanitarian Device Exemption extends to tests that are intended to be run on 4,000 people or less or on a population of 4,000 or less, depending on how you interpret the rule. There's no clinical validity required in order to have a Humanitarian Device Exemption, and that is based on the assumption that a potentially flawed test is better than no test. I suppose you could rewrite the regulation to model it differently, but I'm not sure that's where you want to go with orphan drugs right now. I also think that if you extended it to the 200,000 that orphan drugs are now allowed, you would create an extremely unlevel playing field for genetics versus every other kind of test that would probably be somewhat upsetting to the rest of the community.

DR. FITZGERALD: So now, in doing what this says, I understand what you just mentioned. This apparently would change the regs for tests so that they would have to have clinical utility, right? Because they would be falling under the orphan drug designation, right?

DR. MANSFIELD: I'm saying the current Humanitarian Device Exemption requires just an assumption of clinical validity, not utility. So my feeling on reading this was that you simply wanted to up the number of patients who could receive the test under this exemption.

DR. FITZGERALD: If it's done in conjunction with an orphan drug.

DR. MANSFIELD: Right. So what I'm suggesting is that as the exemption is written now, you are running a test on up to 200,000 people for which you have no clear clinical validity with the assumption that the test may be flawed and that a flawed test is better than no test.

DR. FITZGERALD: Thank you. We may have to go back and look at this one also. That's good information. We'll also flag this one, too, to possibly go back to.

Now we're going to go down to that whole area of clinical validity and utility of pharmacogenomics, and the people who mentioned accuracy can recommend wherever they want that to be first put in. But this is our first recommendation in this area, that "HHS should provide AHRQ, CDC, NIH with additional funds to identify pharmacogenomics technologies that are important from a public health standpoint and support efforts to address gaps in evidence for which clinical validity and utility

evidence is lacking. So CDC's EGAPP Working Group and HuGENet and AHRQ's EPC program may be appropriate mechanisms or models for identifying such technologies and specific evidentiary and research needs." Again this was flagged by the task force as a key recommendation.

DR. ROLLINS: In addition to clinical validity and clinical evidence, we've got to somehow incorporate measures of accuracy, number one. Number two, also utility evidence, I think we need to go further than that. Some people think that pharmacogenomic tests are diagnostic tests. Looking at diagnostic tests, we look at accuracy. Also, we look at how is this test going to be used in terms of management of the patient. I think the wording "management" is going to have to be incorporated in this because if I'm evaluating a particular technology, not only CMS but also other insurers, if tests are lacking in terms of measures of accuracy, at least it should be demonstrated that if a physician uses that test and the results of that test will dictate his or her change in management of the patient, if there's some way we can incorporate "management," because that's what we look at when we look at a diagnostic test, how does this test alter or continue the management of that patient.

DR. FITZGERALD: Now, the management issue, we want to put that in the R&D here, or may that be later on in the application?

DR. ROLLINS: Well, I looked, and it's also applicable to number 7, but if the studies cannot show that this test helps in the management of the patient, then it would be difficult to say how it's applicable in terms of a clinical application. You might even look at a decision tree. Depending on the results of the test, does a physician do A, B, or C? But as I said, it's all involved in the management of the patient.

DR. BRADLEY: I just wanted to bring up that to address Jim's issues about accuracy, the easiest solution here would just be to talk about analytic and clinical validity, the way you do in the narrative, because that will cover analytic sensitivity and specificity and reproducibility and all of that, and accuracy.

DR. FITZGERALD: Just one second. What page are you on?

PARTICIPANT: Thirty.

DR. FITZGERALD: Let me just read what we have in the report, just for clarification purposes. If you look on page 30 of the draft report, under the section on clinical validity and utility, I'm not saying we can't still make this more specific, but it says, "Clinical validity refers to the accuracy with which a test predicts a given clinical outcome. Clinical utility refers to the ability of a pharmacogenomic test to inform clinical decisionmaking," which might include management, "prevent adverse health outcomes and predict outcomes considered important to individuals and families." So maybe where we're not getting the thing here is we're not getting this into the recommendation, or not everybody understands these terms in the same way.

Does that capture, though, some of what -- go ahead, Linda.

DR. BRADLEY: Well, I was just going to say that the sentence before that was the description of analytic validity, which I think is very important in this context.

DR. FITZGERALD: Right, okay.

DR. PAREKH: I was just going to say I think clinical utility as it's defined encompasses management. So I was going to ask James about that. It seems like it's encompassed in utility.

DR. FITZGERALD: Would we need to make that clear in the recommendation, or is it okay to make that clear in the report?

DR. ROLLINS: I know that when we do technology assessments, for example, somebody has submitted cytogenetic testing and they've submitted to us a lot of articles talking about a specific marker, but they don't connect or they don't link how the results of that marker are going to result in the

management of the patient or change in the management of the patient, that's a link that I don't know if we're stressing hard enough, but there's got to be some kind of link between the results and how that patient is going to be managed depending on the results of that particular test.

PARTICIPANT: But that is clinical utility.

DR. PAREKH: I'm just saying if you ask a clinician and you ask them about clinical utility, that's exactly what that is. It's the management of the patient.

DR. FITZGERALD: Right. We can work to make sure that's clear someplace.

DR. FERREIRA-GONZALEZ: So the idea would be to add the analytical and clinical validity and utility evidence.

DR. FITZGERALD: The analytical thing is easy to do, just put "analytical" in there along with clinical.

DR. FERREIRA-GONZALEZ: So that would take care of the accuracy.

DR. FITZGERALD: Right.

DR. RANDHAWA: I support Linda's suggestion. So if the intent of this bullet was to make it focus on clinical outcomes and not analytic validity, then I certainly think we need to capture getting that information. So perhaps you could do that in the first recommendation where you're talking about basic research. There's no mention about analytic validity here in the basic and translational research. So if the intent of this recommendation was to focus only on the clinical outcomes, then to make sure we don't lose analytic validity anywhere in these recommendations, we could perhaps make it more specific in the first recommendation.

DR. FITZGERALD: The first being which one? 1A?

DR. RANDHAWA: The basic and translational research which NIH should support, the basic. In my reading here, when we're developing new knowledge about a test, there is no specific language about analytic performance of the test. So if the intent is to leave this third recommendation more focused on the clinical outcomes, then we could be more specific in laying out the analytic performance in the initial studies.

DR. FITZGERALD: So what you're saying is in either 1A, 1B, 1C or 1D, put it in there?

DR. RANDHAWA: Right.

DR. FITZGERALD: Okay. Following up on Reed's suggestion, pick one, write where it would go, and at the break I'd be happy to get back to that.

DR. RANDHAWA: No problem.

The second comment was I'm speaking here from AHRQ's perspective. The evidence-based practice center program is identified, but when we do these meta-analyses or reports or technology assessments, they're useful in pointing out where the gaps in the evidence are, or where the research needs are. They are not amenable to creating new knowledge or doing new outcomes research to fill in those gaps. I'm reading through these A, B and C, and only within C we have a sub-sector there where public and private health plans should facilitate the generation of new knowledge, but here we're making it conditional, in certain circumstances.

So what are the mechanisms for routinely creating new knowledge for clinical outcomes? We don't really specify that in any of these three, A, B or C here. We could make A more clear by specifying both dimensions. One is appraisal of the existing evidence and pointing out research gaps, but B would then be identifying mechanisms to fill those gaps, which should be programs like, say, the DEcIDE network at AHRQ, or the CERT program at AHRQ, which are more for creating new evidence as opposed to just appraising the existing evidence.

DR. FITZGERALD: As we did here, we're happy to be specific. But would you want that

here? It could probably also go in 3C.

DR. RANDHAWA: It could go anywhere. I just wanted to raise it that I don't find it anywhere in A, B or C.

DR. FITZGERALD: Okay. So we could either add that here, or we could add it to 3C. It looks like that would be a good place. Okay, thank you.

3B, again one that was flagged by the task force as a higher priority. "FDA should encourage manufacturers to submit clinical utility data as part of their premarket applications and post-market surveillance. Request manufacturers' permission to make these data available to the public. Manufacturers should disseminate any significant and non-significant findings on the clinical validity and utility of pharmacogenomic technologies, e.g. through publication in peer-reviewed journals."

Yes, Emily?

DR. WINN-DEEN: I guess reading this again, sort of in isolation, which manufacturers are we talking about? Drug manufacturers? Device manufacturers? I just think it needs a little clarification.

DR. FITZGERALD: We need to clarify.

DR. MANSFIELD: I'm not familiar with the regulations of drugs enough to really say, but I know for devices that evidence of clinical utility is currently not a strict requirement. Many companies who are performing these tests would like to get them to market as quickly as possible, and it's my assumption that that's what the committee would like too. If you delay getting to market by enforcing the provision of strict clinical utility, you may be working against yourself. Some supposition of clinical utility is needed, but actual outcome studies and so on generally take a long time and are not traditionally done for devices.

DR. FITZGERALD: Debra? Or Allen. Your mike is not working, I don't think. Is it on?

DR. RUDMAN: It's on.

DR. FITZGERALD: Okay, there it is.

DR. RUDMAN: A minor point. You may want to include that FDA should encourage the manufacturers to submit pharmacogenetics. Right now it's just all clinical utility data.

DR. FITZGERALD: Okay.

Debra, did you have something too?

DR. LEONARD: I wanted to point out to the committee that in September, CDER development a table of biomarkers and pharmacogenetics tests that actually has an indication in three levels. One is that it's informational, the second is that it's recommended, and the third that testing is required. It provides information with the drug label, and it has references in that table to the studies that have been done to support the pharmacogenetic test relative to a specific drug. It was initiated in September, it was updated in October, and I think this committee should encourage CDER to continue to update that table of information because it's extremely useful as a house system. When we found that, it actually supported some of the pharmacogenetic implementation stuff that we were doing.

So in this recommendation, the FDA is actually making this information, or CDER -- I assume CDER is part of the FDA? I have problems with all the acronyms of knowing who is what, but it says CDER on the top of this table thing. So the FDA is actually doing this, and that's great.

DR. FITZGERALD: We could put that down, if it's okay, where we have "e.g., through publication and peer-reviewed journals," or through the table that is being --

DR. LEONARD: Through the CDER website.

DR. FITZGERALD: Right, the CDER website.

Just for clarification again, to address your issue, Elizabeth. If this said, "FDA should encourage drug manufacturers to submit," that would take the focus and put it on the drug and we

wouldn't have the device issue. Is that correct?

DR. MANSFIELD: I think so, yes.

DR. FITZGERALD: And maybe that's the specification, and then we could do the pharmacogenomic and pharmacogenetic information as well as the clinical utility data.

DR. RUDMAN: I would also make one other recommendation here. It says, "to request manufacturers' permission to make this data available to the public." I certainly would encourage this, but I'm not sure what you mean by "request." When the FDA makes a request, it's viewed sometimes in a regulatory manner. So maybe just the wording needs to be changed.

DR. FITZGERALD: "Encouraged"?

DR. RUDMAN: "Encouraged."

DR. FITZGERALD: Okay, good. Thank you. We don't want to intimidate anyone, except the people here so we keep moving.

Here we go, draft Recommendation 3C. "In certain circumstances, public and private health plans should facilitate the generation of knowledge by conditioning payment of pharmacogenomic technologies on a commitment by test developers to collect data on the clinical validity and clinical utility of pharmacogenomic technologies." Did I read that correctly? It didn't sound good. Anyway, "CMS' draft coverage with evidence development initiative may serve as a model for this practice." We're good on that one. Sylvia is questioning.

MS. AU: I'm a little concerned because you're mixing payment with clinical research. Is this clinical research needing informed consent, and if the person doesn't consent they don't get payment for their treatment?

DR. FITZGERALD: I guess the lack of clarity here is in the "in certain circumstances." So considering the question that you just raised, I think we need to potentially address that problem.

MS. AU: And whether it's identified data or it's unidentified data.

DR. FITZGERALD: Okay, let's flag that one. Since we put it out here now, we've got to deal with those issues. In fact, Sylvia, if you could just jot something down for the break, that would be great and we'll see if we can work that around.

Can we move to 4A? Now we're moving on to the research databases. "HHS should work with the private sector to improve data sharing and interoperability among research, regulatory and health record and claims databases. HHS should work with existing organizations to create uniform genomic data standards, explore ways to harmonize data analysis methodologies, and develop an infrastructure to enable data exchange. Comparable efforts to standardize phenotypic data are also needed." Again, this was flagged by the task force committee as extremely important. This tries to get at that question that we mentioned before about how the different groups and databases can talk to one another. Is everybody happy with this?

Then 4B. "As the data are shared, the privacy of patients and research subjects should continue to be of paramount concern, and HHS should take steps to ensure that the confidentiality of their data is not compromised," again flagged by the task force committee, and again this goes back to that balance I mentioned before that we're trying to strike.

Rochelle?

DR. LONG: I have an observation. I don't know the solution. But if privacy is of paramount concern, this will lessen sharing of data for research purposes.

DR. FITZGERALD: Yes, it will. That was the tension I mentioned earlier.

DR. LONG: Clearly, this is written to allow institutions to hold on to as much data as possible when it comes time to deposit it into databases. This will give them reason to not want to share their data.

Is that exactly the way you want to push it? Please comment, others.

DR. COLLINS: I'm glad Rochelle brought this up because I think this is going to be an issue for all kinds of studies, and pharmacogenomics will be one example. Clearly, privacy and confidentiality are an absolutely important principle, but if one decides that that is the only principle, then basically you have no research databases at all because somehow they might leak or somebody might get access who shouldn't. This is worded in a way that almost makes it sound like that would be your intention. So I think perhaps choosing your wording a little more carefully here to say that confidentiality and privacy are critical principles and every effort should be made to maintain them while also making certain that research can go forward by providing access to qualified scientific researchers.

DR. FITZGERALD: Reed, go ahead.

DR. TUCKSON: I think that is a very well crafted solution here, and I think the committee knows it's obvious. We have to push hard on the privacy paramount attentiveness. I know that a lot of the stuff that's happening in America's health information community which we talked about earlier is really threatened by the concern of the public around this privacy and confidentiality deal, and in some ways if we're not attentive, it makes the whole agenda a non-starter.

I think the way that Francis phrased it is really the way to get at it, and if somebody got that language, I hope that you're writing it down. If not, he needs to say it again.

DR. FITZGERALD: My only fear, Francis, is that the way you stated it does the exact reverse, just listening to the way you phrased it. This is an important concern, but the research must go forward. The "must" is the key thing. I agree with you that we've got to balance this in our language, but --

DR. FERREIRA-GONZALEZ: I think we currently have federal regulations to protect the privacy of human subjects that enter some of this research that can be used into these databases or clinical validity, et cetera, where you use codified or you deidentify this information. So maybe using what is currently in the regulations now to this would suffice that we assure some of the privacy of these individuals, but then we're allowed to continue for the research.

MR. DANNENFELSER: I think that was the basic same point. Can't the demographic data be shared while still protecting the privacy of the individuals?

DR. FITZGERALD: Joe?

DR. TELFAIR: This is a little bit outside of my purview, but I would suggest that maybe you have a couple of e.g. on some of these things. There are models that exist, like the Clinical Networks, that sort of thing, that may be considered in terms of how they go about doing that data sharing and ultimately protect privacy. So I would maybe say, e.g., along Clinical Network lines.

DR. FITZGERALD: Okay, we can put that. I think Francis was concerned with the language, where is the bottom line going to be, and I think what we can do is work on that to just show this is going to be a continuing tension but the question is can it be a creative tension or is this going to be a destructive tension, and hopefully we'll make it creative.

We are scheduled right now for a break. We'll do 5, and then we'll take our break.

FDA guidance for population subgroup data, draft Recommendation number 5. "Race and ethnicity categories should not be used alone when analyzing differences in drug response. FDA should develop guidance that encourages the collection and analysis of genetic and other biological factors that may better explain differences in drug response. When drugs are shown to be effective in certain racial and ethnic subpopulations, FDA should require manufacturers to conduct additional studies to identify biological markers that underlie the differential drug response."

Yes, Jim?

DR. EVANS: The only problem I have with that is the requiring manufacturers to conduct

these studies. These are extraordinarily reasons that range from environment to genetic factors that may be responsible for different racial/ethnic categories responding differently, and I think that by demanding an explanation for that when those things are so complex that they've proven extraordinarily difficult to work out, I just think that's overstating it.

DR. FITZGERALD: Let me see if we can't get at this tension too in a somewhat creative way, because I understand what you're saying. It says here "should require manufacturers to conduct additional studies." It doesn't say "require manufacturers to identify." So you don't have to get the answer.

DR. EVANS: Well, I don't know. I'd argue that if you do show in a statistically rigorous way that a certain group, be they people with blonde hair or people who live in Love Canal, respond differently to a different drug, I think it's laudable to look for those, but I'm not sure if requiring those studies is something that makes a lot of sense from the FDA's standpoint.

DR. FITZGERALD: Reed?

DR. TUCKSON: I think I'm not sure either of what this is trying to do. When you pile all those burdens on the manufacturer, it really seems to me to have a stultifying effect for bringing the product to market, and I'm not sure what advantage you get here.

DR. FITZGERALD: The sense I think we were trying to capture here, and obviously many of you are aware of this in the literature, the discussions going on about the potential effects of pharmacogenomics, that rather than ameliorating racial categories and differences and particularly disparities in health care delivery, that these would actually exacerbate them. But you're right, we could probably take out "require" and --

DR. EVANS: I think you address it very well in the first two paragraphs, and I just don't think the third paragraph adds much and does make it rather confining. So I think just taking out the third paragraph then makes it very reasonable.

DR. FITZGERALD: Allen?

DR. RUDMAN: As you know, there is a drug out there, BiDil, that's currently been approved for that. So I'm not sure what you're exactly recommending. Are you recommending that it be taken off the market?

DR. FITZGERALD: No, no. The recommendation is that the -- again, there have been articles addressing this issue. If one did a study of the population that BiDil is supposed to target, one would still probably find a spectrum of response to that drug, and one might even find a response to the BiDil combination outside of that particular group where you have high responders. So the question here is, is using the category African American something that is socially problematic, problematic to a particular underserved group as it is, in such a way as to say this social detriment raises issues that we need to address, not necessarily by taking the drug off the market but perhaps by better informing ourselves as to what it is that delineates that population for which that particular drug is actually beneficial, or significantly beneficial. That's the intent.

DR. RUDMAN: Okay. I would make a recommendation. I would actually make a comment first. Some of these racial and other criteria are in international agreements. That's just one comment.

But I think what you're really aiming for is to encourage this to move forward from a racial to a genomic, pharmacogenomic --

DR. FITZGERALD: Absolutely. That's the idea.

DR. RUDMAN: So maybe it can be revised to kind of say that. So where race and ethnicity are found to be determining factors, pharmacogenomics should be looked into. I'm not sure if I'm getting to where you're going.

DR. FITZGERALD: I think we're trying to get that in the second paragraph for sure. But in

any case, one of the recommendations is to just cut out paragraph three, which is what you're saying.

DR. TUCKSON: I think, if I understand where we really are here, it's that when you make an interesting observation, that there ought to be efforts that either facilitate the further research into what is actually going on or the recommendation is you're trying to make sure there is a database made available to support such research, and it looks like you're trying to use the FDA as a way of facilitating access to the data that researchers can then use downstream. The question ultimately becomes that everyone would say that it is a good thing to learn more about what this observation means, and that's mother, God and country that we ought to say yes to.

The second question is can you put on the back of the manufacturer a requirement to do that, and I think we're rejecting that in losing paragraph three. The second question is can you put that on the back of the FDA to provide some mechanisms for that to occur, and it seems to me the FDA is saying that may be problematic as well, and I'm not sure what your answer is.

So I think what we are left with is this is an important thing to study and people ought to pay attention to it in the best of all worlds. Researchers will go after it, NIH will give money to go after it, smart people will decide to think about it.

DR. FITZGERALD: In that light, if we put HHS in instead of FDA should develop guidance, that takes the burden off FDA specifically, which may be a good thing to do, but it allows greater breadth.

Yes, Francis, and then Elizabeth.

DR. COLLINS: Let's not undercut this too severely. I mean, many people do believe that the BiDil experience was an unfortunate one, and I happen to be one of those, that the reification of racial categories in a decision about who gets this drug or that drug both does a disservice to the public health because it substitutes an imperfect proxy for what may be much more specific information that just wasn't collected that might predict who is going to respond and who isn't, and of course it has the other negative consequence of implying to the general public that race is something that is biologically determinant, and because the FDA has now approved this drug for African Americans, they must be somehow different, which we know is a vast overstatement of the biological facts of the matter.

So I think it is highly appropriate in this set of recommendations to put something in to discourage that kind of occurrence again, and I think FDA appropriately should be asked to develop guidance, just as your second paragraph says here, to encourage manufacturers who are putting forward this kind of test to do better next time.

DR. FITZGERALD: Elizabeth?

DR. MANSFIELD: I guess I have somewhat of a conflicting opinion. I think that race and ethnicity are certainly very imperfect surrogates. On the other hand, do we want to say, if that's the only surrogate you can come up with, forget it, you don't have a drug? I'm not trying to say that you did say that. I'm saying my own opinion.

DR. FITZGERALD: Right, right.

Joe?

DR. TELFAIR: Knowing that this is an issue, I'm liking the wording that you're using. I think "surrogate" was the word you used. "Proxy" was a word you used. I mean, really, it's what is the meaning behind this and what is the intent, and what I'm saying is the intent is along the lines that there are areas in which disparities occur by which there is an unevenness in terms of how these things are done.

Maybe the point here is to acknowledge that with the first two paragraphs, but then to refer to and put something in a little bit stronger language in your ELSI section related to this, and that would then get at the intent issue as well. You can start with the intent here and leave it at that with the first two

paragraphs, I would agree with my colleague there, and then go to the ELSI issue related to the health disparity issue, which seems to me is something that the committee and everybody is in agreement with and that needs to really be addressed, but maybe in this section where you can make a stronger case for that, because that's something that came up in our group as well, is that we need to find a better place to put something like this.

So that would be my recommendation, because I think it's very confusing many times to use the proxy or the other terms that are being used. We ought to state it plainly that this is what the intent is, and I would recommend that.

DR. FITZGERALD: And we do have, as you know, in the third area, we have some of those. So we could drop the paragraph out here and make sure it's emphasized in the third.

DR. TELFAIR: Or refer to the recommendation. You can always say refer to the recommendation for the intent here, because I do think you do need to really address the intent.

DR. FITZGERALD: Right.

DR. TUCKSON: I would just like to emphasize where Joe is and take Francis' point. I think what we need to state is I think people are reading two different things here. So I think we ought to describe what your concern is. Francis I think teed it up very well, because you don't want to see a misuse. However, in the more positive activity, there needs to be the opportunity for research to do so and so. Nobody else knows that you're talking here about BiDil, so you need to declare what your anxiety is.

DR. FITZGERALD: Okay. We are a little late for our break, but let's do it right here, if that's okay with everybody. It's 11:00 now, and I think we're supposed to have a 15-minute break.

DR. TUCKSON: So if you're not here by 11:15, woe will befall you.

(Laughter.)

DR. TUCKSON: And we're going to have the cameras turned to your vacant spot so all of America will know you're not here.

(Laughter.)

(Recess.)

DR. TUCKSON: Thank you all for resuming on time. I mean to tell you, there are so few people with whom woe will befall. It's amazing.

Mr. Chairman, let's keep going.

DR. FITZGERALD: First of all, I just want to thank everybody for the comments and the insights. They are greatly appreciated. However, I did overstate the case a little bit earlier when I said this was our opportunity to sort of realign the universe and move stars around. The one thing I forgot to tell you is we can't mess with time; it just keeps going. So we have to keep going, and if we can be more succinct and targeted in our comments, that would also be greatly appreciated, but I do not wish to cut you off from making your comments.

So we're going to move on to gatekeepers. Now, again, it's important to understand here what we mean by this term. These were the groups that were identified as those that can enable, halt or redirect the course of pharmacogenomic technologies, and therefore they affect the integration and the patient access. We divided these entities into four groups: industry, the FDA, CMS and other third-party payers, and clinical practice guideline developers. Again, these were the ways that we broke it out. We thought that perhaps this was the most constructive way to do it, but we are willing to hear from you on that issue.

Looking at these groups, again the points of our discussion were are we covering the major issues, is there anything we're missing, and what are the high priorities. So looking at the role of industry, manufacturers' perceptions of risk and return on investment influence whether and how pharmacogenomic

products are developed and marketed. So we talked before about incentives. There are disincentives to develop pharmacogenomic products. That can lead to a segmented market, which can lead to decreased profitability and can cause additional responsibility involved in coordinating co-developed products.

Then there's the role of the FDA. FDA approval affects manufacturing practices, conduct of clinical trials, market clearance, postmarketing surveillance, access to pharmacogenomic products and their use in clinical practice. That raises questions about the adequacy of genetic test regulation, which we will also get into this afternoon, so we don't have to solve all those issues here, the extent to which genetic data submissions will be required, premarket review of co-developed products, and labeling of pharmacogenomic products.

The role of CMS and other third-party payers. Ability to obtain coverage and favorable reimbursement critical to manufacturers' willingness to invest in R&D of new pharmacogenomic products, and the challenges here include the fact that Medicare does not cover preventive services, private plan coverage may be difficult to obtain, especially because of limited clinical validity and utility information, reimbursement may not be adequate, and uncertainty about and variation in plans' evidence expectations.

Then we have the role of the clinical practice guideline developers. So the availability of practice guidelines affect the coverage of pharmacogenomic products and their uptake by health care providers, and evidence-based practice guidelines for pharmacogenomic products are indeed lacking.

So looking at this, are these the major issues? Have we missed anything? Are these the things of highest priority? I open it up to your comments. Remember, we haven't gotten into the recommendations yet. These are just the issues. Everybody seems all right. This is good. We like this brevity.

All right, let's look at the recommendations. Do they work as they are currently worded? Is there anything we're missing? Should some be deleted?

The first one. In looking at these recommendations, this is 6A, and this was flagged by the task force as being of higher priority. "CMS should clarify in writing that pharmacogenomics tests are diagnostic and thus eligible for Medicare coverage."

DR. ROLLINS: It is true that CMS looks at certain pharmacogenomic tests as being diagnostic in patients who have signs and symptoms of a particular disorder. CMS does not look at pharmacogenomic tests as being diagnostic in patients who do not have signs or symptoms of a particular disease. Again, going to the point of we don't cover preventive services, and for a person to have a predisposition for a specific genetic disorder, even though he or she may not have signs or symptoms of it, for that reason it would not be covered under that specific scenario. But as I said, if a patient did have signs and symptoms, then it would be covered.

I think this was one of the recommendations that was made before, that we made earlier, and I think currently the Secretary is looking at whether or not Congress can give us a designation for a prevention category. But at the current time, we don't have that.

DR. FITZGERALD: And if this were to stay as it is written, it would be supporting that change, that you would have a prevention category.

DR. ROLLINS: Correct.

DR. FITZGERALD: So then the question is do we want to support that change?

DR. FERREIRA-GONZALEZ: Could we make a recommendation to support that change so the underserved are being met?

DR. FITZGERALD: Pardon?

DR. FERREIRA-GONZALEZ: Could we make a recommendation to support that change?

DR. FITZGERALD: Well, this does I think, in essence, do that. Do you want to be more specific and say, for example, recommending that --

DR. ROLLINS: You could say, for example, in addition to covering patients who have signs and symptoms of a particular disorder, we're proposing that patients who have a predisposition for a genetic disorder, even though they don't have signs and symptoms of it, the genetic test should be --

DR. FITZGERALD: And as I've just been informed, that would make us consistent with the coverage report that we've already sent along. But I think that specificity is fine to put in there.

Yes, Anand?

DR. PAREKH: And I think another way to say it, if James thinks this is acceptable, is differentiating between primary prevention and secondary prevention. In getting at the heart of the matter, it's primary prevention when individuals are asymptomatic, don't have the signs and symptoms and Medicare would not pay for it. But increasingly, for secondary prevention when there are signs and symptoms, Medicare would potentially pay for it.

DR. FITZGERALD: Francis?

DR. COLLINS: I guess I'm a little confused about signs and symptoms when we talk about pharmacogenomics. So if somebody comes in who has a diagnosis, they have signs and symptoms of an illness, they need a treatment, the treatment would be optimized if a pharmacogenomic test was first done to assess whether this is the right drug at the right dose, would that be currently considered acceptable under Medicare's definitions of when they will cover this kind of test?

DR. ROLLINS: Yes, because the patient would have signs and symptoms, or signs or symptoms, of the disorder.

DR. COLLINS: Okay. They wouldn't yet have signs and symptoms of an adverse drug reaction. You're not requiring that.

DR. ROLLINS: No.

DR. COLLINS: Okay, so that's good. But what this would say is that the earlier conversation we had about doing sort of prospective pharmacogenomic testing as, for instance, with G6PD and the military, would not be something that Medicare would currently cover. You'd have to come in with diagnosable signs and symptoms containing illness for which drug therapy is needed before Medicare would cover the cost of doing that pharmacogenomic test?

DR. ROLLINS: At the current time, that is correct.

DR. COLLINS: Well, obviously, I guess I would agree, then, if it's possible, to expand that universe of opportunities to the prospective one. That would be a good thing, and it is consistent with what SACGHS has previously recommended.

DR. FITZGERALD: Cynthia?

MS. BERRY: I don't know if we need a recommendation on this or not, but I know that CMS has employed the approach of least costly alternative, and in the area of pharmacogenomics perhaps that doesn't apply or it's more difficult to apply, because you can't just say here are two drugs that are comparable and we're going to pay for the cheapest one. There's a budget reason for that, and I'm not saying it's invalid, but as we drill down deeper and the science develops such that some people could not use the least costly alternative, perhaps there's room for at least acknowledging it in the body of the report. I'm not certain that it rises to the level of a recommendation, but as long as we're at the CMS section, I thought I would bring it up. I'm not certain what our recommendation would be.

DR. FITZGERALD: But as far as this recommendation goes, that would still be in play even if we extend this recommendation to a preventive mode as well as a diagnostic one where signs and symptoms are already present. Is that correct?

MS. BERRY: Well, these are tests, and the other would be more once you've got the tests, what therapy would you use.

DR. FITZGERALD: Okay. Thank you. I think we'll definitely, following Jim's and Francis' comments, we'll make this more specific, and also make it clear that it's consistent with our earlier coverage report.

6B. "Health insurance plans should be more transparent in how they make coverage determinations for pharmacogenomic technologies by developing guidelines that define the type, quality and standard of evidence that must be met for pharmacogenomic technologies to be covered. Whenever a particular pharmacogenomic technology is denied coverage because it does not meet these evidentiary standards, health insurance plans should inform the test developer what additional evidence is needed."

Yes, Cynthia?

MS. BERRY: I'm the skunk at the party. I don't know if it goes here, and I think these recommendations are just fine. A question rises, and again, I don't know if it rises to the level of a recommendation or should just simply be touched on briefly in the report, and that is the impact of pharmacogenomics on the development and use of health plan formularies. Formularies are used in an aggressive way to help figure out what therapies are best, how can we manage costs, and this is something that is quite extensive in the private sector, and of course Medicare Advantage beneficiaries are subjected to that as well. There's a difficult tension between figuring out what drugs and therapies you're going to have on your formulary and reimburse for, and pharmacogenomics, because you may have a certain drug on your formulary and you'll pay for that, but some person could not benefit from that drug or therapy because of a particular genetic issue or marker.

So I'm wondering if it is worth considering a recommendation about when we have evidence like that, concrete evidence, not making that individual go through a rigorous appeals process, the standard thing that you have to do if you're going to go off formulary. I don't know what the recommendation would look like. I haven't thought enough about it.

DR. FITZGERALD: I don't want to jump to the next one before anyone else wants to comment, but the next one talks about addressing evidentiary gaps. That's pretty broad, but it sounds to me like in one sense you're addressing an evidentiary gap.

MS. BERRY: I'm saying when the evidence is out there already, how do we manage the tension between health plans' use of formularies and making sure that people have access to the therapies that they need that may not be on a formulary? We don't want to eliminate formularies, but we need to somehow reconcile the two.

DR. FITZGERALD: Reed?

DR. TUCKSON: I want to be careful here, because I'm from that industry, that I don't have a conflict, but the use of the word "more," they should be transparent, and that implies that they're not. I don't think that helps.

DR. FITZGERALD: Oh, I see, I see.

DR. TUCKSON: A small point.

DR. FITZGERALD: We're just trying to get all the flaws out of the glass, that's all.

But thank you, Cynthia, on that. Do you think we need a recommendation directly to that, a formulary recommendation?

MS. BERRY: If I had one I would blurt it out, and I don't, but I think at a minimum it should be acknowledged briefly in the report.

DR. FITZGERALD: As an issue that certainly needs to be --

MS. BERRY: But perhaps someone else has an idea. That's why I just wanted to raise it.

DR. FITZGERALD: If you do later, you can always drop us a line.

Okay, 6C. "HHS should provide resources to relevant agencies to address evidentiary gaps identified by health insurance plans."

Reed?

DR. TUCKSON: I don't want to be the skunk at the party here either.

DR. FITZGERALD: We're getting so many that it doesn't much matter.

(Laughter.)

DR. TUCKSON: To say that the Secretary should provide resources to fill evidentiary gaps, I mean the budgeting process and the prioritization -- we're getting ready to come back with a large pop study -- I mean, there's a lot of stuff on the plate here. I think it's kind of tough to make a serious recommendation that HHS should provide resources. It's pretty definitive here that we're saying this is more important than some other things. I'm not sure how to handle this.

DR. FITZGERALD: Anand?

DR. PAREKH: Off of Reed's point, and maybe Dr. Downing can comment as well, I'm not sure if this recommendation went forward, if the Secretary's office would know what to do with it. Maybe it's just kind of a statement here and there's more in the briefing packet, but it's a bit broad and vague.

DR. FITZGERALD: I'm just making sure that it's the same as it is in here. Okay, this is exactly how it's in our text.

Emily?

DR. WINN-DEEN: I guess the problem I have with it is, as much as from a manufacturer's point of view I'd like to say this is all on HHS' shoulders, I don't think it really is. I mean, I think there's an obligation from both parties, the manufacturers, drugs and devices, to play a part in closing the gap of evidence so that a test can move into normal clinical practice, and it's not just an HHS activity.

DR. FITZGERALD: So would you want to delete or rewrite?

DR. WINN-DEEN: Well, I don't know. I'm not in the delete mode, but I think you need to definitely say to encourage public/private partnerships or something in there.

DR. EVANS: I'm in the delete mode. I think this is so broad as to be meaningless, frankly.

DR. FITZGERALD: All right. But you don't have any specification to give to it which would make it meaningful?

DR. EVANS: No.

DR. FITZGERALD: Scott?

DR. McLEAN: I just want to go back for a second to B. Different health insurance plans will have to make a judgment call on standards of evidence and whether or not something merits inclusion in their services. So there may well be that different insurance plans will have different interpretations of this and offer different pharmacogenomic coverage. That's going to be a marketplace issue, and then the consumers will go out there and say I like this insurance company because it provides me with these services. Is that the intent of putting the burden on the insurance plans to make that judgment?

DR. FITZGERALD: To at least be transparent about what they're doing?

DR. McLEAN: Sure, or to even be in that role in the first place. So each insurance plan will then have to have internal expertise on making judgments about pharmacogenomics, right?

DR. TUCKSON: Well, I think this takes us back to the general conversation about genetic exceptionalism and so forth. At the end of the day, all health plans follow a pretty rigorous and a pretty standard way of viewing the evidence for any of these new things. A lot of it is based on CMS guidance, first of all, so CMS is enormously important in this, and then we all have various ways of doing it. So I

don't think that there will be any super-special thing about pharmacogenomics per se. It's just simply is it in the peer-reviewed literature, is it evidence based, et cetera, and then what is the stuff that Cynthia and Debra commented on in terms of the availability of cost effectiveness kinds of information so you can do the pharmacogenomics and so forth.

So my point is, Scott, in trying to be responsive to you here, that this will be handled the way that everything else is handled. The challenge then becomes having appropriate research and literature assessment available.

DR. FITZGERALD: Okay, thank you.

Gurvaneet, is this on 6C?

DR. RANDHAWA: Yes. I'm wondering if this is not overlapping with 11B, which is also talking about resources and coordination done by the HHS. To me it seems to be speaking to the same issue.

DR. FITZGERALD: Okay. My sense with this is we may have hit a delete for the most part on this, because it is rather broad. So, everybody, is that the general feeling? Okay, I don't see anybody dying in this trench, so we'll let that one go and on to the next.

Again, the next part here is the implementation section, and this is taking the information that is developed in research and gone through the gatekeepers and putting this out into clinical practice. This would involve education and guidance, information technology and pharmacogenomics, economic implications, ethical/legal/social issues, and the coordination of HHS activities. So again, which are the major issues? Are these adequate, and should we get rid of some? Which we've actually done now.

So provider education and guidance. Genetics education and training by health professionals, payers, regulators is insufficient. Limited information is available via labeling and practice guidelines about how to interpret pharmacogenetic test results and how to use them to inform treatment decisions.

These are the issues. Genetics education is needed to help consumers make informed treatment decisions. Direct access to pharmacogenetic testing via over-the-counter sales or direct-to-consumer marketing may increase inappropriate use of these tests. This could lead to increased health care costs, potential for misinterpretation of test results, misinformed health decisionmaking, and adverse health consequences. The uptake of electronic health records is still in its early stages and there's no consensus yet on how genetic information should be stored in these records and who should have access to the stored data. Obviously, lack of harmonized standards for storing and exchanging genomic data, and need for pharmacogenomic decision support tools and reminder systems.

Economic implications. The use of these technologies will likely add to health care costs, at least in the short term. Need to examine the benefits and costs of investment in these technologies, and there's little research -- we've heard this before -- on the cost effectiveness of pharmacogenomics interventions.

What are some of the ELSI issues that we haven't raised yet? Financial barriers to pharmacogenomic products, although that has been raised now; high co-pays under insurance and no insurance can result in access disparities; concerns about genetic discrimination, which we talked about a little bit; and liability risk if the provider fails to administer recommended tests.

In the coordination area there are lots of activities that are ongoing. We have a list in Appendix A. There may be more there, but as you can see it's already an extensive list, 23 pages, and yet there's no single coordinated framework or action plan to address pharmacogenomic challenges or share information about activities among the federal agencies.

These are the issues that we have highlighted. Is everybody good with these issues? Is there anything that we've missed? Is there anything that you think is inappropriately highlighted?

DR. LONG: May I just comment?

DR. FITZGERALD: Sure.

DR. LONG: I do think there are some activities on behalf of professional organizations, professional medical organizations and coalitions among organizations. So Slide 65 sort of dismisses everything as insufficient. I mean, there are nascent activities going on to educate practicing physicians, to incorporate it into medical curricula, among genetic counselors, among human genetics testing groups. So it's a little bit all dismissed.

DR. FITZGERALD: Well, the intent there is not to dismiss anything. The intent is to acknowledge that even in spite of what's being done, as you mentioned, sort of in a nascent way, is not sufficient. We don't want to stop here. We don't want to say that where we are is a good place.

DR. LONG: Nascent is what I'm thinking.

DR. FITZGERALD: How about if we say "is currently insufficient"? Is that okay?

DR. LONG: Yes.

DR. FITZGERALD: We don't want to downplay anything, because everything that's going on now is certainly needed, but we need more.

Yes, Francis?

DR. COLLINS: Again, just a fine nuanced point here. In Slide 68, this implication that pharmacogenomics will add to health care costs, well, maybe not if what you do is reduce the incidence of adverse drug reactions, which cost a huge amount both in terms of health care economics and in terms of human suffering. So maybe that's a little too strongly worded there, as if it's a definite uptick in the overall expenses of the medical care system. I would argue that really ought not to be the case.

DR. FITZGERALD: Well, we do have the word "likely" in there. The question is if you had to make a guess which way it was going to go, which way do you think it's going to go?

DR. COLLINS: I don't know.

DR. FITZGERALD: Debra?

DR. LEONARD: But what you could say is that pharmacogenetic technologies are an additional cost to the health care system, or the use of pharmacogenetics is a new development in the health care system, and then the need to examine the benefits and costs of investment or use of pharmacogenetic technologies is your second bullet. It's new, so it's not something that's currently being done. But in the balance, the second point is the question of is it going to be cost effective and save on length of stay or adverse reactions such that the cost of a $300 test outweighs the savings.

DR. FITZGERALD: Well, again, remember that these are issues and not recommendations. So what we're doing is raising these as issues, and in the discussion, where we look at the economic implications, we do in a sense -- this is bulleting what's in here, and let me just read that. "The rapidly increasing cost of health care is a major concern in the United States. Technological innovation is among the most important drivers of those costs," which, just as you mentioned, it is a new technology. "While new technologies may improve the length and quality of life or be cost effective, they almost invariably increase total costs."

DR. EVANS: But I think that Francis' point is right. I think there should be an acknowledgement in this first bullet that they may add to health care costs, but on the other hand may actually reduce costs, which is different from cost effectiveness. Cost effectiveness says it's worth the money. It is conceivable that pharmacogenomics will save money.

DR. COLLINS: That analysis has already been done for warfarin. If you incorporated right now, based on what we know, just P450 and BKRC1 testing, you would save money overall for the health care system because of all those adverse events that you would have predicted and prevented.

DR. FERREIRA-GONZALEZ: Taking up that point, when you look at infectious disease, when we introduced HPV testing for Pap smears, you increase the cost of taking care of that particular patient, but the overall cost of the health care has been significantly reduced. So maybe that's how we can phrase it, that maybe we're adding a test to that patient, but the overall cost will be significant savings.

DR. FITZGERALD: Right.

Cynthia?

MS. BERRY: Another thing that we should factor in, and I think we could craft a recommendation on this, but in the real world application we understand the cost savings overall downstream. Federal programs have to pay attention to what the Congressional Budget Office would say. So any changes, legislative changes in federal program coverage and other statutory changes are all going to be dependent on whether CBO decides there are cost savings or not, and traditionally CBO does not recognize downstream savings or avoiding hospitalizations or avoiding adverse drug events. They simply say what's the cost of the therapy, how many people would benefit from the therapy, multiply that and then add in a few additional numbers for the woodwork effect, and suddenly that's the cost. It's frustrating to everybody in health policy because we know that in the real world we can achieve savings, but in the world that federal programs have to pay attention to, they can't get CBO to acknowledge those savings. If there's some way we can craft a recommendation, whether it's pushing for some form of dynamic scoring, or if that's a bad word call it something else, that would push CBO to at least consider these types of data that would help make the case and that would lead to enhanced coverage, at least in federal programs. But it's a real problem that we face.

DR. EVANS: I think that would be a tremendously important idea. I didn't realize that about CBO's perspective, which seems unbelievably limited, and maybe that should be a separate recommendation, take out that first bullet and say something like pharmacogenomics may increase costs but ultimately, in an overall sense, may decrease costs, and add something about how CBO's perspective should --

DR. FITZGERALD: Just for this issue, if everybody would look -- it's on page 9 of your executive summary. Number 9 is the economic value of pharmacogenomics, and that is another recommendation that we are going to come to. We do seem to be getting a little bit of an overlap here, so one way to deal with that would be to either change this first bullet and deal with the issue in 9, deal with it here -- I mean, we have to just figure out where we want to go with this. We could in this one -- the first bullet could say, "Currently there is concern that the use of PGx technologies will likely add to health care costs" or "may add to health care costs." We could do it that way, "there is concern."

DR. COLLINS: Or you could just drop the first bullet.

DR. FITZGERALD: And pick it up in 9, right.

Emily?

DR. WINN-DEEN: I'm just a little confused because these are not the recommendations we're looking at here. These are just summaries of what's in the text.

DR. FITZGERALD: Number 9 is where we pick it up. That's right. These are the issues that we're talking about here, and that goes to 9. I'm sorry.

DR. COLLINS: But let me then argue that the text you read us needs some tweaking because it overstates that we know what the consequence is going to be in a very negative way.

DR. FITZGERALD: Right. So the reality is there is concern. I think we can say that. I mean, that empirically we can say in these issues.

Yes, sir, Michael?

DR. AMOS: I think that what everybody is kind of worried about is that somebody will look at

this one statement and take it to several orders of magnitude higher than it really means, and by taking it out or recrafting --

DR. FITZGERALD: They can't see this statement. This is an issue that's in the report. But you're right, we can rework that part of the report that I did read.

DR. AMOS: But the critical piece is, yes, it's going to cost a lot of money to develop these technologies, but the goal is to lower health care costs.

DR. FITZGERALD: Understandable, understandable. We can go back, Francis, in that section and rework that.

Any other issues that we covered that are raising red flags? No? Okay, then let's get to the recommendations, 7A.

DR. HANS: I actually had one point.

DR. FITZGERALD: Sure.

DR. HANS: I'm a broken record on this point, for those who are in the other work group. The last point is an argument that can be made for NIH's entire budget, and I hate once again to create an exceptional argument for this area of technology and would hope that the discussion in the report acknowledges that this is not specific for this technology or this application. It is overall for all medical technology, so it's not exceptionalized in any way.

DR. FITZGERALD: Oh, I see. Okay, good point. To be honest, I'm not quite sure how that comes out in the report, but I'll go back and look at that and make sure that that's also not the case.

In 7A, again this was flagged by the task force as a high priority. "As evidence of clinical validity and utility for a pharmacogenomics technology accrues, HHS should support the preparation of meta-analyses and technology assessments summarizing the evidence base. These analyses and assessments should be disseminated to professional organizations to facilitate their development of clinical practice guidelines," which gets back to something Rochelle mentioned earlier about the way people are trying to get up to speed on this.

Anybody have a comment?

DR. ROLLINS: You see a lot of meta-analysis looking at randomized clinical trials, as well as meta-analysis looking at cohort and case-control studies. It's extremely rare that you find meta-analysis of diagnostic studies simply because of the receiver operator characteristics, as well as the changing endpoints. I'd suggest instead of using the word "meta-analysis" you might want to use the words "systematic reviews," which a meta-analysis is, and you can say "systematic reviews looking at how test results were used in the management of patients," or something like that, again reiterating the word "management," but taking out the word "meta-analysis" and using "systematic reviews."

DR. FITZGERALD: "Systematic reviews," which is a broader term, which should be including meta-analyses and others. That's reasonable. All right, good. Thank you.

7B. "HHS agencies should collaborate with federal, state and private organizations to develop, catalog and disseminate case studies and practice models in the use of pharmacogenomics technologies."

Anybody? Everybody's good with that? All right.

7C. "HHS should provide resources to professional organizations that will help enable their membership to meet established competencies on the appropriate use of these technologies," again trying to facilitate what's already ongoing, which we judge to be a good thing.

Yes, Michael?

DR. AMOS: I'm sorry. Just on B, the drug companies and diagnostic companies do a lot of this as far as working with physicians and laboratories, reference laboratories in trying to teach them how to use their products. So maybe industry would be included in this. Because we've asked industry to do a

lot, maybe we can help industry.

DR. FITZGERALD: So you would say here "should collaborate with federal, state, industry and private organizations."

DR. AMOS: When you say "private organizations," does that include industry?

DR. FITZGERALD: Yes, I think.

DR. AMOS: Okay.

DR. FITZGERALD: But do you think we need to emphasize it? That's my question.

DR. AMOS: If it's included, then everybody's comfortable with that. That's fine.

DR. FITZGERALD: Good. And then C was providing resources to professional organizations. We're good with that.

I'm sorry. Cynthia is not.

MS. BERRY: C1 maybe. I throw this out to the group to find out if you think that there's a certain element of reporting that we would want to ask providers to engage in. What I'm trying to do is think about if there's a way to weave pay for performance, weave pharmacogenomics into the pay for performance concept that HHS might be moving towards, which is to incentivize physicians and other providers by paying them a little bit more to do certain things, and down the road the idea would be for quality measures. But initially, I think it will start out as reporting. So if they report certain data in, they will get enhanced Medicare reimbursement. Is there some recommendation that we can talk about, or is it all too preliminary, that would weave in reporting of data, what kind of data that could be incorporated in the pay for performance approach? I don't know if the science is still too new and we're not there yet, but if there is data that physicians would have that would be useful, if we would incentivize them to report that data somewhere, and then that could be woven into the pay for performance approach.

PARTICIPANT: We have to make sure they're covered first.

DR. FITZGERALD: Reed?

DR. TUCKSON: I think this is, Cynthia, right down the middle of the plate for what we started the meeting off with when Sheila was here regarding the America's Health Information Community and so forth. So this is the essence of what that's all trying to do, to find a way to connect the information around clinical practice that derives from a physician's office records and elevate that up in a more convenient way to larger activities. So I think we should try to find a way to connect that into the AHIC activity. I think that's the way you sort of get at that.

As regards the specific thing here, I'm still struggling with this one. I think that if we're saying that HHS should work with professional societies to facilitate the continuing professional development of their members, that's fine to me. But the idea that the government is somehow or another going to write a check to professional societies to help them do a better job in this area, then you get the radiology imaging committee comes forward and says, all right, where's my check for that, and it goes on and on and on and gets absurd.

At the end of the day, this is what professional societies do. That's what they're supposed to be doing. So the idea that the government is going to subsidize those societies to do this, clearly there must be some things that we can all do to help them to do their job. So we'd be working with them to facilitate the continuing professional development of the physician. That seems reasonable.

DR. FITZGERALD: Right. So right there, you're saying that using the words "provide resources," everybody is going to just think money instead of resources, which is broader than just money. Okay, good point.

Joe?

DR. TELFAIR: I was just thinking not too different than what Reed just said, and that's

because I don't know if this exists already. But efforts at either providing a mechanism for coordination or to coordinate, help and assist organizations in coordinating the effort there, because that would mean that you have a cross-organizational or even a collaborative, if you will, group that has representation from a number of organizations that will probably continue to work on what they're working on but that would have a number of things built in, which is the transparency issue that we need to talk about, the accountability issues that will be there, as well as having up to date, real-time assessments of the efforts that are going on.

So that's what I'm recommending, that instead of saying resources, saying coordination, provide a mechanism for coordination or facilitate coordination, whatever way you want to put it, but the idea would be that we would make a recommendation, and this may be something that's already there that just needs to be tweaked a bit that would be almost cost efficient on that, essentially. That's along the lines of what Reed was saying, but I was just thinking when I read this that that would actually be a better thing than that.

DR. FITZGERALD: Reed?

DR. TUCKSON: I think that's terrific. To nuance my comment, on the one hand I am legitimately concerned that HHS would be sending public money that's in short supply to the societies to accomplish this. On the other hand, the societies get very freaked out if government is going to try to coordinate their efforts to tell them how to practice medicine. So I think the idea of facilitating a rational effort where people are trying to work together, but the government certainly shouldn't try to coordinate medical societies in terms of how they're going to practice their profession. I mean, that's their expertise, but they need to be supported.

So I think the way you phrased it was good. I just realized I needed to give the other half of that balance/nuance here.

DR. FITZGERALD: Okay. So what do we have right now? How about "to facilitate the ongoing professional development of their membership that will enable their membership to meet established competencies"?

DR. EVANS: Again, can't we just say "work with," to "work with professional organizations"? Because you sure don't want to imply, like Reed says, that the government is going to be coordinating. Facilitating could also mean giving money.

DR. FITZGERALD: I like "work with."

DR. TELFAIR: I understand the facilitation part being difficult, because it is sort of what to do, but it seems to me that there are models that already exist around other things. I guess my point is that whatever way the wording comes out, it really needs to be a joint collaborative effort with the HHS and professional organizations.

DR. FITZGERALD: What we could do is we could say "HHS should work with," and then say "along the lines of," and if you could give us the examples of those models -- you don't have to do it now -- we could use those as an example, and that way you give an idea of how we should go. That's 7B.

DR. AMOS: So once again, industry has a lot of activity in this area in educating their customers.

DR. FITZGERALD: Right. We could use those models, right?

DR. AMOS: Well, I think what you want is some universal resources, some database or teaching tool that everyone can use, not just the professional societies, that would help industry as well to do what they do, because there's a significant activity that industry undertakes in working with their customers.

DR. FITZGERALD: So we're back in 7B again?

DR. AMOS: No, I think it's for both. I mean, you say professional organizations, but I think it's industry as well.

DR. FITZGERALD: So you're saying "HHS should work with professional organizations and industry." But how does that help enable their membership meet established competencies?

DR. AMOS: Well, you'd have to change it a little bit, but I think the role of industry in educating their customers and making the resource available to industry, the goal is to improve health care, and industry plays a large part in the teaching.

DR. FITZGERALD: Right. I'm just trying to make sure we don't have that somewhere else down the road here, which we might. We'll flag industry, and then we'll see if we've got it anywhere else down the road.

Anybody else?

DR. HANS: I have a few concerns, actually, about that last suggestion. The motivations of industry for providing information to practitioners, there are a variety of motivations in that. I would want the subcommittee to examine all the aspects of that suggestion. I would just say that the VA has published two reports on this issue through the National Center for Ethics in Health Care, the National Ethics Committee.

DR. FITZGERALD: Okay. Thank you.

7D was one which, again, the task force flagged. "FDA should continue to work with drug and diagnostic manufacturers to provide adequate labeling information so that clinicians can make dosing decisions based on pharmacogenomic test results. The labeling should clearly describe the test's analytic and clinical validity, and provide dosing guidelines based on test results." So we got the analytic in here anyway.

DR. LONG: I was thinking of saying you might not want to box yourself into dosing decisions, just decisions. At some time a test is going to come out which tells you which drug to use. Twice you refer to dosing, and you could just eliminate that.

DR. FITZGERALD: Okay, that clinicians can make decisions based on that. Right, okay.

DR. EVANS: As somebody who encounters a lot of confusion among clinicians about how to use these things, it may sound trivial but I would put specific guidelines based on test results. In other words, physicians are very unfamiliar with these types of things and are going to need very specific guidance. I think we should emphasize that.

DR. FITZGERALD: Okay. So we'll take out "dosing" and put in "specific."

DR. LEONARD: You may want to say "specific guidelines" or "recommendations" or whatever, such as dosing or drug selection.

DR. FITZGERALD: Okay, good.

DR. MANSFIELD: To slice this even finer, I think you might want to say which label you're talking about. The diagnostic label already has analytical and clinical validity usually of the test, but the drug label does not, as far as I'm aware. So you might want to point towards which label you're talking about.

DR. FITZGERALD: So instead of saying both drug and diagnostic?

DR. WINN-DEEN: I think we discussed this at the task force, and I don't know why the change didn't get made. But the drug labeling provides the dosing kind of information, and the diagnostic is the one that should have the performance characteristics.

DR. FERREIRA-GONZALEZ: Yes, because, for instance, you can do genotyping 2G6, which is going to be used for many different drugs.

DR. WINN-DEEN: Right. So we need to just clarify which parts of that are for the diagnostics

and which are for the drugs.

DR. FITZGERALD: So what you want to do is tie drug to dosing and diagnostic to selection?

DR. WINN-DEEN: Well, diagnostic is the thing that's going to have all the analytical characteristics that you're talking about, analytical and clinical validity.

DR. FITZGERALD: So everybody is comfortable with the general thrust of this. How about, Emily, if we rework that a little bit?

DR. WINN-DEEN: Sure.

DR. FITZGERALD: Okay, good. And we'll put in those other suggestions at the end about what Debra was talking about.

Okay, 7E. "FDA and NIH should continue their efforts to provide up to date, real-time prescription drug label/package insert information. The Internet-based DailyMed project currently underway will be wide-reaching, but to ensure that all sectors of the public have access to this information, these agencies should develop other ways to reach members of the public who may not have or use Internet access." Okay? Good.

7F. "The Office of National Coordinator for Health Information Technology should promote the incorporation of pharmacogenomic test information into electronic health records, as well as decision support systems and tools that can notify providers about pharmacogenomic test and labeling information that could help them make appropriate treatment and dosing decisions." Okay? Good. Great. Thank you.

7G. "Until the electronic health record becomes a universal feature of the health care delivery system, HHS should identify other ways to make best pharmacogenomic practices more readily available to health providers." This may also add, Reed, to the "working with professional organizations." All right, great.

Now information for the public. "HHS should fund studies of public awareness of the benefits, risks and limitations of pharmacogenomic technologies," and I think this got to an earlier issue we were talking about, hype versus what's the reality, where are we with the technology. So this would be part of that. Everybody is on board. Great.

8B, again one flagged by the task force. "HHS should ensure that educational resources are widely available through federal websites and other appropriate media to inform decisions about the use of pharmacogenomic technologies." This is just public awareness. Good.

8C. "HHS should dedicate resources to public consultation activities to gauge the public's receptiveness to and concerns about these technologies and their willingness to participate in clinical research studies involving pharmacogenomics." Here I do believe resources would include funding.

Joe?

DR. TELFAIR: Just a question of clarification, and maybe this is for your group. The issue of literacy, health literacy, in terms of the use of public education, I'm assuming that that was something that was taken into account in terms of how information is given out, level of understanding, because this one is related. I mean, I was waiting for this. So it does make a difference if it's understood before you can actually comment.

DR. FITZGERALD: Right, right. My understanding is literacy would be involved across the board. In the projects that have been done so far, and maybe Francis can tell us what the situation is currently with their consultation, but I do believe in some of the things that have been done that was taken into consideration, how to engage the people who were at these meetings that were held to get public engagement.

DR. COLLINS: That set of meetings is primarily focused on the question of large-scale

population cohort studies. So to the extent that you can map across those reactions into this area, there might be some information to be gleaned there, but it's certainly not asking the specific questions --

DR. FITZGERALD: No, but is literacy an issue that's taken into consideration when you're addressing that?

DR. COLLINS: Yes.

DR. FITZGERALD: Right. I think it is across the board. Thanks.

Cindy?

MS. BERRY: I was wondering if we might consider deleting 8A because I'd go out on a limb to say that there's very little public awareness. I don't know that HHS needs to fund a study about public awareness. My guess is they probably don't know anything and we should just move right into assuming that they don't know what they need to know and that they should provide resources to help educate the public.

DR. FITZGERALD: Hang on one second. Just let me make sure here that this is accurate. I think this was preliminary to 8C, but you're right, if you're doing public consultation you're presumably going to find out what the public knows and doesn't know. But in any case, yes.

Joe?

DR. TELFAIR: What I would actually suggest is that under HHS, if you look at what's going on in HRSA, which is focused on access, if you look at what's there, there are projects past, current, and in process related to this issue of public awareness. Maybe the recommendation would be that they use existing mechanisms to enhance, instead of just assuming that they don't exist. So I would focus on that. Again, it's using what's already there and just tapping into that to use for this purpose.

DR. FITZGERALD: So we could just say HHS should continue to fund studies, and then cite the ones that you mentioned, such as, et cetera.

DR. TELFAIR: They already have in place the commitment to fund these. It's not studies but it's awareness projects.

DR. FITZGERALD: Oh, that's the education piece then. I think we have three levels, and I'm just wondering if we need three. We have awareness, education, and then public consultation. So are we saying that we can fold 8A into 8C? Is that the general sense here? We could always just say awareness and consultation? Okay. Then that would help because we can get rid of one. All right, then we'll do that, fold 8A into 8C.

Reed?

DR. TUCKSON: Just one point of order as you continue to go through this. I'm trying to see if we can find Greg to just comment. They're going to look for him. I think it's important to connect this, at least one recommendation, if the committee is willing, to whatever it is that this personalized health agenda is that HHS is already doing. Is that in a different section? Because if it is, I don't want to be redundant. But I think HHS has pretty well telegraphed to us where they're going to spend their money and where their energy is. So I think that if you know there's a train leaving the station with lots of gas in it, you might want to jump on board that train. Anything else is sort of listening as the train goes by.

DR. FITZGERALD: Right, and I think in our discussions with Greg, this is one of the reasons we tried to pick some for higher priority rather than lower, because this is where the Secretary's personalized medicine initiative was already.

DR. TUCKSON: So that helps me, then, that you're putting it there because you know that there's a train. What I'm saying is you might want to say I'm going to catch the 3:09 outbound to Philadelphia.

DR. FITZGERALD: Well, we know there's a light at the end of the tunnel. This time we're

hoping it's a train.

(Laughter.)

DR. LONG: May I follow up on that, too? It's an observation again, reflecting back on Slide 80. It's referring to electronic --

DR. FITZGERALD: I'm sorry?

DR. LONG: 80, 7G. It's referring to electronic health records, as though they're universal, and they're not right now.

DR. FITZGERALD: No, it says "until."

DR. LONG: Right now, for example, in HMOs there are a lot of electronic health records, but they're different from organization to organization, and I think I'm reflecting on what you're saying, that one of the goals here is getting things uniform so you can do studies across groups.

DR. FITZGERALD: That's one, right.

DR. LONG: And you might need to be more --

DR. FITZGERALD: In the interim, we want to do this, okay? So we do have a thing where we say we need to put those databases together, absolutely, and they've got to talk to one another, absolutely. In the meantime, we've got to also continue to not let this fall through the cracks.

Yes, Joe?

DR. TELFAIR: Just a model that you recommend is what already exists in state genetic health plans, what is part of the list of things that state genetic health plans should be working on. This comes out of HRSA, MCHB. Just a point of reference.

DR. FITZGERALD: Okay. This is for which one?

DR. TELFAIR: For the recommendation I was making earlier in relationship to --

DR. FITZGERALD: Educational resources?

DR. TELFAIR: Yes. Since A and C are going to be combined --

DR. FITZGERALD: Okay, great. Thank you.

Then there was a comment back here. Do you have a microphone back there somewhere? Oh, okay, you got it. I think it has to come on. Go ahead, just try it.

DR. MITTMAN: I'm Dr. Ilana Suez Mittman, and I'm with the Maryland Office of Minorities and Health Disparities. I would try not to merge. I really like 8A through C as they are, and I think that there is a very important distinction between education and awareness of the public, engaging perceptions of all groups about this technology and their desires and needs and how those can be met. So I would try not to combine or merge any of those initiatives as they're individually distinctive, I think.

DR. FITZGERALD: Okay.

Yes, Barbara?

DR. McGRATH: I think that's terrific. Maybe what I would do is build on that and talk about -- I'm going back and forth here. I agree that we don't necessarily need studies on awareness, but we definitely do on perceptions and opinions and beliefs. So maybe using that specific language of perceptions rather than awareness would keep it clear, separate from awareness. Does that make sense?

DR. FITZGERALD: Okay. So you're saying for 8A, "HHS should fund studies of public perceptions and beliefs of the benefits, risks and limitations of pharmacogenomic technologies." Is that correct?

DR. McGRATH: I'm by nature a deleter, so in C I would put the words "public perception" in there.

DR. FITZGERALD: Oh, got it, to gauge the public's receptiveness to. Okay, thank you.

We're jumping around just a little, but I think we're good with 8. Is that correct?

Now we're on to 9. This was, again, one that was flagged by the task force and something important since it's come up several times, about the economic value of pharmacogenomics. "HHS should determine the economic value of investments in pharmacogenomic research and development relative to investments in other health and non-health-related areas. This assessment should analyze the effects on society as a whole, as well as each individual stakeholder." This goes back to that discussion we were having before. Is it going to affect an individual? How is it going to affect society? How does it fit into the whole larger picture?

Debra?

DR. LEONARD: I'm just concerned by the emphasis on the economic value of the research and development, as opposed to the use of pharmacogenomic technologies.

DR. FITZGERALD: Okay. I think we could easily put that in, research, development and use.

DR. LEONARD: Well, do you want to assess the economic value of the research and development? The Secretary has already come and said that he's investing in this. This is a high priority. I mean, are we going back and asking him to assess the first three research and development recommendations to say the cost effectiveness of those or the value of those, or are we talking about really the clinical use of pharmacogenetics, which is the part that's here? I mean, that's the part we're in, the section of the recommendations we're in.

DR. FITZGERALD: Right, right.

DR. LEONARD: The clinical use of these.

DR. FITZGERALD: My sense was, if I remember correctly from our meeting, that it was difficult to tease these all apart. I mean, I think use was supposed to be in here anyway. It was sort of implied, although you're right, it should be put in there specifically.

DR. LEONARD: But couldn't it just be reworded that HHS should determine the economic value of pharmacogenetics relative to investments in other --

DR. FITZGERALD: Right, we could just put "investments in pharmacogenetics relative to investments," right, and not run into that problem.

DR. EVANS: It seems to me in this area might be the most appropriate place for the previous discussion, like what Cynthia brought up, explicitly saying that pharmacogenomics does hold the possibility of lowering health care costs and that this should be looked at in some kind of global sense in not in a limited sense, so that we encourage the CBO to --

DR. FITZGERALD: I think this is what we have in that second paragraph.

DR. EVANS: But I think it should be more explicit.

DR. FITZGERALD: Okay. So the effects on society as a whole as well as each individual stakeholder. Why don't you write it out?

DR. EVANS: Okay.

DR. FITZGERALD: Now, do we need the CBO example?

MS. GOODWIN: That's only for legislation.

DR. FITZGERALD: That's kind of legislative limited, right.

MS. BERRY: Well, it is. So it pertains to federal programs. The private sector is not bound by what CBO does, but it's also an awkward, unrealistic world, CBO, but it's something that we have to face. So I think it probably needs its own little recommendation.

DR. FITZGERALD: Recommendation, or just put it in the report?

MS. BERRY: Well, start out by putting it into the report. Now, if we're going to weave it into this same recommendation, we could maybe direct HHS to drill down a little bit more into the types of data that CBO might be receptive to examining. Maybe we can get at CBO indirectly that way and not

have a new recommendation but amend this current one.

DR. FITZGERALD: Could you write up a possibility for that? Okay. I think it could fit in sort of like "such as looking at this particular issue."

DR. FERREIRA-GONZALEZ: I'm just trying to figure out that we don't lose some of the points that Debra was trying to make earlier about outcomes research and will we allow for funding for investigators to look at the economic benefits or the impact on the whole health care. So have we covered that in the first part of research and development, or should we add in this economic value that maybe HHS should fund some of this kind of research?

DR. FITZGERALD: Well, I think what we decided here anyway was to drop -- we would just say "the economic value of investments in pharmacogenetics relative to investments in others." Is that okay? Because it's inclusive.

DR. FERREIRA-GONZALEZ: Determining the economic value, will that provide funding for investigators to do outcomes research? Is that part of that?

DR. LEONARD: That was added back in the other research and development recommendations, I think.

DR. FITZGERALD: Oh, back in the first section? We're looking at that right now. As we look at that, anything else on 9?

Okay, we move to 10, ELSI research. "NIH should fund more research on the ethical, legal and social implications of pharmacogenomics. Gaps in current knowledge include questions about whether integration of pharmacogenomics into clinical and public health knowledge will exacerbate health and health care disparities, limit access to or decrease the quality of health care, increase medical liability, or result in genetic discrimination. Steps should be taken by HHS to address any problems identified through this research."

Does this capture it? Francis?

DR. COLLINS: Just the notion that we are, after all, in a zero sum at the present time as far as NIH budget. So if you say more research, the implication there is that you will do less research of something else. If that's what you mean, then okay, say it. But if what you really mean is that NIH should continue to encourage research on the ethical, legal and social implications of pharmacogenomics, that might be a little easier to fold into all of the other ELSI needs that are out there, because there are plenty of them.

DR. LONG: I also endorse encouraging high-quality applications, and they will get funded through the present system, rather than needing to start a new program.

DR. FITZGERALD: Absolutely. I hope we weren't necessarily implying starting a new program. But what's the level of funding right now?

DR. COLLINS: For pharmacogenomics research?

DR. FITZGERALD: For ELSI.

DR. COLLINS: Oh. For ELSI, it's about $20 million a year.

DR. FITZGERALD: And what's the percentage? Do you know?

DR. COLLINS: It's 5 percent of the NHGRI budget, and there's ELSI research going on in other institutes as well that's not captured in that number.

DR. FITZGERALD: Right. So we should say "continue to fund." "To ensure"?

DR. COLLINS: Or encourage.

DR. FITZGERALD: "Encourage funding." But we have funding.

DR. LONG: We need to encourage people to apply the high-quality applications. It's promote, encourage, help, assist, development of.

DR. FITZGERALD: Joe?

DR. TELFAIR: I think I'm going to add something, actually, to what's being said, because the reality is that you have more than one mechanism within DHHS that's looking at these issues, and it seems to me that it's a very straightforward process, something that actually was done not too long ago by Francis' shop, which is to do some work looking across agencies and programs that already exist to collaborate on high-quality research in this area, because you're supporting an effort that exists and you're just reinforcing an effort that exists and you're not adding anything to that beyond having them just reinforce, which is a good thing, what is already there and should continue, which is cross-cutting.

DR. FITZGERALD: Right. Now, my question is does that fall under the next recommendation, which is trying to coordinate all the HHS pharmacogenomics activities, which I presume would include ELSI? I don't want to duplicate recommendations if we don't have to. I'm presuming that includes ELSI, if that's okay. Or do you think we need to emphasize this? What we could do in that one is give an example such as the ELSI endeavors that are ongoing at various institutions, something like that.

DR. TELFAIR: I just think that if you're going to make a recommendation such as this, given the current environment, given what we anticipate to be the environment for a bit, we need to make recommendations that are going to be looked at as being realistic. That's all I'm really saying. So I'll leave it up to you to decide.

To me, the whole idea of coordinating and collaborating is an effort right now that's a big emphasis. If the recommendation is going to be there for something to be done, that's the direction it would go. I don't want to delete something, but I'm just saying that 10 and 11, to me, go together to form something a little bit stronger and more realistic.

DR. COLLINS: So how about for that first bullet that instead you word it something like "NIH should encourage high-quality research on the ethical, legal and social implications of pharmacogenomics in collaboration with other HHS agencies."

DR. FITZGERALD: Okay. Great. That's good. I'm good with that.

Jim?

DR. EVANS: So moving on, I hope, the third paragraph or sentence, the last sentence seems so -- I'm not sure that the HHS would know what to do with that. That seems unbelievably broad, and I'm not in favor of leaving things in that aren't -- I think maybe you can explain. I missed the last conference call.

DR. FITZGERALD: Right. I think the idea here was just to say whatever is discovered in the research should then be followed up on. I mean, you're right, in one sense one could assume that would be done. I think the idea was rather than assume, state. But if you have a different way, a better way of --

DR. EVANS: I'm just struggling with it because it seems so broad, and I'm just not sure if I were in the HHS office I'd know what to do with it.

DR. LEONARD: The solution may not be something that HHS can do anything about either.

DR. PAREKH: I think that's a very important point. If one of these tests actually does limit access or decrease health care quality, it's not that HHS is going to have the magic bullet to solve that.

DR. EVANS: I think that all of our recommendations have the implication that they aren't just going to lie there. You could probably add that to every recommendation we make, so why do it here?

DR. FITZGERALD: Okay.

DR. EVANS: The one other thing that I'd ask is in the ELSI recommendations, it seems to me from previous discussions of the group that the possibility of litigation looms very large as a driver for the

adoption of pharmacogenomics into medicine. I'm just wondering if that should somewhere be explicit in the ELSI chunk. There's a unique or a very powerful relationship between the legal issues and the --

DR. FITZGERALD: Right. So increasing medical liability is --

DR. EVANS: Maybe just acknowledging that that is likely to be or is seen by many to be a real driver of its adoption.

DR. WINN-DEEN: Jim, I think there's a section in the report that goes into that. We just didn't have it in a recommendation because we weren't sure that that was anything HHS really had control over.

DR. EVANS: That's fine.

DR. FITZGERALD: Debra?

DR. LEONARD: As we move through the recommendations, there are a lot where we're asking NIH to support research on various things. I would recommend that the subcommittee pull all those together and see how much we're recommending NIH to spend more money that doesn't exist and how to prioritize those, because that will probably be something that HHS will do, and we're not giving any relative priority to these things. So I think that might be useful.

DR. FITZGERALD: As you go back through the ones we did flag, again the ones with the little stars were the ones we were saying were of higher priority.

DR. LEONARD: Maybe pulling out all the ones for funding and looking at them as a group, because when you just kind of go through, money would be nice and money would be nice, and more studies would be nice, but what are our priorities to the Secretary?

DR. FITZGERALD: So pull this out? Do you have a format?

DR. LEONARD: I don't mean pull it out. I mean pull it out to look at it and see what you're recommending as an overall thing and see if you want to prioritize those in any way. I don't know if that then is incorporated into the recommendations, whether there's a little paragraph that says of all the funding recommendations our order of priority would be this. I don't know how you want to do it, but there are a lot of recommendations in there for funding with no prioritization for the Secretary.

DR. WINN-DEEN: The appendix at the back where it talks about what all the agencies are doing already I think is a reflection of let's call it current funding. So it's not like we're going from zero to something. We're just saying these are the areas where we feel funding should continue to be applied to. I'm not sure that we're making any recommendation to increase overall funding for this but just to make sure that these, whatever five or six or seven areas, are addressed.

DR. LEONARD: But has there been an assessment of whether or not there are gaps in the current things being done relative to our recommendations where there are real gaps that need to be filled, as opposed to continued emphasis on things that are ongoing?

DR. WINN-DEEN: I think that's a great segue into item number 11.

DR. FITZGERALD: We can do that. Let's just address that, then, I guess.

Draft Recommendation 11. "An interagency work group should be established to review SACGHS' recommendations, assess whether and how to implement them, monitor the Department's progress, and report back to SACGHS. At the request of the agencies, the work group could also serve as a forum for discussion of specific activities." This is at least our attempt to get at some of the coordination issues that have come up and was a recommendation of our task force that seems to be okay.

Then looking at 11B, "HHS should assess the level and adequacy of resources being devoted to support the integration of pharmacogenomics into clinical and public health practice to be sure current and future gaps and opportunities can be addressed." So I agree, Debra, in one sense that there is a bit of prioritizing that we can do, but I think there's also some that we can say we are going to highlight these issues, and obviously the Secretary knows better than we about the resources and can do some of that

prioritizing.

Yes, Linda?

DR. BRADLEY: Well, this is certainly something I would support, but whether you need to be a little bit more specific there. In other words, what comes to mind when I read this are areas where maybe we do need some additional funding; for instance, postmarket surveillance of tests that are entering practice, outcomes research that's already been mentioned. This might be a place to really put that, and also to resolve the identified gaps in knowledge that are going to come out of these different processes of looking at the evidence. So this might be a place to maybe specify some of those things.

DR. FITZGERALD: One of the things we wrestled with, of course, is how specific should we get. What do you tell the Secretary to do? What do you let the Secretary decide to do? But I think in a situation like this it's completely legitimate to put in a list of for instance or such as. If you would like to write that list, I'd be happy to give those as examples. Again, we don't want to necessarily dictate to the Secretary to do this rather than that, but certainly to give ideas, which I think is our mandate.

DR. HANS: On 11A, the task force may just want to consider whether adding a little bit of language there saying the Department should consider inviting participation of other federal agencies as appropriate, or something like that. There may be areas where other departments may contribute to that.

DR. FITZGERALD: Yes, and actually we did bat that around a little bit in the meeting. If you think that's a good thing, good. We were sort of on the fence about whether that was good or not.

We do have time. Wow. All right. This is good. Now, Yvette has worked on some of the ones we sort of flagged to come back to because we were wrestling with how to do them. Do you have that list? Why don't we start with number 2? Let's see how fast we can go through this.

Which one? Which slide, though? Do you know?

PARTICIPANT: Recommendation 2A.

DR. FITZGERALD: Okay. "HHS should provide FDA with the necessary resources to develop guidance documents about best practices for the co-development of pharmacogenomics drugs and diagnostics. This guidance should promote collaboration between the drug and diagnostic industries."

Oh, 2D? Oh, that's right, we did it backwards. I'm sorry, my fault.

This is the one, the Humanitarian Device Exemption regulation. "So that incentives for the development of orphan drugs are extended to pharmacogenomic tests that are intended to be used in conjunction with the orphan drugs," and this is the one where the exemption could lead to unanticipated and undesirable consequences. So is there a way that we can rework this to get to the goal that we're trying to get to?

Elizabeth?

DR. MANSFIELD: I might suggest that you don't recommend amending a specific thing but looking at ways to encourage pharmacogenomic testing in general rather than saying take this rule and change it.

DR. FITZGERALD: So instead of trying to be specific, as we tried to be there, to back off and be a little more generic. "FDA should investigate"?

DR. WINN-DEEN: Can I make a suggestion?

DR. FITZGERALD: Sure, please, anybody.

DR. WINN-DEEN: What I was thinking is that what we really want to recommend here is that the same incentives apply to orphan drugs as with their companion diagnostic. There are quite different incentives. There are financial incentives and only one test in the marketplace incentives.

DR. FITZGERALD: Right, so that's what I'm saying. Is just saying incentives going to be

enough, or do we need to be more specific than that?

DR. MANSFIELD: I think that might work.

DR. FITZGERALD: Okay. Is everybody else comfortable with that?

DR. WINN-DEEN: That allows people to look at the legalities of it.

DR. FITZGERALD: Right, and we don't trap ourselves in a place where we don't want to be, absolutely. Is everybody good? Good. Excellent.

Next, Slide 39, 2C. "HHS should advance the further development of abandoned drugs by facilitating access to information about such drugs. Incentives will be needed to encourage the voluntary submission of proprietary data by pharmaceutical companies." We got hung up here because some people see this as doing two separate things. One suggestion during the break was that after the term "proprietary data" we add in "of abandoned drugs by pharmaceutical companies," making both paragraphs specific to the subset of the whole thing being abandoned drugs and leaving the broader incentive issues.

Where's Debra? I think this was her thing.

DR. LEONARD: I still want to know who it's being submitted to.

DR. EVANS: To get around that, we could put sharing, "encourage the sharing of data."

DR. FITZGERALD: "Encourage the sharing of proprietary data." Now, you would want voluntary sharing, I'm presuming.

DR. EVANS: Yes.

DR. FITZGERALD: Debra, to whom?

DR. LEONARD: Well, if it's sharing, then it's not submitting to someone, and that's fine.

DR. FITZGERALD: Good. All right, excellent.

Next, Slide 43. This was the clinical validity and utility. "In certain circumstances, public and private health plans should facilitate the generation of knowledge by conditioning payment of pharmacogenomic technologies on a commitment by test developers to collect data on the clinical validity and clinical utility of pharmacogenomics technologies. CMS' draft coverage with evidence development initiative may serve as a model for this practice." We're going to add here "analytic," I believe.

DR. EVANS: I think one of the problems several of us had focused around the issue of who decides clinical utility and conditioning payment based on the studies of clinical utility. I think there's a certain conflict of interest there. Obviously, insurers want to see clinical utility, but I think also it's up to the people practicing medicine to figure out whether things demonstrate clinical utility, and I'm just concerned about making the payers almost like the ultimate arbiter of conditioning payment based on their assessment of clinical utility.

DR. FITZGERALD: Reed?

DR. TUCKSON: Could we hear from CMS? I'm curious to see this from CMS' point of view. You already, I would assume, do this. I mean, I'm not sure what this does other than, again, argue for having the knowledge, the research, the data that tells you whether or not these criteria are being met.

DR. ROLLINS: We currently do determine payment based on what we perceive as what's considered effective. Even though physicians as well as others may feel that a particular technology might be helpful, our premise is we take a look at the totality of all the data currently available and make a determination of whether or not it's considered reasonable and necessary for a specific condition. Based on that, and I'm sure some people would say we shouldn't do it this way, we essentially dictate what gets paid for and what doesn't get paid for. So what's currently being requested currently falls under the realm of what we do.

DR. FITZGERALD: Gurvaneet?

DR. RANDHAWA: I wonder if it would be useful to remove ourselves from a discussion about the payer's specific perspective here, because I think what we're trying to get at in this recommendation is, one, a mechanism to identify where the gaps in knowledge are, which is what the EPCs and the EGAPP and the other entities are doing, and the second mechanism is how to fund knowledge or outcomes research. The payer is just one element. Maybe there could be private/public partnerships with the payers, but there could be federally funded programs, there could be privately funded programs creating the evidence. It could be payers, it could be developers, it could be other entities.

So I think we're looking at a broader issue of how do we assess whether there's enough evidence, and then when there is not, how do we clear the new evidence, what are the mechanisms for that. The payer's perspective is just one element to this discussion.

DR. HANS: Kevin, I do wonder whether the recommendation in 6B actually covers the direction that this discussion is going. That is, insuring that when coverage decisions are made, they're made on a transparent basis and the reasons for those coverage decisions are provided back to the various manufacturers. So it really gets at the same point in some ways, without putting the circumstances of conditioning payment on, following up on.

DR. FITZGERALD: Gurvaneet, does that capture the larger issue that you were discussing?

DR. RANDHAWA: Yes, I think it's helpful to capture the issue and also to give some specific direction. If you are thinking there should be some collaborative efforts between different entities, payers could be one perspective. There could be other things we could focus on. If you think of some programs, then we could just give some examples of what programs. For example, from our perspective, the way I could look at this is if you're talking about creating new evidence, then the mechanism would be either funding R01 grants or funding cooperative agreements such as the CERT program or the DEcIDE network. But the EPC would be a different program where we're just assessing the currently published evidence or the systematic reviews.

DR. FITZGERALD: Reed?

DR. TUCKSON: What I think we're doing here is I think that what we are saying is that given that public and private purchasers make coverage decisions or payment decisions based upon demonstration of data, like clinical utility, clinical validity and the others that we've talked about in other sections, we urge that mechanisms occur that will have government working with various entities to facilitate that knowledge being developed, that information being developed so that these functions can be achieved. So without trying to rewrite it, when you go back and the subcommittee looks forward to it, which I'd remind you all that what we're trying to do with this discussion is decide whether you're going to let this report go forward for public comment, which I won't fast-forward to, but I would say that I think what you're going to find is that you've got several recommendations now that all speak to the same idea of facilitating the collection of knowledge, data, studies and so forth, by a variety of entities, and I think this just becomes one of those.

So I think the way you phrase it is in recognition of the fact that people are going to need this data to make these decisions, let's work together to try to get it.

DR. FITZGERALD: Okay, that sounds good. Do you want to write that one up?

DR. ROLLINS: I'd like to reiterate a point. It is true that CMS does have the coverage with evidence development for those promising technologies. A promising technology is one where there may be insufficient evidence showing that it's been effective, and that may be due to the fact that there are only a limited number of studies out there, but the studies out there do look promising. Unfortunately, they're not sufficient for us to say it is reasonable and necessary. So as I say, we do have a number of projects

that do fall under coverage with evidence development, but as I said they've got to be promising, but unfortunately they don't have enough justification to show that they're effective. Whether or not any of the pharmacogenetic tests would fall under this category is something that would have to be determined by CMS or some other payer if they chose to go through that route.

DR. FITZGERALD: Does that fall under your general conceptualization, Reed?

DR. TUCKSON: Yes, sir. I'm doing my assignment, sir.

DR. FITZGERALD: Very good. All right. I like to see that.

Next, let's let Reed work on that.

That's it? Well, this is great. What I'd like to do now, then, is turn our attention to where we want to go. Obviously, we've gotten wonderful input today on a lot of these, very helpful, very insightful, and also brief, which is wonderful. So now the question is what do we do to revise the report and the recommendations based upon the input we have received, and then how do we move forward? I'm not sure exactly of the range of options here, but one thing I will suggest is the possibility that we take the various recommendations we have received on the recommendations, work those in, we could email people those recommendations in their revised form. Then what we'll do is the old if we don't hear back from you to veto the process, then we'll go forward with the recommendations as they are phrased. If you come back to us with a veto, then we will try to engage that process and eventually speed these things along so we can then move forward with the Lewin Group doing the stakeholder and expert interviews pretty much on schedule.

How does that sound to people? Cynthia?

MS. BERRY: I have just some minor editorial things that don't merit full group discussion and taking up time. Is there a process --

DR. FITZGERALD: You mean in the report?

MS. BERRY: Yes. Should we just tear this out and hand them to Suzanne or whoever, so we don't waste people's time?

DR. FITZGERALD: Sure. If there's information that you think would be good to be in the report, let us know, please. We've already indicated with some things -- we could rework the report, too. Absolutely.

Does that process sound reasonable to everyone? If so, I think that's what we will do. We will work as quickly as we can. I'm going to be very unpopular with some people here, but okay. We will try to get those back to you. We'll tell you how much time we need to have your responses, and then if we can pretty much move ahead, we will do that so the Lewin Group can get going on the stakeholder interviews and we can seek public comment. If that is okay with everyone, that is what we will try to do, and I believe that that pretty much wraps up what we were told to do today.

DR. TUCKSON: Isn't he good?

(Applause.)

DR. TUCKSON: Masterful, masterful.

It's time for lunch.

I need support. I assume and hope that the boxed lunch deal got circulated in time for the boxed lunches to be made. I hope that Chira did not stop the process when it got to her.

The other thing is what time do we come back? The people who are not in the boxed lunch group know that there's this terrific restaurant right next door. There's the cafeteria behind you and something forward. You can turn left or turn right and food will be there waiting.

We come back at exactly at 1:45. So we'll see you at 1:45.

(Whereupon, at 12:50 p.m., the meeting was recessed for lunch, to reconvene at 1:45 p.m.)

AFTERNOON SESSION (1:48 p.m.)

DR. TUCKSON: Thank you all very much. We will now turn our attention to the issue of gene patents and licensing practices. In March of 2004, the committee identified this as a high-priority issue because we had some concerns about adverse effects on access to genetic tests and services. At that time, however, the National Academy of Science had just begun a study on gene patents for the NIH, and we decided to postpone a decision on whether to undertake our own in-depth study until the National Academy's work was complete. That report, which was titled "Reaping the Benefits of Genomic and Proteomic Research," was published in the fall of 2005. In March of this year Debra Leonard, Jim Evans and Emily Winn-Deen, the team appointed to review that study, reported that its recommendations sufficiently addressed intellectual property concerns in the research realm but did not fully examine the impact of patents and licensing practices on patient access; very different.

In June we gathered more information on this topic before reaching a very clear conclusion that

we needed to embark on an in-depth study of the effects of gene patents and licensing practices on patient access. We roughed out a scope for the study, discussed several investigational approaches, established a task force to guide our work on this issue, and tapped/drafted/hijacked Jim Evans to serve as task force chair.

Jim will now present on the work of the task force and fine-tune the study scope in developing the detailed work plan. We have two hours for this session. Our task is to discuss the task force recommended approach and give Jim and the committee some clear direction and marching orders so that he can lead the group forward.

So, Jim, as we turn it to you, again, I want you to be real clear about what it is you want from us. I mean, we can give you marching orders to lead forward, but we can give you marching orders that lead you up Mt. Everest and you'll never get there. So how specific do you want from us, and what do you want to achieve by the end of this two-hour session?

DR. EVANS: Thanks. This is obviously an extraordinarily complex topic, and it's a topic that really, I think more so than any other item that the committee has taken on, with the exception of genetic discrimination, really elicits passions in people, and I think that what we're after today is really three things. We would like folks to weigh in on the scope, which we spent a lot of time trying to determine what the scope of our investigation is going to be, we would like input on the study questions that we have defined, and we would like input from everyone about how we have proposed to go about this. None of these things are written in stone. So this is an opportunity early on for people to really change what we're doing. I certainly don't hold myself out as an expert on gene patenting, so we need lots of input from people.

This is the membership of the task force as it currently exists. Let me introduce a couple of people. One is not here, and that's Mara Aspinall, president of Genzyme, who has a role in the committee. But in addition, Brian Stanton, who is sitting right over to my right, is with the NIH Office of Technology Transfer.

Brian, if you'd raise your hand?

I think that most people know the other members of the committee.

The activities to date, to summarize very briefly because Reed has really already done it, in March of '04 it was really defined as one of the priority issues. In October of '05, Debra Leonard convened a small group to look at these issues, and then in March '06 many of you remember that at that point we were able to evaluate the National Academy report. It was thought before that report came out that perhaps it would really have done our work for us. That really is not the case. The National Academy report was quite heavy in looking at the research implications of gene patents. They were extraordinarily light on the issue that we feel is most important in the Secretary's committee, and that is ultimately patient access. So because patient access we see as our salient interest, we felt that more work needed to be done and that there was a role for this committee to take up issues of patenting that were not addressed by the National Academy report.

In June '06, we decided to move ahead with an in-depth study, discussed the scope and work plan, and established the task force that is reporting to you now. The first task force meeting was, as you can see, quite recently. We have come up with the scope and study proposals, and the goal of today's session is to try to reach consensus on that scope, on the study questions, and on the way forward.

Now, I'm going to go through a few things and then we'll have a chance to talk about these in detail, because I know people will want to weigh in on this. So I'm going to hold off for a moment on the proposed scope statement. We may want to modify it. One of our goals is obviously to be very balanced. I think everyone recognizes that gene patenting provides both benefits to this whole endeavor of genetics

in medicine, but it also has certain downsides, and our ultimate goal is to try to guide things so that we can effect that balance to the favorable extent. You can follow the scope in the table folders that you got.

So we also wanted to define for you some of our terminology. I've referred a couple of times here to patient access. You will see the term "clinical access" used throughout our discussions, and just so everybody knows what we mean by that, patient access is pretty self-explanatory. We want patients to have full access to emerging technologies and things that will benefit them. When we say clinical access, we are also trying to capture the idea of the development of tests and the integration of genetic testing, for example, into patient care. This also subsumes issues that relate to reimbursement and cost. In other words, patient access hinges on a lot of upstream types of things, and we want to try to capture that flavor.

I would also keep in mind as we go through this that we are oftentimes looking at proxies for patient access when we look at the effects of patents. For example, we heard a lot of information from Debra, from Mildred Cho about, for example, the ability of clinical laboratories to roll out new tests and to offer genetic testing. Our charge as a committee is not really to look out for the welfare of molecular biology laboratories, right? Our charge is to look out for patient access, but that may be the best proxy we can get for those things.

So keep in mind the fact that we're oftentimes going to be looking at perhaps imperfect proxies to judge patient access.

So the study questions are the following, and again, we'll have a chance momentarily to go through these in detail. I'm just going to give you the 30,000-foot overview here.

What are the overall effects of patenting on clinical access? What are the quantitative and qualitative data for the positive and negative effects of gene patenting and licensing practices -- that's an extremely important part of this -- on clinical access? If there are problems, where do those problems occur? Are they in the development stage? Are they in the reimbursement stage? Are they in the integration stage?

I think we need to think seriously about current licensing practices for two reasons. One is they're obviously very important in patient access, in the ability to roll out predictive tests, et cetera. They also may represent an area where we can have some influence because, of course, patents policy is based in the U.S. Constitution, so we're probably not going to recommend amending the Constitution. On the other hand, licensing is something that may prove a more tractable tool. If we identify problems, we want to think about the solutions.

The effects on cost is extremely important. That gets directly to patient access. When tests are prohibitively expensive, that's a problem. What we would like to assess is are there data that address the effect of patents on the ultimate cost of genetic tests, for example, and are there economic data that analyze the contributions of patents to these things?

We'd like to perhaps look at the effects on development of tests. Do patents and licensing practices as currently seen create barriers to the development and implementation of clinical tests?

This is one that I think is up for some discussion as to whether it even belongs on our plate in this task force, and that is the issue of quality of testing. It's been argued, of course, that when there's a patent on a particular test, it hampers the ability to engage in independent verification of test results and therefore has a deleterious impact on the quality of testing. That may not fall within our purview, but it's something to discuss.

We want to quickly go through the study approaches. What are the types of things that can be employed to assess the direct effect of gene patents and licensing practices on patient access? So if those studies don't exist, what are they? What are alternative models that are practical? Again, we're not interested here in going off on a tangent, and as Reed alluded to, trying to climb Mt. Everest. We're

interested in practical models that might relieve any problems that are found without harming the good things, the beneficial effects of current patent and licensing practices.

So with that preamble, we can now get to the discussion, and the first thing to discuss before we get to study questions is the scope. Now, we came up with this scope, and I'll read it to you. I've already heard some very legitimate criticisms that we might be able to improve it by incorporating.

"While recognizing the benefits and importance of patenting in innovation and technology development, SACGHS will explore whether current gene patenting and licensing practices are having adverse effects on patient access to genetic technologies and ultimately on the public's health."

So I'll throw it open and let people make comments about that scope.

Brian?

MR. STANTON: Thank you, everybody. I appreciate the opportunity to be part of this.

When the emails were going back and forth about how to define a fairly substantial problem, my concern was that the scope of the study question can influence the way people approach the pursuit of the answers to the questions. So my thought was that my preference would be that we not use the word "adverse" right in the scoping document of the scoping question, that rather we leave it a little more open-ended and use the study questions themselves. So rather than say "adverse effects," that the working group explore the effect or what effects gene patenting and licensing practices are having on patients access to genetic technologies, thereby leaving it open to both looking at positive and negative.

The reason I suggest that is because I think that as we explore this what we're going to find, from my own experience, is two things. One, on the gene patenting side what we're going to find is that sometimes patents get in the way, and sometimes it's the quality of the patents that gets in the way. So it's not necessarily the patenting and the IP, per se. The second thing is, when it comes to licensing practices, similarly that's something we have in our controls. If we look at what the effect is, where it's good and where it's bad, because there are both, and what factors push the balance in one direction or another. Then we can look at very operative outcomes to see where the system needs to be tweaked without changing the Constitution, which I don't know if we necessarily need to pull off the table but it's probably a little more cumbersome.

DR. EVANS: We probably need three hours for that.

MR. STANTON: Yes, we probably need three hours for that one.

So thank you very much.

DR. EVANS: So we could, for example, amend this to say "SACGHS will explore the positive and negative balance which exists in the current gene patenting and licensing practices, with an eye towards identifying how best to enhance that balance," something along those lines.

Other people's suggestions or comments?

Emily?

DR. WINN-DEEN: I mean, I think if you just want to keep it really neutral, you can just keep the first part of it and then say "SACGHS will explore whether current gene patenting and licensing practices are having an effect on patient access," et cetera.

DR. EVANS: I'm sure they're having an effect, right? I guess what we would want to do is follow that up and say are there things that we can suggest, practical issues that we can suggest that would enhance that balance or something, right?

Other suggestions?

(No response.)

DR. EVANS: I think if we start with "while recognizing," starting with the "while" means there's something coming, right? There's something negative coming. So would people be comfortable

with a statement that really starts in with that second clause, that we'll explore current gene patenting and licensing practices in order to determine the balance of positive and negative effects on patient access, with an eye towards suggestions that could further enhance or enhance the positive side of that balance? Brian?

MR. STANTON: That would address my issue.

DR. FITZGERALD: Jim?

DR. EVANS: Yes.

DR. FITZGERALD: So your positive balance is the public's health?

DR. EVANS: Yes, right, and I think we should continue to emphasize that our role, that we see our mandate as ultimately coming down to patient access or the public's health, and you may notice the apostrophe there, that we aren't just talking about public health, we're talking about the public's health, which is different. It may sound nit-picky, but I think it's an important distinction.

DR. RANDHAWA: Just a question.

DR. EVANS: Gurvaneet?

DR. RANDHAWA: In the current phrasing here, the way I understand this, if you're focusing on patient access and ultimately on public health, and we losing the effect on patient outcomes?

DR. EVANS: No. Well, I would think that when you're talking about the public's health, that inherent in that would be outcomes, would be the kind of outcomes we desire. I'd maintain that that is inherent to any idea of a patient's health.

DR. RANDHAWA: Well, just to make my comment more clear, the reason I'm bringing this up is if we are assuming that because of patenting that there is proprietary information that cannot be shared, and knowing that is useful to determine how good the test is, then inherently there would be something about what are the outcomes of the testing and not just access to the test. I don't know if that concept has been clarified in the scope here.

DR. EVANS: I don't think it's within our purview to really decide on a case by case basis what tests are of benefit to people, et cetera. I think it's fair for us to assume going into this that there will be technology that is subject to patent law and licensing type practices that does indeed have a beneficial effect on outcomes, et cetera. So my own bias is that we need to assume that we are talking about tests that are found to be legitimate, that that's not our charge here, to look at how you determine what tests have a good outcome, et cetera. We're going to assume, I think, for purposes of this that those tests exist and that they are subject to patent law. Am I answering your question?

DR. RANDHAWA: I'm just trying to clarify the scope, that's all. You answered my question.

DR. EVANS: Yes, and that actually gets to a discussion in a minute about ensuring the quality of tests, which I'm not sure even belongs in our scope. But when we get to that, maybe we should discuss it.

Now, I can go back to the study questions one by one, and I should probably go ahead and do that. To remind you, the first study question is the overall effects, then the effects on development of tests, the location of possibly problems, impact of licensing, effects on cost, on quality, and then further study and alternative models. So I think that what I'm going to do now is I'm just going to zip back here to those study questions and we can take those one by one.

MR. STANTON: Jim?

DR. EVANS: Yes.

MR. STANTON: Before we get into the detailed questions, I do have a question. As I've looked internationally at the question of access in relation to genetic testing, the context of the national system in which the question is being asked sometimes can bring different answers. So I have a question

as to whether or not we need to either put it in the beginning of the document as part of the purpose or whether we need to contextualize each individual question to say within a given national system, because there are different constraints within different systems. It's a thought to put on the table for this group whether or not we want to specifically limit it to within the U.S. system and its reimbursement or whether we want to globalize it.

DR. EVANS: Certainly I think the assumption of the task force has been that we're dealing with U.S. practices and the effect within our system. That's not to say that we don't feel like we might be able to get very useful information by talking to folks from other countries in different systems. But I think it's implicit in all this that we know who the Secretary works for, right? It's not another country.

So the first one is really the overarching issue of the overall effects of patenting on clinical access. "What is the quantitative and qualitative evidence for positive or negative effects of gene patents and licensing practices on clinical access?" That's kind of the lead-off study question that in a way summarizes in the broadest terms what we're looking at.

Comments? Suggestions?

DR. AMOS: Are you looking at economic quantitative and qualitative evidence?

DR. EVANS: Well, not necessarily.

DR. AMOS: You may want to spell that out a little bit more and define what exactly specific benefits you were actually --

DR. EVANS: Right. So, for example, what we're getting at is are there data out there that directly or indirectly assess the impact of current practices on patient access? Can you show, by whatever means, and that could be economic but it could be the inability, for example, of laboratories to develop tests, et cetera, are there data? What are the data out there for determining the current impact of patent and license practice? Do you find it too broad?

DR. AMOS: I guess I just want to know what you mean by "impact."

DR. EVANS: Well, okay. Is it things that are enhancing or limiting patient access? Our ultimate goal is to look at patient access. So when we're talking about having an impact on patient access, we're talking about are patients able to reap the benefits of these technologies?

DR. AMOS: So we'd be looking at the benefits of having a patent for a company as far as the acceleration of that technology, as well as --

DR. EVANS: That could certainly fall into are there data that show because patents are in place, because of licensing practices, this test was able to be accelerated, was able to get out there, whereas it wouldn't have happened without current patent practices. So that would certainly fall into that.

DR. TUCKSON: I think it is fairly broad. I think we need to sort of drill in. First of all, I think you should split the two between what are the positive issues, what are the negative issues, because it's so broad. But then I think if you start defining in clear terms at the beginning of the report what you mean by "access," since the question that Mike is raising is the premise of the entire activity, I think you've got to be really, really clear about what does access mean, and then I think what this question becomes is what would be the level of evidence that you would require for being significant, for saying that there is an issue. I think what you're asking is things like would it be the numbers of people, would it be the price of the drug, would it be the price of the licensing. I think that's what really people are asking, giving examples of what that quantitative and qualitative would mean.

DR. EVANS: All right. So we could have some sub-points there. We could split it into positive and negative and have some sub-points, examples of the kinds of things that we're talking about with impact on patient access.

So the location of possible problems, where within the health care system are barriers, if those

exist, present? For example, in the development of tests, in the reimbursement of testing. So trying to in this sense drill down and figure out where those problems exist, if they are found. So in the first study question, what are the data for positives and negatives, and then where in the health care system do those exist? Some of these things have already been addressed by the National Academy report. But again, that focused primarily on extremely upstream kinds of stuff, and we again want to keep this focused on patient access.

DR. TUCKSON: So I think here what would be useful would be if this question could be accompanied by the chain of evidence, as it were, sort of saying let's start here, and by laying it out you're saying this is the menu of possibilities. But it would really, I think, advance everybody if we could see A, then B to C, to D to E.

DR. EVANS: That's a great idea. Yes, we could kind of show the flow from initial basic research, which again might not fall within our purview, and we can mention that, all the way to the patient being able to get reimbursed for this test.

DR. RANDHAWA: Just following up on that chain of evidence thought, usually we also have some comparator in that chain of evidence. So are we thinking that in this case the comparison would be to non-patented diagnostics? Would it be to patented therapeutics? What are we comparing it to?

DR. EVANS: You get to one of the difficult problems in here, which is what's your control group? If you're going to say what's the effect on patient access of having a patent, what you'd like to do is be able to compare that with no patent. That's very difficult to do with gene patents now because the way to do that, one way you could envision, would be seeing what happens when things go off patent. Well, there hasn't been enough time for that, right? That really raises one of the things that we struggled with as we talked about it, which is how do you quantitate these effects?

So I don't have an easy answer for you. I don't think there is an easy answer. There might be in 20 years when things have gone off patent and you can see. One example would be, one way of getting to this would be perhaps in looking at other systems where the patents aren't or the licensing isn't as restrictive. But your question I think is a really good one. It's one that we don't have a good answer for, and that's kind of one of the things we struggle with as we get to our methods for trying to carry this out.

DR. LEONARD: But I think you can go beyond patented or not patented, because there are a variety of licensing procedures that are used. So there's broad licensing at a reasonable royalty rate versus exclusive licensing versus proprietary testing, and you could look at the relative effects of those, although they are comparing one test to another test, and so you're also comparing apples and oranges in that the tests are not the same across all the different licensing practices. But you could look at the different licensing practices.

MR. STANTON: What I would suggest is that this question and three forward, the effect on development of tests, loci of possible problems, this question is focusing on the health care system, and to refine that and address some of these issues we might say where within the health care system and what elements of the IP spectrum are affecting the effective provision of clinical --

DR. EVANS: And elements of the IP --

MR. STANTON: In other words, in the research phase we'd say there might be preclinical aspects, there's IP development, there's patents. Once you get the patent delivered and you're going to deliver the test, maybe licensing issues. So you have this convergence between where in the IP spectrum, from the patent application process all the way down to licensing and delivery, or not, because there's the MTA issue as well, and then the different components of the health care system.

So that looks at which problem or solution may be present at which component of the delivery system, and then three questions down we ask, okay, now that we've identified which component of the

IP system affects which part of the health care system, I guess, or spectrum, then we can go ahead and find out, okay, now that we know the convergence between which part of IP and which part of the health care delivery stream, now we go in and say, okay, is there a solution. So trying to find the convergence of those two components might clarify this question and bring it into the third one forward.

DR. EVANS: Okay. So moving on, I think that something that has been mentioned a lot here is worth emphasizing on its own, and that is the impact of licensing practices. Are licensing practices affecting the ability of industry and academia to develop accessible genetic technologies? What role do technology transfer programs play in influencing clinical access to genetic technologies? And then what are the downstream affects of licensing practices on clinical access?

I think that licensing issues probably deserve a lot of attention because of the possibility that these are things that can be more readily changed than some other aspects of patenting practice.

Comments?

DR. TUCKSON: So this is very much like the earlier one around what are the data sets. So what would be the criteria to determine that licensing practices had an effect? How would you segregate out that piece of the puzzle? I have no idea what I'm saying. I'm just trying to play around with ideas. Would it be that the relative proportion of expense of an ultimate test divided by the licensing fee was less than 30 percent?

DR. EVANS: Or do you factor in the reimbursement, that a percentage of plans that reimburse for this test or that test, what the cost is, et cetera?

DR. TUCKSON: Then the flip side of that is, again playing this out, of 100 manufacturers interviewed or developers interviewed, 3 percent said without a licensing fee I wouldn't do this, it's not worth my time. Therefore, there would be no test. This is where I think the real work -- actually, I'm kind of warming to this task now. This is pretty exciting. It would be to try to figure those things out.

DR. EVANS: Right.

DR. TUCKSON: So what would be the metrics?

DR. EVANS: And we get in a moment to some of those ways of trying to address those.

The effect on cost is obviously integrally related to patient access. Some of these tests are extraordinarily expensive, and there's all kinds of debate about just how expensive should they be. What we would like to try to figure out is the quantitative -- and I suspect we'll also have to deal with qualitative data -- on licensing practices, gene patents, ultimately on the pricing of genetic tests, and some of these types of data may come from the economic world that analyze the contribution of gene patents to their ultimate cost, and then again ultimately how does that affect patient access, because that's what we're most interested in.

Comments? Questions?

(No response.)

DR. EVANS: Okay. The effect on development of tests. Again, this is a very --

DR. LEONARD: Sorry. The way this is worded is it's a yes/no question. I don't mean to wordsmith, but we probably want to write it as does any quantitative or qualitative evidence indicate adverse effects?

DR. EVANS: Address the magnitude, for example.

DR. LEONARD: Right.

DR. EVANS: Because I think we probably all agree that --

DR. LEONARD: And again, Brian, I don't know if you want "adverse" out of there.

MR. STANTON: I was probably going to do that offline, but yes, because again the question is going to prejudice the answer. So let's make it neutral and see. I had a conversation with the Patent

Office last week and I said if you would do -- I was there until two years ago, so I can say this. If we, when I was there, would have done a better job, then maybe we wouldn't have so many issues. So where the break points are and where the trigger points are is really important to find in a neutral manner.

DR. EVANS: Yes. I think that our role should be to look at these things and then let the chips fall, right? There's no reason we need to go into it with preconceptions just because there are popular preconceptions.

DR. AMOS: James?

DR. EVANS: Yes?

DR. AMOS: I think the only fair way to look at this is if you really take all of the genetic tests, the world of genetic testing and you look at the value that has been created by the ability of a company to patent and get protection in order to be able to afford to develop the test, and identify specific examples of how limited licensing practice or having a patent has specifically kept a product or a test from getting to the clinic.

DR. EVANS: Or once it's in the clinic, it's kept from patients being able to get access to it, which exists now. These are very complex --

DR. AMOS: I'm talking about actually in clinical practice.

DR. EVANS: So am I. There are lots of tests out there that many of our patients can't get because, for example, they're so expensive. So I think you have to look at the whole gamut, right? Does that make sense?

DR. AMOS: Sure, and that gets back to insurance issues as well.

DR. EVANS: Right.

DR. AMOS: But I think it's critical to be fair.

DR. EVANS: I couldn't agree more, and believe me, I understand there's a certain default kind of feeling among many people that gene patents are bad, and we don't want to, I think, come across as saying gene patents are bad. I think we need to take a very balanced approach because you're right, we all recognize that there are incentives that I'm sure are very good in bringing tests to fruition that might never have come to fruition, but I think that we also can't shy away from when they do limit patient access and do cause problems. That's one of the reasons we're here to look at it.

DR. McGRATH: I just would agree with keeping it balanced and neutral but not try to neutralize the language too much, because we are representing the patient side of it. There are other bodies around that are looking for the positive effects of patents. We don't need to do that here. So my recommendation would be to keep the words "positive" and "negative" in there and not to just get rid of both of them, not to just have it neutral but keep both.

DR. EVANS: Yes, I think that's good to constantly keep in mind that we're looking at both the positive and negative effects, because I don't think that we certainly want to come at this from the idea that everything is rosy or that everything is evil about patents and licensing practices. Fair enough? Okay.

So the effect of development on tests. This is, again, one of these upstream issues, and we should probably say to gene patents and/or licensing practices enhance or create barriers to the development and implementation of clinical tests, because one could certainly argue that perhaps they enhance as well, and we could probably be more balanced in this.

DR. WINN-DEEN: You don't want something that's just going to give you a yes or no answer, right? So you want to somehow get into the details of in what ways does it --

DR. EVANS: How do gene patents -- there you go. Right, right. "In what ways" or "how do gene patents."

This one, I'm not sure if this belongs within our purview, so let me read it. "Is the quality of genetic testing affected by gene patenting and licensing practices? Are current patent and licensing practices having an adverse effect on the independent verification of test results?"

The genesis of this concern really stemmed from Recommendation 13 of the National Academy report, which said, okay, there could certainly arise situations in which only a single laboratory is doing a test, and that therefore there wouldn't be any quality control, right? I'm not sure this really falls within our purview. Perhaps this falls better in CMS or somebody who is more concerned with quality of testing. Again, our concern is with patient access, and I'm kind of presuming, getting to Gurvaneet's previous question, I'm kind of presuming that we're concerned about the tests that make a difference and the quality tests, and that it really isn't within our bailiwick to be deciding about quality.

But what do people think? Is this within our purview?

DR. HANS: Jim, could I ask a clarifying question? I know that this question came out of really the second part of that compound question; that is, no independent verification of tests. But in that first statement about quality, is the following hypothesis included or not in quality? That is, there are seven different genetic changes that are responsible for a certain condition. One lab owns three and another lab owns four. The lab that owns three has decided not to pursue them but is not giving anybody else access to being able to use those. I would say that that is not a very high-quality test, then, if you can only look at four of seven. Is that included or excluded from this definition?

DR. EVANS: That's a very good point, and I hadn't really thought about that particular spin on the idea of quality. In a way, I think that is subsumed under patient access to genetic testing. If people, because of a patent, are not able to get tests for three of the seven genes that can be responsible for it, that would be an access issue, not so much a quality issue, but I see how it could be spun that way.

DR. COLLINS: I hear why you're questioning whether this fits in here, but I don't know how you can really separate the idea of patient access to tests from the idea of those tests actually being meaningful. I do think there's a serious issue here, and the National Academy, while highlighting it and making sort of a suggestion, it's not clear to me that anything is going to happen with that. So to leave this untouched I think would be unfortunate. I think there is a real issue when you have tests that have been exclusively licensed to a single provider, that there is therefore no natural way, through an objective outside evaluation, assess that quality outside of what perhaps ultimately will get done by other government oversight but which right now is a bit unclear. So I think it belongs on your list.

DR. EVANS: I'm certainly fine with keeping it in there. I think you both make good points.

DR. LEONARD: Well, also, if you look at the broader charge to SACGHS, quality of genetic tests is what got this whole committee started to begin with.

DR. EVANS: Before it was SACGHS.

DR. LEONARD: Right. So I think this is smack in the middle of what SACGHS is supposed to be doing.

DR. EVANS: Okay. Great.

MR. STANTON: Hi, Francis. How are you doing?

(Laughter.)

MR. STANTON: Francis and I have had a number of discussions over the years.

I agree 100 percent with the quality as an issue. The only reason I would suggest that maybe it's not for this particular task force is the following reason. I think Jim said it very well. If we look at the broader question of where is the convergence of intellectual property and licensing on the ability to even have the test in the first place, then the derivative question is how does that affect the quality of that product? But if we can't even get to the first base of I can't get the genes together for the gene trip to do

the test, or I can't get the five genes to do a prostate -- I was looking at a prostate test the other day where it needed seven genes to do it, and they only had access to six.

So there's a qualitative question, which is fairly subjective from a medical perspective, and there's the -- I hate to say objective in IP, because nothing's objective, but there's a question of how does IP get there, and then once we're there, if we can have all the genes, do you need them or not? And I wonder if that's a separate question that's for this committee but not for this study.

That would be my point, that the quality of the test itself isn't the charge here, although it's an important question. The question is can you get to the genes in the first place so that doctors can determine how to put the test together.

DR. LEONARD: But it goes beyond that, because sometimes you can't even do the test. So you end up with a sole provider of a test because they're exclusively enforcing their right to do that test, they decide the national standards of how that test will be done, the testing method, and so you aren't getting the broad medical community doing the test and developing a consensus standard. So it affects the quality of testing beyond just whether you can get the license to use all the genes necessary for a particular test, because this is single-gene tests that you can't even do.

DR. COLLINS: Yes, I would submit that this is one of those that could fall through the cracks. I hear what you're saying, Brian, in terms of this being slightly on the periphery of the main sort of focus of this particular study, but at the same time this would also be on the periphery of a study that looked at quality of genetic testing. They would probably not pay that much attention to this particular issue.

DR. EVANS: And they'd say that --

DR. COLLINS: That's patenting and licensing. So if it's going to be captured, why not capture it now?

DR. EVANS: I tend to agree with that, and I think that I'm going to argue against what I said before, just to show how open-minded I am. As somebody who orders genetic tests all the time, I do lament the fact that there are certain tests that I can only get from, say, a particular laboratory that I have been far from impressed by, and that is an impact on patient access to good genetic testing. So I think there's a reasonable consensus to keep this in.

DR. FERREIRA-GONZALEZ: I would like to add to the issue of the quality of the testing, not just only if you can access the test but something that was mentioned earlier. If you only get access to three mutations and not seven mutations that you're supposed to, then we are obligated or allowed only to offer an assay that might be 70 percent sensitive, versus if we can get to the other patents or licenses of those particular patents, we can improve the sensitivity of the assay that we can provide, not only for the reference laboratory but also for the manufacturers, too.

DR. EVANS: Yes, and I think that the issue is very persuasive to me that this could fall through the cracks in another committee. Since it could be seen as peripheral to others, we might as well tackle it.

Study approaches. What quantitative and qualitative approaches can be employed? So on the one hand we're asking what are the data out there for the effective patents and licensing practices on these issues? Here we're asking what are the approaches that could be employed to assess the direct impact of gene patents and licensing practices on patient access to genetic technology if those do not currently exist in the literature? We're going to talk a bit more about this. It's a bit of a departure from what the SACGHS has done in the past. So I would suggest that perhaps, unless there are driving questions, we hold this for a second discussion until we get to that aspect of our study plan.

DR. LEONARD: But could we just say what additional quantitative and qualitative approaches not identified by the above?

DR. EVANS: Okay, that sounds good.

Are there feasible alternative models and innovations that could be applied to the patent and licensing system to preserve its inherent incentives? I think feasible is an extraordinarily important part of this statement. This is such a thorny issue. There are so many stakeholders, and there are a lot of constraints on what we can do and on what the Secretary can do that I think we have to focus on feasible.

DR. FITZGERALD: Just on this one, Jim, I understand the reasons behind focusing on the U.S. situation, but in this one might we want to look more broadly just to see if there's something out there globally that might be more useful?

DR. EVANS: Yes, and I think that we could add something to the effect that we'd like to cast a wide net, continue to keep it feasible but cast a wide net in alternative models.

DR. AMOS: So when you're trying to do the study, will you actually provide a list of the constraints? I mean, there are going to be things that we just can't get by.

DR. EVANS: Right.

DR. AMOS: So you have to build your story within that context.

DR. EVANS: Yes, and I think that what we envision, as you'll see in a minute here, is that we would like to convene a roundtable in order to start to approach some of these models, and that will have to take into account, again getting it feasible, what those constraints are.

DR. AMOS: So, for instance, I think the Secretary of HHS can do a lot with regard to proposing new licensing procedures for NIH, but I think it's going to be more difficult for industry, and that would require laws. Also, it kind of flies in the face of administration policies to promote industry, not limit things like that.

DR. EVANS: Correct me if I'm wrong, Reed, but certainly the committee has not been shy necessarily where we see a need about encouraging the Secretary to promote certain types of legislation with Congress, et cetera. Look at the genetic discrimination issues, right? We know that the Secretary can't mandate genetic discrimination. That has to ultimately be done through Congress. But I think it's not unreasonable if we identify alternative models, things that could be done, even if they aren't in the direct abilities of the Secretary, that the Secretary, she or he, can still have an influence on that.

DR. LEONARD: So while we've taken out "adverse" in all the other things and made it positive and negative, can we do the same thing to this to say "could be applied to the patent and licensing system to mitigate any negative effects while preserving its inherent incentives"?

DR. EVANS: Sounds good to me.

DR. LEONARD: Because we want the balance.

DR. EVANS: Right.

So we've gone through the study question topics, and we come now to the proposed study plan, which has four components. We feel that an in-depth study is in order to figure out what are the data that are out there now that address these questions, that address the issues that ultimately get to patient access in the current environment, both from a positive and negative standpoint. We feel that a public consultation process is especially important with this topic, and we can talk about that more in just a minute as we go through each of these things.

Again, I think that I'm continually amazed at how both little knowledge is out there among even the fairly knowledgeable members of the public about gene patents and the fact that they exist, and I think that's in combination with the fact that one gets very strong feelings from people when they learn about these things. I think it's very important that we have an extremely open process that elicits public perceptions, feelings, and ultimately the public's goals in this. So that, I think, is an important part of this and I think can be compared with the process we pursued when discussing genetic discrimination. That

was something the public had strong feelings about and a strong stake in.

DR. TUCKSON: Yes. However, I want to be careful, at least that in my mind, that I remain open. If you say -- and you didn't mean this, so I'm being deliberately provocative -- dear public, do you realize that people make money on licensing these things and it elevates your cost of access to these things? Grrr, looking for somebody to kill. On the other hand, phrased a different way --

DR. EVANS: Right.

DR. TUCKSON: So I think it's going to be extremely important that the public consultation process be engaged once there is a clear set of facts, information, reasonable methodological data, derived facts, and then sort of saying there are some choices and some issues that need to be addressed. But I think the work is really on the front end to define if there is a problem, the magnitude of the problem, the elements of that problem, before the public really gets brought into this.

DR. LEONARD: But part of what this public consultation process is to define is, is there a patient access problem that is happening individual patient by individual patient that we don't know about and would never find out about by any studies that have been done to date? Kind of like the genetic non-discrimination public comment. Is anyone experiencing this?

DR. TUCKSON: Let me take advantage of your experience and ask do we now know enough to know how much of that is because of licensing independent of any other factor?

DR. LEONARD: I don't think we know. But, for example, the Canavan families brought a lawsuit against the holder of the patent. So there is an effect on an individual patent level, at least for that one. There may be others that we're not aware of where disease organizations haven't brought a lawsuit, and I think that's the qualitative evidence that we may be able to get to that others can't if we do ask this question of the public.

DR. TUCKSON: So the way in which you would ask -- excuse me, Jim. I'm breaking every rule that I've established here. It would then, I think, Debra, mean that you have enough ability to phrase the question to the public that would say do you believe that you have been denied access because of patenting or licensing issues, and here are criteria that you can use to determine whether it was simply not affordability but in fact was patenting and licensing, given that so much of the patenting and licensing is below the water. The patient may not perceive it, so they may just interpret some things as, yes, I think it's probably in there, I think I've been denied it because things cost a lot.

DR. EVANS: The same is very true of, for example, genetic discrimination. People's anecdotal experiences weren't necessarily what really happened, and yet it seemed like an important thing to pursue.

DR. FITZGERALD: Just one thing on this. It might be critical to decide in this process, as Reed's questions have sort of elucidated, who are experts and who is the public, in the sense that I would consider some of the people that Debra is thinking about, like patient advocacy group people and all that, to be expert in some sense. They're expert exactly in that type of information. Are there people who are being blocked because of patents and licenses and that kind of thing, or are there people who are engaged in lawsuits or something like that? If those are the people who we're thinking about in the public comment process, absolutely, we've got to hear from them even before we can establish the language we're going to use to do perhaps a more broad public inquiry.

DR. LEONARD: And when we did the genetic non-discrimination public comment, we heard from patients, genetic counselors, physicians. I mean, it was at a number of levels, and I think you could do that process similarly with this.

DR. TUCKSON: Well, I'll back off on this and just say that the thing I'm going to be attentive to in looking at this is going to be the language that is used to describe whether or not you feel that you have been harmed in this regard.

DR. LEONARD: But that would have to be reviewed by this committee.

DR. TUCKSON: I'm just saying I can withdraw because I think that's where the art of it is, in the description.

DR. McGRATH: I'm going back to the earlier ones where I was really happy to see the emphasis on qualitative and quantitative research. When I read that, I was thinking that it would address issues just like this. So I'm wondering is it really consultation or is it rigorous qualitative research trying to get at these questions? Are you really trying to consult with individuals or you're trying to gather that data in the research phase? In my mind I could see it more as the research phase rather than as a separate consultative phase.

DR. EVANS: Yes, I think that's a good point. I think that one of the things that drove us to consider this whole issue of a more formal and a more elaborate public consultation, as opposed to what happens every time a report goes out, which is the public sees it after it's been drafted, one of the things that drove that is how difficult we all realize the task is of figuring out the impact of gene patents, et cetera, on patient access, and we are not probably going to have pristine quantitative research that demonstrates in a controlled fashion the effects, and we are going to have to rely to some extent on qualitative research, qualitative experiences and comments of various stakeholders.

DR. FERREIRA-GONZALEZ: Jim, going back also to in-depth public research studies and the public consultation process, maybe we need to propose the research that is being performed in a systematic way. When you go back to in-depth research study, if you're going to do a review of the literature on the ability of laboratories to bring new testing and the constraints because of current patent practices, I think you'll find a very different environment five years ago versus what you see today. You'll see, for example, if you asked me five years ago, in my laboratory did I have any problems with this, I would have said no. But if you ask me today, I would say in the last four months I was not able to bring six different tests in our laboratory. So it's a very different environment.

So maybe what we need to do is not just an in-depth research of the literature but also maybe to charge some of these.

DR. EVANS: Exactly, and that's actually something we get to in just a minute.

DR. TUCKSON: So what you have, then, if you go back to the points that I heard from all three now, is the public consultation process includes consulting with advocacy organizations, the public at large, and people like you, so we get all three of these constituencies coming forward.

DR. LEONARD: Maybe it could be called a public data gathering process, or information gathering process.

DR. EVANS: Sure.

DR. LEONARD: Because we're using the literature, number one, getting what information we can from published studies, the literature that's out there. The second is experiences of different groups who might have been affected to indicate whether there's a problem, and then the international perspective. These are just three ways. I didn't mean to jump ahead to the international perspectives. Those three would lead into the development of a comprehensive report to the Secretary where we could provide what information we found, but we could also say where the problems are and whether studies are needed, whether certain things need to be addressed by policies, these kinds of things.

DR. EVANS: So going ahead to the international perspectives, I think that as we deliberated, as we put this together, we all realized that perhaps we could learn something from the models in other countries. Obviously, we're going to have to be very careful to keep such comparisons germane and feasible. We exist in very different political and governmental situations, so we're not going to be able to transplant practices from another country into the U.S. However, we might be able to learn something

that has been implemented in other countries that have dealt with these things. It would be kind of crazy, I think, to ignore the world experience with this if it could inform us, and then the development of a comprehensive report.

Now, going in-depth into these things, the in-depth research, we want to refine the study topics for literature review in the relatively near future and start a contract for that literature review. We'll commission that and then see what types of gaps, by the spring of '07, exist. At that point, then, what we have envisioned is a roundtable that would identify what gaps exist that are quite amenable to further data in a fairly near-term type of perspective, and what we have envisioned is if there are discrete types of questions that don't have an answer simply because the data isn't out there, the study hasn't been done and it's relatively straightforward, at that point we could actually commission limited studies in order to address those gaps.

If we find on review of the literature that all the questions are answered, we don't need that. If we find that, well, the questions aren't answered but there really doesn't seem to be anything very feasible, then we wouldn't go on to this. But if there are practical types of things that could be commissioned that would help fill those gaps, we'd have an opportunity to do that through this committee.

DR. AMOS: What sort of things do you envision finding in the literature? I mean, it seems to me that people are not going to talk a lot in the literature about their failures.

DR. EVANS: Well, in the literature or not, you look at Mildred Cho and Debra Leonard's work looking at the ability to develop certain clinical tests, those data are already a little bit old, and it could be, for example, what Andrea said a minute ago, that the landscape is changing quickly. Would it be wise to commission some kind of update to look at how is the field changing, how is the landscape changing? So I think that most of these things will be proxies. Most of these will be proxies for patient access that hinge on the ability to develop a test, the ability to offer a test, cost issues. I could imagine that there may well be a body of economic literature that has used modeling to look at aspects of the ultimate effects of access that gene patents and licensing affect.

DR. AMOS: What about a parallel study, like a questionnaire or something like that, some sort of survey that could be administered, maybe through the College of American Pathologists, that would actually -- I think the people who are actually using the tests and running the tests would have a pretty good handle on, like you said, Andrea, about what really the limits are and what they haven't been able to do.

DR. EVANS: Right. So if those things are either too old or they aren't out there, I think that's exactly the kind of thing that we could commission that would be affordable, because we can't commission a -- it has to be affordable and it has to be doable in a relatively short period of time, right? And that kind of thing could be.

MR. STANTON: Jim, as I listen to this, I think I'm finding one gap here, and that is the benchmark against which we're going to measure our results. When I hear that somebody can't deliver a genetic test, my ears prick up because I'm a big supporter of IP. But the other question is what's the standard of care and where are we going to gather the data or gather the opinion as to what should be the standard of care so we have a benchmark against which to measure what should be provided? What's the ultimate goal to provide and what's feasible to provide given economics, given our tangible situation? So if we don't have that somewhere, and maybe it's when we consult with the experts that we have to get some input somewhere about what an appropriate standard is --

DR. EVANS: Kind of what an appropriate level of access is or something like that?

MR. STANTON: Yes.

DR. LEONARD: Are you talking about access or are you talking about whether that test is

medically necessary for patient management?

MR. STANTON: Well, I guess I'm going to have to leave it to you, to the other side of the table to figure out the answer to that. What I'm saying is that in the abstract to say that the patient doesn't have access, the question that just came to mind as I was going through the methodology is should they have access to X versus Y, and when in the spectrum of medical care does that come into play? If, as we're going through our consultative process, we don't ask that question as to where it fits into the care process, then we're going to have this study in isolation.

DR. EVANS: Right. I think that could be addressed by -- well, you're talking about a survey. A survey could not just be administered to laboratory directors but to genetic counselors, to geneticists who have had experiences in which there was limitation because of the current licensing practices. This really gets to this issue of commissioned studies.

This, I think, we actually did not word very well. We are not interested here in expanding the literature per se. That is not our intent, and I think we should edit this a little bit. What I think this should be taken to mean is we don't want to reinvent the wheel. We want to look at where there are fillable gaps that we can commission a study in order to address. In that sense, it would make a contribution to the literature. But our real goal is not to make a contribution to the literature, it's to answer specific questions that we raise and recommendations that we can then make.

Emily?

DR. WINN-DEEN: I have two concerns. One is that if you don't go out in a very neutral way and do what I would call market research, you're likely to get a biased outcome here, because I think that some of the previous studies had a hypothesis in mind.

DR. EVANS: An axe to grind?

DR. WINN-DEEN: And they did a study that supported their hypothesis, good or bad. That's what science is all about in the general term. But I think in this case what we're trying to understand is what really is the scope of the problem.

The other thing is that I think if you only talk to lab directors, you'll never know why companies made a decision to do or not do. So I think you should make sure that you're looking at that side as well. This is the job I do at my company. I do in and out licensing, and depending on how somebody asks me questions, I could tell you just the horror stories or I could tell you the whole story of how 90 percent of the time it's okay, 5 percent of the time it's a pain in the ass but I get it done, and 5 percent of the time I can't get the license that I want. So I think it's really important that whoever we commission to do this has a script that is not biased by the way it's written.

DR. EVANS: There's a refrain here, because Reed was saying much the same thing, I think appropriately, about the public consultation process. We don't want to bias the results by asking questions in the wrong way, and I think that's something we definitely need to keep in mind.

DR. FERREIRA-GONZALEZ: Jim?

DR. EVANS: Yes?

DR. FERREIRA-GONZALEZ: I also would like to see that we get not only an unbiased process in this, but looking from the two different perspectives of academia or laboratories, independent laboratories and industry, what has been the issues in licensing from different individuals and how that impacts on the overall cost, but not only in the overall cost or even access, but has it delayed access to the testing. Sometimes you have to wait a year to get reagents available because there's some litigation or some patents already. So access is not only being able to offer the test today but also have you been delayed in offering the test because of these issues, a year or six months.

DR. EVANS: Yes, I think that's an appropriate caution about who we address and how we ask

them these questions. That's critical.

DR. AMOS: So will there be a prospective aspect to this report as well, or are you just looking at what's happened in the past that has blocked things?

DR. EVANS: Yes.

DR. AMOS: Because I think what I would like to see personally for the future of health care in the United States is some sort of plan or some sort of vision for what we could do to help get around some of these barriers as we move forward if there are any changes in the patent laws or anything like that, but also within the constraints of what the laws are now and what we have to live with now, what specific things we can do to help get around some of these things and make these things more accessible to the patient.

DR. EVANS: Yes, and what I would see is that as far as the specific studies that we commission, they're going to have to be very modest in terms of time and scope. But I could certainly envision in our final report really encouraging exactly that type of thing on a prospective basis that would look to the future.

The public consultation process. I think we have --

DR. HANS: Jim, just on the last point, I realize that Dr. Zerhouni and the Office of the Director can weigh in at any time, whether we ask them or not, but I realize that they're currently cogitating about what NIH can do on patenting and licensing. I'm not sure in what context, whether it's just in response to the IOM report or whether these issues are also in their minds at the moment. I wondered whether the committee had officially asked the NIH director whether there were particular perspectives or questions that they wanted to ensure were in the development of the scope.

DR. EVANS: No, I don't think so.

Sarah?

MS. CARR: Brian, do you want to speak to it, or Phyllis? Both of you are serving, aren't you, on the working group?

MR. STANTON: Well, we can come back to it. We're meeting again. We're not finalizing the study yet, so we haven't gotten to that stage yet as to the analysis of the Academy report.

MS. CARR: Well, I think it's safe to say that the working group has been paying close attention to Recommendation 13 in addition to the others in the report, and they're aware of SACGHS' interest in this issue and the patient access part of it, and they may speak to that, or I guess there are a variety of options on the table that may be presented to Dr. Zerhouni, one of which might support the work this committee is doing, and I think they just haven't finished cogitating completely.

MR. STANTON: Actually, I'd add this to Reed. I would say in some of the discussions it's okay that this committee is doing some of the work so we don't have to do it. So I guess the question is maybe there needs to be a conversation at some point between the two committee chairs and simply say how are we going to split up some of the questions, because we're looking at each other and sort of waiting for the other one to finish something.

DR. TUCKSON: We think you should do all the hard work and we get all the credit.

DR. EVANS: There you go. I like that.

(Laughter.)

DR. EVANS: We really, I think, have covered this ground. The take-home message, I think, from the discussion about the public consultation process is that we have to be very careful how we word these issues, and we have to try to target the appropriate public, some of whom will be experts in their own right because of their own experiences with these diseases, some of whom will have other interests. So we were thinking that we would solicit public comments over a two-month period and that that would

be in early next year. We would invite key stakeholders to an SACGHS meeting next summer and then ultimately develop a final product that documented these public comments.

With regard to the international perspectives, we will identify and invite international experts that have written on these topics or have some position in which they deal with these things as part of their bread and butter, and then develop questions for an international roundtable session that I think, again, needs to keep as a primary focus the whole time the practical types of things that we can learn and not just kind of pie in the sky types of issues, and then next fall have the roundtable session.

As far as developing a comprehensive report, we hope that by late spring of '07 and ongoing to develop a first draft, then solicit public comments on the report by late summer, and by sometime in mid '08 have an actual report that we could submit to the Secretary. What we would like to get feedback from today is do you feel that the components of this approach will achieve the study goals? What do you think about the timetable, specifics about the methods that should be used to solicit perspectives from the interested stakeholders, and how can patients and consumers who have been affected by gene patent issues be identified? Again, that's a very difficult situation because, just like in the discrimination sense, who knows whether I was denied this because of patent issues or whether I was really discriminated against?

That said, I think, again, involving the public is an important aspect of this because it is something that people feel strongly about.

Comments? Questions? Advice?

Emily?

DR. WINN-DEEN: Well, much as I don't like to say the timetable is too short, I think the timetable would be fine if you're not going to go out and try to get new information. But unless you're going to do that in parallel with the literature, I think it's probably a little ambitious.

DR. EVANS: Yes, I actually agree with you. As I was going through it just now, I was thinking, God, are we nuts?

(Laughter.)

DR. WINN-DEEN: Yes.

DR. EVANS: Yes, exactly. Now, it is true that we can pursue some of these aims in parallel, right? But I agree with you that we might have to revise this to be a bit more realistic since we're doing two things that are, in and of themselves, time-consuming. One is the public consultation period, and the other being, gosh, that we're really looking to generate some new data, if that's needed.

DR. HANS: Just thinking a little bit about what's gone back and forth on getting input from the public and the experts that work in the area, and yet we know that it's very difficult to determine exactly the reasons why access was denied, if I was writing a scope of work for a contract, I might include an option in the contract to do some case studies following the consultation period so that you could further explore what you got out of it, to go back to the companies, to go back to people and say we heard about this and we would like to find out more what that is about and all the reasons for the access. So you might have the option later if you found there were some issues that you wanted to explore more, that you had the flexibility in the contracting to be able to go back and do some case studies.

DR. EVANS: Yes, I like that, so you aren't just left hanging if you get interesting things you'd like to follow up. Okay.

Finally, as far as next steps, we'll revise the scope, we'll revise the study proposal, we'll revise the timetable and move forward and come back to you with our progress.

DR. TUCKSON: Jim, since you're really at the end of this, first of all, this is terrific. I really think that the methodology here is going to push this thing forward in a way that I hadn't thought of, and

just the way you get at it, the way you try to answer the question of the significance of, the criteria, is I think going to be very interesting. I'm just starting to wonder whether or not there is some expertise or consultative advice that is different from what would normally be in this sort of domain that you may have to draw on, ways of trying to crack a problem like this. I'm trying to use examples that I'm not trying to stick by, but what percent of licensing fee versus total cost is a significant number. I mean, how do you think about that? Are there health economists -- excuse me, regular economists, not even health economists, that this is how they make their living?

DR. EVANS: Right. What you bring up is exactly right. This is a really difficult issue. Trying to quantitate and characterize the impact of patents and licensing on something as downstream as patient access is immensely difficult, because we know that you can come up with all kinds of theoretical pluses and minuses to the whole thing. So not to be too much of a pessimist, I think it's entirely possible that we'll come through this and say we don't know, that we don't come up with definitive types of data that address this, but I think we have to try. It's clearly important, and we have to be creative in the people we ask and in the methods we use to try to get at those things, because we're not going to get direct answers. A lot of it is going to be by proxy, and I agree with you that the economists may have things to offer, et cetera, but it is very tough.

DR. TUCKSON: So we're going to all have to help them. The committee is bright and we've got a lot of smart people on it to sort of reach out and think of it in other ways. This reminds me of an IOM committee that I was involved with, the consequences of uninsureds, and it's interesting once you start to try to calculate the economic cost of uninsurance on a community. It's not traditional health stuff, and you start getting into a whole variety of downstream things, which almost brought in the need to invent a methodology for thinking about something like that.

So anyway, this is terrific.

Are there any other closeouts? Jim has still got the steering wheel for the closing.

DR. EVANS: Just basically other questions on the work plan? Other suggestions?

DR. PAREKH: Jim, a quick question. Is there any hypothesis that we have here, or given that it's a research study we're obviously not trying to couch it in one way or another? That's the first question.

DR. EVANS: Well, I think that the hypotheses will probably have to wait until we see what the gaps are, right? If we identify gaps that are fillable, once we look closely at the literature I guess we could formulate hypotheses. But actually, I feel like it's important to try to maintain a large degree of neutrality about these things and say, okay, here's a question that isn't answered, and let's see if there's an answer. So this really isn't, in my mind, really hypothesis generated or hypothesis driven.

DR. PAREKH: Whenever this concludes, in 2008 or 2009, the end product, do you see this being more of a report or potentially recommendations?

DR. EVANS: What I really hope for, and I don't know if we're going to be able to accomplish this, would be actual recommendations. I mean, the real dream here would be we identify some things that are good and some things that are bad and we say, look, here are three or four discrete things that the Secretary could work towards that would enhance that ultimate positive/negative ratio of the pluses and minuses to gene patents on patient access. So I would hope that we would have some tangible recommendations. I don't know if we're going to because I don't know if we're going to be able to get the kind of concrete data that would allow for discrete recommendations, but I certainly think that's what we should shoot for.

DR. PAREKH: Thanks.

DR. RANDHAWA: I should have asked this earlier, but just a clarifying question about the

scope. How are we defining the test? Is it strictly a genetic test in the context of a genetic counselor/geneticist, or is it a more broad-based definition?

DR. EVANS: Well, I think in a way what we're talking about here doesn't matter so much on the modality of testing as it does on whether gene patents affect that, right? So if people are doing -- as we all know, you can do genetic tests without ever looking at a gene, right? But if gene patenting doesn't have an impact, then I think it's definitely outside our purview. So I would just try to keep in focus the fact that we're interested in how gene patents affect testing. Usually I think that will rely on looking at either the gene or its expression in a fairly proximal sense, but I think that would be the answer.

DR. RANDHAWA: The only reason I'm asking that is I don't know to what extent is patenting common in testing platforms and methodologies, as opposed to specific genes. Are we going to be exploring that or not?

DR. EVANS: Say that again. Looking at --

DR. RANDHAWA: Again, I'm no expert here, but, for example, say microarray technology or proteomic technologies which are not looking at specific genes but a platform or a methodology is being patented.

DR. EVANS: Right. Let me think, because I hadn't really thought about it in those terms. I don't think we're talking here about the patenting of technologies and platforms, and please weigh in if this isn't what you all perceive. I think we're interested in, again, how the taking out of patents on genes, on specific genes have an impact on all this. That's different from, say, patenting a technique for sequencing, or patenting a technique for analyzing expression. Would you agree with me on that?

MR. STANTON: You said something earlier that I agreed with, and then you phrased it a little differently, so maybe clarification is useful. When I think of a gene patent, you said gene patents and closely allied or first derivatives technologies, the gene expression product or the gene. The gene: what does that encompass? Maybe one of the things we're going to have to do as we start down this road is define what we mean by that patent family.

I will share the experience that two years ago my office tried to ask the question of the effectiveness of NIH's licensing and said what are the metrics we should use, and we found that you can't use a single metric. So in the same way, if we were to look at the entire family of patents, I think we wouldn't be able to get any answers. So maybe the first thing we should do is sit down as a group and say what do we mean by a gene patent, and then that will lead us into our case studies so that we can -- I think Sherrie's suggestion is fantastic, to use that so we formulate our questions with very concrete algorithms in that way.

DR. EVANS: I agree. So I think your question is a good one.

MR. STANTON: It's right on point.

DR. EVANS: Right. We obviously do need to define that, and the trick really comes in at how far downstream from the gene do you go. I think we would all agree that a new sequencing technology would not be something that is within our purview, but I think we have to decide whether it goes beyond the patenting of a specific sequence or, say, alleles, SNPs.

DR. AMOS: I'll give you a specific example of how a gene patent can affect other testing. When you own the rights to a gene sequence, you own all the rights to use, to make, to have used, to have made, et cetera. So in any case where somebody wants to develop a protein test and they have to express that protein recombinantly, they can't use your patent unless you license it. So it's pretty broad.

DR. EVANS: But that would be people who own the patent on the sequence of that gene, right?

DR. AMOS: That's the whole point.

DR. EVANS: And that would be important for us to analyze, what the impact is.

DR. AMOS: It goes beyond just a test to see if somebody has a specific SNP.

DR. EVANS: Absolutely. Exactly. So when somebody owns the patent on a sequence, they own the whole shebang, right.

DR. FITZGERALD: Jim, just one other wrinkle to that, though. I mean, I think you also have to take into consideration the fact, certainly in some of the cancer tests that might be developed, that you could have gene expression changes that aren't due to any somatic or germ line mutation but just an epigenetic change, a methylation difference or something. So you probably wouldn't want to be quite so narrow to demand that it would have to be --

DR. EVANS: Well, the question again is would those types of things be covered by somebody who owned a patent on the sequence of that gene and its alleles?

DR. FITZGERALD: No, not necessarily, but they could presumably patent the information involved in the methylation testing. Therefore, you'd still have something that would be acting like a genetic test the way you're defining it.

DR. FERREIRA-GONZALEZ: I think what we were thinking about here is not just going to inherited disorders. Don't focus just on inherited germ line mutations or changes. Expand that to allelic variances and also somatic changes that cause cancer, which is a genetic disease.

DR. EVANS: Well, again, I think what this gets back to is if somebody owns the patent on a gene sequence and its allelic derivatives, if that is used in their assay or in somebody else's assay, research, diagnostic test, it's covered by that patent.

DR. AMOS: Yes, if it can be used to block somebody else from doing something that's going to help a patient.

DR. RANDHAWA: Help me out here, because I'm still not sure I understand how this would apply to proteomic tests, which are looking at profiles of proteins or peptides.

DR. EVANS: I don't think it would, unless they used in their technology the sequence, just like you described. If they need to create a peptide from the gene that you have patented, then it would have an impact on it. But as far as a technique that uses NMR to look at proteomic degradation products in the serum to diagnose something, that would not be related. That wouldn't fall under the issue. There's a lot of confusion and gray areas about what's a genetic test and what isn't, and that's very legitimate. But as far as what's a gene patent, I think we can probably come to a pretty concrete definition for that, and it's the patenting of the sequence and its allelic variants.

DR. HANS: Jim, just to remind everybody, it's in the statement that you have in your scope of work, but the charter for the committee actually covers both sides; that is, gene patents and access to genetic technologies. So you still have to define genetic technologies.

DR. EVANS: But I see us as linking that, gene patents and the impact on access to technologies.

DR. HANS: Genetic technologies. It says "genetic."

DR. EVANS: Exactly, but starting with gene patents.

DR. HANS: But I see it as overlapping circles, and you're only doing that which is colored in the center.

DR. EVANS: Right, which I think is, in and of itself, a huge bite to chew off. I think we need to focus on the impact of patenting gene sequences and alleles. That would make sense to me.

DR. LEONARD: However, everything that's gone on with gene patents is likely to occur further down the road with proteins and proteomics, since proteomics is more nascent than genomics. So whatever recommendations are made relevant to gene patents could easily be translated and applied at an

earlier phase and hopefully prevent less of the exclusivity in clinical practice on the proteomic side.

DR. EVANS: That's a good point.

I think we're actually a little ahead of schedule.

DR. TUCKSON: For which you get an extra cookie.

(Laughter.)

DR. TUCKSON: Didn't he do a good job? Thank you. Good job. You get some applause, too, by the way.

(Applause.)

DR. TUCKSON: This is going to be a fun one. This is really going to be fun.

Public testimony. No, you're not getting a break yet. This is the public testimony.

DR. LEONARD: There isn't a break scheduled. So can't we have one?

DR. TUCKSON: There wasn't a break scheduled? Why don't we take five?

(Recess.)

DR. TUCKSON: We are reconvened.

One of our critical functions is to serve as -- I knew there'd be trouble over there with the caffeine -- a public forum for deliberations on the broad range of health and societal issues raised by the development and use of genetic technologies. So we do greatly value the input we receive from the public. We set aside time each day of our meetings to hear from members of the public, and we welcome and appreciate the views they share with us. In the interest of our full schedule, I'd ask the commentators to keep their remarks to five minutes. We have copies of your full statements which will be made a part of the meeting record.

Today we will hear from Dr. Mittman, who works for the Maryland Department of Health but is speaking on her own today.

Dr. Mittman?

DR. MITTMAN: Good afternoon and thank you for letting me be here and make my comments. Understanding the genetic basis of life has an overarching impact on the ideological frames within which people view themselves, their actions, and others in society. Whereas in the past scientists targeted ethnically-defined groups for the study of mostly rare or recessively inherited conditions, a new paradigm shift is driving studies to target more common afflictions such as diabetes, hypertension and asthma, conditions with a lifetime risk of at least 60 percent in the general population. In order to facilitate these studies, scientists are once again turning to genetically simplified population isolates such as the old order Amish, Finnish, Icelanders, and Ashkenazi Jews.

The "Jewish" case in genomic research is particularly troubling. In my research, I identified that we can learn a lot by focusing on this population that is quite experienced in population-based studies. The Ashkenazi Jewish population has received disproportionate attention with respect to genetic mapping as genomic researchers have capitalized for decades on the ease of founder mutations, the relative simplicity of gene patterns, and the perceived willingness of Jewish individuals and families to partake in genetic testing.

The disproportionate targeting of Ashkenazi Jews for genomic studies and the obvious lack of sensitive social studies on the impact of such research on this population was very costly for this group. Unlike other populations targeted for genomic studies, Jews carry the scars of the Holocaust, calculated genocide rooted in the "scientific" notion that Jews are members of an inferior race. Jewish community leaders indeed are concerned that the focus on the genetics of Jews will revive the fallacy of the inferiority of the Jewish people and lead to stigmatization and discrimination of this group.

Although American Jews constitute a distinct cultural and religious minority group, they

receive little attention in the minority health literature, as do other religious minority groups like Hindus and Moslems. In spite of the racial, ethnic, cultural and economic diversity of Jews, they are often viewed as a monolithic group and stereotypically portrayed as a model minority of affluent, well-connected, and well-educated people. Even when social studies are conducted on perceptions of Jewish community members related to genetic testing, no distinction is made as to the various subgroups that make up the Jewish community, and conclusions tend to be generalized to the entire Jewish population. As an example, a recent study published this month in the American Journal of Public Health portrays Ashkenazi Jews as an advantaged group receiving preferential treatment in genetics and enjoying easy access to BLCA testing at the expense of other less advantaged groups.

There are many issues pertaining to the U.S. Ashkenazi Jewish population that are at times overlooked. Conservative estimates suggest that more than 600,000 Jews are recent immigrants to the U.S., and thus may face linguistic, economic and cultural barriers to health care. American Judaism is also diverse with respect to religious sub-denominations. The majority of U.S. Jews define themselves in religious terms. Forty percent are conservative, 30 percent are reform, and about 11 percent are orthodox. The various branches of Jewish religious denominations differ in their interpretation of the level of adherence to the written and oral laws of the Jewish religion. While conservative and reform Jews may be fully Americanized and share the values of surrounding communities, orthodox Jews strictly adhere to ancient rules dictated by the Torah and maintain very distinct cultural and religious beliefs.

Importantly, the Jewish population shows wide socioeconomic disparities. While the average Jewish household income is well over the national average, one-fifth of Jewish households fall in the lowest income category.

It has been well documented the (inaudible) identified in the Ashkenazi Jewish population have inadvertently led to discrimination and stigmatization of this group. Moreover my dissertation, which focused on the impact of genetic screening on the orthodox Jewish community, identified serious issues related to within-group discrimination, especially related to marriage prospects in this population which largely utilizes arranged marriages. It appears that an alarmingly growing segment of the population, especially women, are finding it hard to secure a match in part because of perceived undesirable genetic endowment. In this community, inability to marry and procreate may doom a person to a meaningless existence. These issues seem to emerge from misconceptions propagating within the Jewish community with respect to its genetic endowment. This may be the result of linking Jews with common disorders. For example, some of the studies already under way to identify genes for common disorders which target Ashkenazi Jews include inherited mental disorders such as schizophrenia and bipolar disease, autism and Alzheimer's disease.

Targeting socially identifiable communities for genetic studies possesses a serious risk that socially constructed prejudices will be defined in biological terms. Linkage of ethnically and socially defined groups with diseases and particular therapy regimens, as we spoke about earlier in the case of BiDil, stands to deemphasize a host of important social and environmental construct in disease causation and treatment and encourages stereotypes leading to unequal access to medical intervention, and as a whole could lead to widening health disparities.

In summary, I recommend that when studying public perceptions related to large population-based genetic studies, we should explain the definition of vulnerable populations. They should include all stakeholders, especially those groups already experienced with population studies in order to truly make every voice count. Second, as exigent genetic technology impacts health and health care disparities, it might be beneficial to have federal officers charged with eliminating health disparities take part in these important deliberations.

Thank you.

DR. TUCKSON: Thank you very much. Thank you for taking the time to do that. Let me just, before you run away, as if there are any questions. I think you were very specific about how you want us to consider your comments, especially in the context of the large population study analysis, but I wonder if people have any other comments.

DR. McGRATH: It's not a question but a great thank-you for bringing to our attention more specific examples of phrases we throw around easily here, genetic discrimination and stigma. After a while we sort of forget what those phrases mean, but thanks for doing that.

DR. TUCKSON: Thank you very much.

Dr. Debra Leonard is presenting on behalf of the Association of Molecular Pathology.

DR. LEONARD: This isn't to make light of my comments. Reed, members of the committee, good afternoon. I'm changing hats from a previous member of the SACGHS --

(Laughter.)

DR. LEONARD: -- to representing the Association for Molecular Pathology, also known as AMP. So I want to make clear that I am representing AMP here. I'll take the hat off so you don't think that this is totally humorous.

The purpose of these comments is to provide AMP's perspective on four issues relevant to the charge of the SACGHS. First are two draft guidances from the FDA on ASRs and IVDMIAs. AMP is finalizing comments to the FDA on two draft guidances which raise concern for the membership of AMP.

The first draft guidance, entitled "Commercially Distributed Analyte-Specific Reagents (ASRs): Frequently Asked Questions," defines a much narrower interpretation of the ASR rule than is currently in practice. AMP is concerned that these more stringent interpretations will limit the availability of ASRs, which provide high-quality reagents for the validation of laboratory developed tests by clinical laboratories under CLIA regulations. If ASRs become more limited in availability, either laboratories will find other sources for these reagents that are of poorer quality, such as research reagents, or laboratories will stop performing many tests that are currently standard of care. This could lead to decreased patient access to molecular testing services.

The second draft guidance, entitled "In Vitro Diagnostic Multivariate Index Assays (IVDMIAs)," defines the FDA's regulatory approach to complex multivariable tests. While AMP agrees that complex tests with interpretive algorithms that are not transparent and are able to be manipulated by the laboratory warrant FDA regulation, the use of an interpretive algorithm is routine in medical practice and should not in and of itself raise specific concerns with the FDA.

The purpose of raising these issues with SACGHS today is to assure that this advisory committee is aware of these draft guidances, and I was not aware at the time that these were being presented right after the public comment period, and their potential impact on genetic testing services. Once AMP finalizes its comments in response to the two draft guidances, the letter can be provided to SACGHS, if that would be of interest.

My second point of concern is the tabling of CLIA genetics specialty regulations. AMP is very concerned by the recent decision not to incorporate a genetic specialty into CLIA regulations. Frankly, we are mystified by this action, which follows years of largely favorable comment from the clinical laboratory and genetics communities in response to the initial CDC's Notice of Proposed Rulemaking. The current CLIA regulations, which have not changed in almost 20 years relative to genetics, define genetic testing in terms of classical cytogenetics only. Defining genetic and molecular diagnostic testing explicitly would allow for appropriate regulation and oversight of these tests by the agency best suited and legally mandated to regulate laboratories performing these clinical tests. Defining a genetics

specialty within the CLIA regulations would promote expansion of proficiency testing programs, provide better oversight of genetic tests, and reassure the public and members of Congress about the quality of genetic testing performed in CLIA-certified laboratories. The members of AMP strongly urge SACGHS to bring this concern to CMS and CDC and encourage the incorporation of a genetic specialty within the CLIA regulations.

The third issue is assessment of coverage and reimbursement for genetic testing services. AMP members perform genetic tests and other types of molecular tests for the management of patient care. We remain concerned that the CPT codes and reimbursement levels set for these codes are less than the cost to perform these tests. While the SACGHS report on coverage and reimbursement issues made recommendations that CMS develop a plan to address this issue, AMP is not aware of any action taken to date on this issue. AMP applauds SACGHS for its recommendations and asks SACGHS to follow up to determine if action will be taken to correct the inadequate payment levels for these CPT codes.

Finally, the gene patent issue. AMP asks that SACGHS give full consideration to the negative impact of exclusive licensing and enforcement practices for gene patents on the future of genetic testing. We understand that SACGHS set this as a high-priority issue and is now formulating an approach to investigate the impact of gene patents on patient access to molecular tests. AMP wants to assure SACGHS that gene patent enforcement continues to limit the tests clinical molecular laboratories can perform for their patients. We urge SACGHS to develop a plan of recommendations to the Secretary of Health and Human Services to address the clinical impact of these practices.

AMP remains, as always, available to the SACGHS to assist with or provide additional information for your thoughtful deliberations and important work. On behalf of AMP, I thank you for the opportunity to speak to you today.

DR. TUCKSON: All right. With that hat still on, are there any questions to follow up?

(No response.)

DR. TUCKSON: Terrific. So you'll be available? Since we're about to turn to one of the key recommendations you made, which is around the oversight issues, you'll be able to --

DR. LEONARD: You're also going to hear about the FDA draft guidances as well as you'll hear from Judy Yost, I believe, about the CLIA decision not to have a genetic specialty.

DR. TUCKSON: Okay, that's what I'm getting at. We're getting ready to get into the oversight stuff, the CLIA and --

DR. LEONARD: And I didn't know that you were hearing about those otherwise.

DR. TUCKSON: Great. This is perfect. So we'll have a chance to follow up specifically in just a second. Thank you very much. Very well done.

Please note that there are written public comments also from the International Society of Nurses in Genetics, ISONG, in your table folders.

If there are others in the audience who would like to make comments, we have another public comment period scheduled tomorrow. Please sign up at the registration desk if you would like to speak at that session.

We're now going to turn to the session on oversight of genetic technologies and genetic testing laboratories. There is an issue brief on oversight in Tab 6 of your briefing books. I think it's important that you take a chance, if you haven't yet, to study that. To set the stage for our presentations and discussions, I'm going to review a bit of the background on this important issue, particularly for the members of the committee who are new.

Oversight of genetic tests has been a public policy concern for over a decade. Both FDA and CMS have responsibility for regulating genetic tests and for regulating genetic testing laboratories.

Currently, genetic tests developed in-house by individual labs are subject to less regulation than commercially distributed genetic tests. Most genetic tests that are currently available are in-house genetic tests.

By the way, we're using this word "in-house" because we have banned the use of the word "home brew."

DR. LEONARD: But it's still not a house. It's laboratory developed.

(Laughter.)

DR. TUCKSON: Today it's in-house. We'll keep trying. At least it ain't home brew.

DR. LEONARD: At least you stopped me brewing, but I'm still working from home, you know?

(Laughter.)

DR. TUCKSON: All right, with that modification.

In addition, as we know from Judy Yost's presentation in June, regulations governing clinical laboratories, the Clinical Laboratory Improvement Amendments, or CLIA, are currently lacking specific provisions for laboratories performing genetic tests. Ensuring the quality and validity of genetic tests has always been a high priority for our committee and for our predecessor committee, the Secretary's Advisory Committee on Genetic Testing, SACGT. SACGT issued a report in July of 2000 that concluded that a critical gap existed in the oversight of genetic tests relating to clinical validity and that a new multifaceted oversight framework was needed. There were three components of SACGT's recommended framework.

First, FDA should be responsible for the review, approval, and labeling of all new genetic tests that have moved beyond the basic research phase, and the level of review applied by the FDA should collate with the level of scrutiny warranted by the test.

Second, CLIA regulations should provide more specific provisions for ensuring the quality of the laboratories conducting genetic tests.

Third, a collaboration between the public and private sectors, coordinated by CDC, was needed to advance the collection and analysis of data on the clinical validity and utility of genetic tests.

In 2001, then Secretary of Health and Human Services, Donna Shalala, accepted these recommendations and indicated that HHS would proceed in a step-wise way, resources permitting, to enhance oversight of genetic tests, including laboratory-developed tests. In 2003, SACGT's requested briefings from CMS and FDA about the status of oversight efforts, FDA reported that the agency had no plans at that time to regulate laboratory-developed tests. At the time, there were questions about whether FDA had statutory authority to regulate laboratory-developed tests. CMS reported that plans were underway to add a genetic specialty to the CLIA regulations. At our meeting in March of this year, however, we heard public comments questioning why CMS has not moved forward with the proposed rule amending the CLIA regulations. In June we invited Judy Yost to update us on those plans. Ms. Yost indicated then that the rulemaking process was proceeding, that proposed regulations have been developed and were in clearance within CMS and that if all went well, we might see proposed amendments by early 2007.

At the end of the meeting in June, we decided to revisit the oversight issue at this meeting to have a more in-depth discussion about whether any gaps in oversight persist, and I would indicate any gaps in oversight persist that we think are important enough for us to be attentive to. Today we'll be updated, first by CMS and then by FDA, and then have a focused discussion on whether SACGHS should undertake further activity in this area. What I mean by that is should we move beyond a monitoring role and undertake some deeper fact-finding and analysis.

So let's be clear. What we are saying that we want you to do is to listen carefully to whether or not there are significant gaps in oversight but not just to discover that there may be gaps but to discover whether or not those gaps, in our role as representing the interests of the public, whether those gaps deserve further attention. So it's not just saying that there's a gap; it's is that gap worthy of further effort and attention by this committee. So those are the two things we're going to do.

Let's start with Thomas Hamilton and Judith Yost. Steve is going to go first? Do we want Steve to go first?

In that case, we're going to turn to Dr. Gutman. You may recall that Dr. Gutman's last presentation to us was in March when he reported on FDA's Critical Path Initiative and the agencies efforts to facilitate getting cutting-edge medical products to the marketplace. He described FDA guidances on pharmacogenomic tests that were released in February of '06.

Today, Steve will clarify the current regulatory paradigm at FDA related to oversight of genetic tests and tell us about some additional guidances that FDA has issued on this topic.

Steve, please proceed.

DR. GUTMAN: I'm going to describe. I'm not sure "clarify" is the right word. FDA has been involved in the regulation of medical devices in general, and of in vitro diagnostic devices -- that's our co-term for lab tests -- in particular since passage of the Medical Device Amendments of 1976. Those amendments introduce for the first time a variety of general controls for lab tests, including requirements for companies making them to registering their products, to follow good manufacturing practices, and to report adverse events.

As a result of those general controls, for the first time in our history we had a menu of tests on the market. We had mechanisms for showing that companies produce those tests consistently following good manufacturing practices over time, and we had mechanisms for assuring that companies that experienced or identified postmarket adverse events would report those events to FDA and then hopefully collaboratively, if necessary coercively, we would work together to resolve whatever had gone wrong. That entire regulatory framework was based on a risk-based regulatory process.

The 1976 law also introduced for the first time in the U.S., in fact for the first time on this planet, a requirement for premarket review before a new medical device could enter the marketplace. Although that review occurs in very different kinds of administrative packages, there is a common core in our interests. That core is demonstrating that the test is analytically reliable. I would argue that until analytical performance is locked in, you are playing in a sandbox with no sand. For some tests the story might stop there. For hemoglobin we don't generally ask that you demonstrate clinically that hemoglobin is associated with anemia, but for a new genomic marker of unknown significance we might be quite interested in understanding what the clinical meaning of that signal would be. Then for all products we are very interested in labeling and ensuring there are adequate instructions for use, there's a clear intended use, that there's clear performance, and that the limitations -- and I've yet to see a test that doesn't have some either analytical or biological limitations -- are clearly limned.

FDA regulations, as Reed suggested, is not the only path for a new test to come to market. To try and keep Debra happy, I will try and use the term "laboratory-developed test" rather than "in-house" or "home brew" test. These are diagnostic tests created in a single lab for use at that specific lab. They have been called in-house or home brew tests. Use of a laboratory-developed test is, in fact, a very well established practice, that there has historically been a broadening of tests fielded off of this particular practice.

But it's not an entirely trouble-free practice in that there are differences between the regulatory route for the product that visits FDA and for the product that doesn't visit FDA. Some of the differences

are that for the product that is developed as a laboratory-developed test, there is no requirement for discrete premarket review, there is no specific separation or segmentation between the research phase and the clinical phase of product use, there is no prohibition against demonstrating clinical validity but there is no explicit requirement for clinical validity, and the outcome of those differences result in some very colorful players. Anyone who hasn't looked at the recent GAO report that was described at the Congressional Committee for Aging might want to go on the 'Net and look at those to see at one extreme some of the very colorful players.

In 1997, the FDA published an analyte-specific reagent rule. It was viewed by us as an incremental change or increase in our regulation of laboratory-developed tests, although it was defined as a down-regulation, since by default analyte-specific reagents -- and we define those to provide an actual comprehensible English definition of them, but I would characterize them as the building blocks or the active ingredients of the laboratory-developed test. We define those as tests that were subject to regulation, and the regulation was a requirement for general controls such as registration and listing, good manufacturing practices, adverse result reporting, but we drew back from requiring general premarket review.

This was not an accident. The analyte-specific reagent rule was deliberately developed to create a safe harbor for laboratory-developed tests to create clarity to allow this practice to go on unimpeded, but to go on with some increased quality because we were trying to care for the building blocks themselves, and also increase transparency in that there were some labeling requirements which said I am a home brew test and FDA doesn't have a lot to do with me. It's crafted a little differently than that, but that's what it's saying.

I suppose if there's anything startling, if you go back to the preamble to the ASR rule, it codifies the fact that in spite of the ASR rule, that FDA did have, in fact it always has had, although in some cases it's been rather silent, perhaps notably silent, it's always had the belief that laboratory-developed tests are in fact within the definition of medical devices, and that laboratories creating those tests are in fact within the definition of sponsors or manufacturers, and all of these are subject to FDA jurisdiction under the 1976 act.

The ASR rule was a very well-named rule. I know and love and was in fact one of many authors who tried to get it right, but it had some surprising and disturbing unintended consequences, and that was that as a follow-up to that rule there was either inadvertent or perhaps in some cases deliberate abuse of the rule in that what people began to do is to take essentially what were either kits or large pieces of kits and call them ASRs. So I say a kit in ASR clothing. To make decisions about test optimization that were intended to fall within the purview of the laboratory, companies began to do that, and to make implicit claims. So again, either inadvertently or deliberately, the ASR rule to a certain extent went right over a cliff.

The guidance in 2006 was intended to do nothing more and nothing less than to clarify where you fall over the cliff. It may or may not have perfectly and brilliantly clarified it, and we are anxious to get input, but we are very intent on not having people take kits, call them ASRs, and market them outside the construct of U.S. laws. So we are very interested in getting that right. So the intent of this document was to better clarify the definition of an ASR, the limitations on marketing of ASRs. From our perspective there is nothing new in substance, spirit or meaning. There may be something new in examples for this document.

This document is not intended -- and this is either good or bad news -- it is not intended to eliminate legitimate home brew testing. It's not a frontal attack on home brew testing, although it might be an interesting dialogue in terms of what FDA might construe as legitimate home brew testing. The

labs, in fact, have the same responsibility in this document that they did when the rule was published, that they have to step to the plate and say I designed, I developed, I made, I validate, I stand behind this test. So that's the nidus, that's the intent, that's the spirit of the ASR Q&A guidances, and comments on those guidances close in the first week of December. We are exploring the possibility of at least a one-month extension.

It is very important to note that the ASR rule does, in fact, provide a Class I exempt status to the building blocks of home brew assays, but it didn't go any further than that. It didn't either help or hurt. It didn't provide benefit or provide harm to the laboratory test itself. The ASR rule by itself did not exempt laboratory-developed tests. FDA's action not to regulate laboratory tests remains grounded in the same history, in the same thread as a matter of enforcement discretion, not as a matter of legal exemption. I think there may be some folks outside the agency or within the agency confused by that.

So laboratory-developed tests can't use the ASR exemption. They can appeal or apply benefit from FDA's historic use of enforcement discretion. But, in fact, if you see anything, and the next guidance highlights it, it's that FDA is appreciating changes in laboratory-developed tests that makes the gap for at least some products more disturbing than it has been in the past. The lack of premarket review, the lack of a research to clinical threshold, the lack of parity, as a matter of fairness to various sub-constituencies in industry, the lack of discreet evaluation, and the lack of clinical validation for some assays, particularly novel and cutting-edge and high-risk assays in this wonderful world of 2006, are of interest, and FDA is honestly trying to reassess and do soul-searching in this area.

That, I guess, is startling to various constituencies in part because there has been a period of silence by the agency. All the things that Reed said I did in fact probably say at a previous SACGHS meeting. It's startling because it's an expression of authority, although I would argue that the document was hardly the most dramatic expression of authority. If you want the most dramatic expression of authority, you should go to the GAO minutes on the Congressional hearing on the aging where some nut started to express his authority.

The good news and the bad news is that this is actually not new stuff. This is old stuff. There's nothing new under the sun. That's what I try to tell my daughter at least, and she tries to tell me what is new and what I don't understand. Also, I must tell you that I've stolen this line from a conversation with Dr. Mansfield during our unofficial FDA catch-up break, which is that this is very much like a Dickens novel. You've seen the first chapter, and you haven't seen the last chapter, but assuming that FDA or assuming that I am working with Charles, the last chapter hasn't been written. So I do assure you that there's plenty of time for people to put great ideas on the table about what FDA should do, and there's still time to put on the table about what FDA shouldn't do. It would be better if the ideas put on the table addressed what FDA is worried about. To speak to any groups in any sector that are actually addressing those issues, that's good news for FDA.

The multivariate guidance is a specific example of a guidance that is fueled by FDA's concern that perhaps it wasn't such a great idea not to regulate all laboratory-developed devices, and that perhaps the blanket application of enforcement discretion is not a particularly brilliant public health move for all laboratory-developed devices. The IVDMIAs I think have been -- this document has been overread, because while it's clearly a signal, it is a much narrower signal than I think the laboratory community or the community in general has appreciated. When we were thinking about the IVDMIAs that we were worried about and interested in, we were thinking about one dozen or two dozen products that might be percolating toward or on the market, and maybe this would be an incredible growth area in five or ten years. We weren't looking at dozens, hundreds or thousands of submissions. That never crossed our minds when we crafted this document.

But we were really worried about a growing category of tests that seemed to us not to fit Judy Yost's mold, not to be the kind of thing an average inspector, whether working for CAP and COLA or CMS would be able to actually assess and understand. Tests had produced novelty with new safety and effectiveness concerns and tests that we thought were very poor fits for enforcement discretion.

So we thought of this. We still think of this. Maybe we didn't communicate it right, or maybe we did communicate it right and it was misread, or maybe we didn't write it right. I don't know. We were looking at a narrow niche of devices, and those devices were devices that had the use of software-driven and software-derived, and I'm talking about complex software, algorithms or formulas, that those algorithms or formulas would take information and create a patient-specific score or index, and that a nominally trained pathologist or oncologist or cardiologist or neurologist would look at that index and say what the hell does that mean and wouldn't know what that meant unless he or she contacted the sponsor and essentially had someone color it in for them in order to explain what the hell it meant, and wouldn't in fact be able to second-guess it if their life depended on it. So that's what we really intended.

What we clearly did not intend was that all algorithms would fall in this category. We never imagined that. We didn't intend to go after all software. I do think there should be a bit more regulation of FDA in the area of software, but a lot of the software, laboratory information systems in general outside of blood banking, in fact only require software quality systems. They don't require premarket review at all. We're not interested in regulating things for the sake of regulation. The device, just because it's multivariate, doesn't automatically mean it's an IVDMIA. Of course, if in doubt, someone needs to chat with FDA. In fact, if we've accomplished nothing else, we've caught the attention of companies in this area and have begun triaging and making decisions about tests that actually don't deserve this designation and tests that, in fact, truly do.

I would argue that the novelty in this profile was intended to be different than for other laboratory-developed devices, and if folks think we haven't got that right, you can tell us in the first week of December, and we are working on an extension of a month. It's not a great analogy, but the analogy that I was thinking of was one where you have a cabinet with a combination lock, and you hand the cabinet and the combination lock to either the laboratorian or the oncologist, cardiologist, neurologist, infectious disease doc, whoever is going to use it, and if their life depended on it, they couldn't unlock the cabinet without the combination from whoever made the cabinet. So it was a very unique circumstance where a physician wouldn't be able to interpret that information by himself or by herself.

Whatever the scope, whether this turns out to be a few or moderate or I've underestimated it and it's many, we're not interested in regulating to death low-risk devices. So this was also risk-based, with low-risk products probably headed for exemption, moderate-risk products headed for 510(k)s and streamlined administrative review, and for scary devices that might make determinations about getting life-saving treatment or not getting life-saving treatment, those might deserve to be Class III products.

What does FDA regulation get you? Wherever we go and whatever tangled web we weave and whatever direction we go, it gets you independent assessment of data and labeling, it gets you a review that's informed by evaluation standards, yet grounded in the 1997 Modernization Act, which told us to be most focused on regulatory threshold and least burdensome, and if it's focused, good science is good science. So we're quibbling over administrative niceties here. I would argue that if the test is being used now, it's a question of the annoyance of regulation, of having to put it in the package and send it to me. If you don't have good science, then shame on you, and you ought to think about would I use the test in my mother, would I use the test in my husband or wife. And if the answer is yes, you're not going to have trouble with the FDA.

So our deal is to promote public health by getting good products out quickly. Our deal is to

protect public health by keeping bad products off the market. We don't actually have the strongest laws in the world. Ours aren't quite as strong as in drugs, and very frequently we take very blemished tests and we label them. We do believe in transparency. If you want to see what our regulatory process is like, go to Google and type in not OVID but the reverse, OIVD, and we make all of our regulatory decisions a matter of public record. So if you want to know what we did with cystic fibrosis, with UGT1A1, with the Roche Amplichip, with the latest PSA test, all you need to do is go on our website. Everything we do, if we ask too few questions, if we ask too many questions, it's all a matter of public record and you are always free, everyone is free, and in fact lots of people aren't shy about telling us what we're doing well and what we're doing poorly in the way of premarket review.

We do like to think that our mantra is good science and that if our science is good, if our science is focused, you can get rid of us. You can get us out of the picture, but you can't get rid of the damn pesky questions we're wanting to put on the table. Thank you.

DR. TUCKSON: Thank you, Steve. Before you go, I notice that our colleagues from CMS are here, and we're going to turn to them in a second. Let me just ask you one thing, and then we'll open this whole thing up for discussion.

I guess I just want you to be as simple and straightforward as possible.

DR. GUTMAN: That's hard for me.

(Laughter.)

DR. TUCKSON: No, it isn't. You're the best person to ask this question. If we're sitting here as a committee trying to make sure that we are being attentive to our responsibility for thinking about issues that protect the public in this regard, and we're trying to figure out whether there is a gap that we should be attentive to, you and FDA, you get paid. That's what you do is protect the public in this regard. So this is all you guys do all day long.

DR. GUTMAN: We dream about this stuff.

(Laughter.)

DR. TUCKSON: You dream about this. So the question becomes, when you boil down your presentation about good science and good public health and yadda, yadda, yadda, at the end of the day do you consider from your perspective, does FDA consider there to be a gap or not that anybody should be worried about? Is the sum of your report saying all is well, return to your homes?

(Laughter.)

DR. TUCKSON: Or are you saying something different?

DR. GUTMAN: Yes. The problem as I see it is that there is a partial gap because the sector we don't regulate and the sector that Judy does regulate is very heterogeneous. So there are entities that do it very, very well, and there are people in that community that I would turn to if I had a question that I didn't know the answer to. There are people sitting at this table that if I had a hard submission I would be wanting to call them for advice. So when it's good, it's very, very good, and when it's mediocre, it's kind of mediocre, and when it's bad, it's really awful. So there is not a uniform gap. There is unequivocally in my mind a gap. There are a variety of ways to address that gap. FDA isn't the only way. I think FDA is not a bad way.

DR. TUCKSON: Steve, people are not smart about this like you are, and we're getting ready to have the CMS walk right up here. Would you please, with your expertise, define the gap? What is this gap from your point of view?

DR. GUTMAN: From my point of view there are three things. As good as CLIA, as good as CAP, as good as COLA, as good as JCAHO are, they can't go in in a credible way in one or two or even three days and actually figure out what's going on in the data. Judy has been too generous with me in

terms of sharing validation packages and information from multiple endpoints, and I've seen a lot of bad data manipulated in odd ways from people who do it because they don't know, from people who do it in spite of the fact that they do know. So, one, there is a gap.

There is some value to independent data assessment and labeling. I think there's value added to that. The second is that this is a very competitive universe. I understand that both labs and companies are not like me. They're not against public health, but their bottom line is their stockholders. With labs, it's their hospital administrators. There are economic pressures that make their decisionmaking process different than ours, but I would say that there are differences in decisionmaking, and in the laboratory community there is a capacity that does not exist in the IVD community, which is after the first publication you can spring to life as a non-research test. All you need is that first publication.

Then the third gap is that I do think, and you can ask Judy or you can ask her boss, I do think there are differences in the law itself, in the reg itself, in the ability to go after clinical validation. I believe that we have that as a core principle, and I believe CLIA has that as a basic limitation.

DR. TUCKSON: Thank you. So you'll stay there, or nearby, and we're going to turn to Tom Hamilton, director of Survey and Certification Group for CMS, and Judy Yost, director of the Division of Labs and Acute Care Services for the Centers for Medicaid Services.

Now, Tom, I think you're going first. Is that right? Both you and Judy. However you weave it into what you're going to present, can you please also highlight, when you get to that part of your presentation, what you see as the gap and help us to understand whether you're on the -- well, let me just leave it at that. So you understand where the question is, and the context of this question for us who are not as sharp as you are about this is given that your job is to protect the public, make it simple for us to tell us whether all is well and we should return to our homes or whether there is something really important that we should attend to. But we just need you to be clear about all this after you've made the formal presentation, which I'm sure will be clear.

MR. HAMILTON: Thanks very much, and thank you for inviting us. I'm Thomas Hamilton. I'm the director of the Survey and Certification Group, and Judy Yost I think you all know. She heads up our Division of Clinical Laboratory Amendments.

What we're going to do is switch off a little bit and walk through the PowerPoint. Judy is going to start with a little background on the Clinical Laboratory Improvement Amendments in order to put this into context, because there is some misunderstanding about what CLIA can and cannot do and about some of our priorities. So we'll start with the background, and then I'll come in in the middle and talk a little bit about one of the controversies of the day, which is whether or not there will be a genetic specialty regulation promulgated, and then Judy will pick up again and talk a little bit more about CLIA, and then we'll open it up, if that's all right with you.

MS. YOST: And good afternoon as well. This is near the end of the day but this is a really exciting topic. Again, I think as Thomas indicated, these are the things we're going to walk through, and also to provide you an update on what happened at that hearing regarding direct-to-consumer testing earlier this summer. We've also been asked to provide a little synopsis of what the New York State Genetic Testing Program does under their state licensure law as well, and then we'll move forward.

Just as Reed so aptly did, he provided you some background on the history, and I think you can't go forward without knowing what that is. But I think before I begin, I think it's very important to say that CMS' goal in administering CLIA is to ensure the highest quality testing for all types of testing, because as many of you know, 70 percent of all health care decisions are based on a laboratory result.

The final CLIA regulations were published back in 1992 and do cover all testing in the United States, including genetic testing. A task force was convened by the NIH and Department of Energy back

in 1997. They released a report that did not provide specific recommendations but did say that CLIA should be augmented. Following that recommendation and at the request of the Secretary, CMS and FDA and CDC actually worked offline together to discuss how we would implement genetic testing oversight under new regulations and what tasks lie in front of us and how we could work together to accomplish them.

Based on that recommendation, however, the CLIA Act committee, which is our advisory committee, the CLIA technical advisory committee, did convene a work group of experts who subsequently provided a whole listing of recommendations to us regarding the changes that should be made to CLIA for genetic testing. Of course, SACGT, which was the precursor of your committee, did also support those recommendations. Then subsequent to that, CDC did publish a Notice of Intent. What that Notice of Intent did was to list that recommendations and to also list the existing CLIA requirements that corresponded to those so that individuals could then comment as to whether that particular improvement might be needed.

Interestingly enough, the comments to that Notice of Intent were pretty mixed. Some people were for changes to CLIA, others were not. But as a result, CLIAC did revise its recommendations in 2001.

Following that, CMS actually published final regulations. So even though you say nothing has been done to CLIA in 20 years, actually we published a rather comprehensive final quality control regulation in 2003, which actually strengthened quality control for all testing, and it also included some of the recommendations from CLIAC as well. Some of those things that were added to that QC regulation from the CLIAC included quality control for PCR testing, unidirectional work flow to prevent specimen contamination, enhanced confidentiality requirements, as well as enhanced result reporting requirements.

As a result of that Notice of Intent, however, there were still a number of open issues, some of which are still unresolved. Also, the CLIAC's recommendations were beyond the scope of CLIA. They included such things as patient consent, which of course is not included under CLIA. Because the field is relatively new and dynamic, and I think we all heard that today, there is concern internally and externally about perhaps writing prescriptive requirements that could, in fact, limit the laboratories from using new tests in their technologies.

I'd also like to, because I think I did myself a disservice when I first presented this to yourselves and to other committees as far as a summary and an overview of CLIA. I promise I will not go into excruciating detail, but I would like to show you a little bit more of the scope of CLIA because I don't think I've really done that before. I have to say that this audience is relatively unique in that you are folks who want regulation. Most of the people I talk to are people who don't want us there, never want to see us again, and so the minimum burden that we can provide is all they want to hear about. So in that respect, I've always been relatively conservative about providing an overview of the regulations. So today I'd like to give you just a little bit more detail, not to describe it but to show it to you at least.

The first and foremost requirement that I'd like to talk about is quality control. Quality control is easy to describe. It's a real-time evaluation of test quality because it's something you do every day. You want to check that your test is working before you report your results. But that's all we ever really talked about. We didn't really say that -- quality control includes all of these things, not just the fact that you're running something every day to check the test, but you have to do all these other procedures under CLIA currently in order to show that the test is working. So it's very important to mention that.

The last thing on the list are the specialty requirements. I think it's also important to note that these are actually created to correspond to Medicare payment codes. That was the reason the laboratory specialties were created in the first place, things like hematology and microbiology and so forth. But as

you see as we go on through this presentation, you'll see that they only are a very small piece of the CLIA regulations. Sometimes there will be a specific quality control requirement for something like, under hematology, coagulation tests, because they are unique. So a certain type of QC is required for those tests. So they're very limited in scope.

Currently there is no genetic testing specialty, as was previously stated. However, tests that are considered genetic are actually currently dispersed throughout all the different laboratory specialties that exist, although because we did strengthen quality control in 2003, we made it from anything the manufacturer could call a quality control to something very specific and very stringent, two levels of external QC every day of testing. We felt that the need to have as many specialties as previously existed was no longer necessary because we had strengthened everything overall. So the number of specialties has actually -- instead of adding, which we've never done, they've actually been reduced over time.

In addition, I think I'd like to also mention that (inaudible) information that indicated that there were laboratories that did not have specialty certifications. We went through the CLIA database and actually discovered that there are no laboratories existing currently that do not have some type of specialty certification and are doing non-waive types of testing. The interesting factor is that CLIA, as you know, is user fee-funded. Therefore, the fees that the labs are assessed under the CLIA program to pay for its costs actually use that specialty information to calculate the fees. So there's an absolute need for us. We need our money to operate this program, and so thereby every laboratory has a specialty certification.

Again, quality control tells you if the test is working each day before you report your patient results. It should monitor the test operator, it should monitor the actual analysis, the procedure that the lab is doing, and also the environment where the test is being performed. For example, if the lab is too hot, many test systems don't work and provide incorrect results. So it is important to perform that quality control.

The next regulation or requirement or standard I'd like to talk about is proficiency testing. Proficiency testing is a measure of long-term accuracy of the laboratory testing. It's not something that you can use on a daily basis because you don't get your PT results from your provider for three months. So if those test results went out and you didn't do any quality control, PT isn't going to help you here. It's just going to tell you from afar that the test system is working on an ongoing basis, and you don't need to have a specialty in order to perform proficiency testing. All non-waived laboratories have to perform some fashion of proficiency testing.

Currently in the regulations there are 83 tests listed that must have formal PT performed. However, there are at least a thousand different tests that a laboratory might wish to perform, and CLIA has a corollary requirement for those types of tests because twice a year the laboratory has to do a check to ensure the accuracy of those tests. So you have to do one or the other. You can't escape from PT, but you can see that for the most part, most tests do not have formal PT required under CLIA in the regulations currently.

In addition, our surveyors look at that. They look to see what the lab is actually doing twice a year. They're not just looking at the PT results that you get from a PT program. They're looking to see what the lab is actually doing, and if they're not doing it right or they're not doing it at all, they cite those deficiencies. I actually pulled some data, and it's cited quite frequently. So they're clearly looking.

DR. TUCKSON: Judy, let me just make sure of one thing here. Are these genetic tests, or is this non-genetics?

MS. YOST: This is CLIA. This is CLIA overall.

DR. TUCKSON: I just want to specifically know, does this relate to genetics?

MS. YOST: No. I need to provide you a context for where you're going.

Also, we checked with the College of American Pathologists and ACMG because they jointly have a proficiency testing program currently for 46 categories of genetic testing, proficiency testing right now, and there are approximately 16 to 300 laboratories involved in those programs. We understand that there are about 600 laboratories in the United States that do genetic testing currently. However, again, because there is no formal PT required for genetic testing right now in the CLIA regulations, the labs have to perform the twice-yearly evaluation. So a statement that a certain percentage of labs are enrolled in PT has no relevance for compliance with CLIA, because it's not required.

Also, we saw that there was a recent article in which potential errors were considered to be possible problems in genetic testing in some laboratories. However, in evaluating the data more closely, it indicates that most of the problems that were self-reported and certainly qualified as being potential were actually in the pre- and post-analytic phase of testing. Thereby, specific requirements for genetic testing would not have affected these errors at all. The requirements that would apply would be the pre- and post-analytic requirements already in place in CLIA. Pre- and post-analytic requirements are those things that refer to specimen collection and processing and result reporting.

In addition, you can see that there are also requirements for record-keeping, confidentiality, specimen integrity and labeling, and for handling of complaints.

Because most genetic tests are considered high complexity, there are a number of required positions in the laboratory for all high-complexity tests currently. These include the laboratory director, who has the overall responsibility under CLIA to ensure the quality of testing. In addition to responsibilities under CLIA, there are educational, experiential and training requirements for each position listed under CLIA as well. The responsibilities correspond for the laboratory director to all of the CLIA quality standards. In many cases, the laboratory director is cited as a deficiency during a survey if there are significant quality problems in the laboratory. The clinical consultant is responsible for ensuring that appropriate tests are ordered and result interpretations are correct. The technical supervisor has the responsibility for the scientific and technical aspects of the laboratory's testing and the selection of appropriate tests. The general supervisor is responsible for the day to day oversight in the laboratory.

Also, each individual in the laboratory who manages and does testing must have competency checked once each year, and when a new test is added, that's twice per year. So competency is not proficiency testing.

Last but most importantly, under CLIA there is quality assurance. This is an ongoing mechanism, an overall plan that the laboratory must have to assess the quality of its own testing, to solve its own problems, to communicate with its clients, its patients, its staff. It encompasses all of the CLIA quality standards. I guess you'd call it a package deal, and that's why I have the package there, because if you take quality control and proficiency testing, personnel requirements, and record-keeping, those four sides and wrap them in a box, that provides your quality assurance.

All laboratories that perform non-waive tests, including genetic tests, are surveyed every two years. If there is a complaint alleged against the laboratory, that is followed up immediately. The survey process is outcome oriented, and we utilize an educational approach. That is, any laboratory which does not meet a requirement has a deficiency cited. However, the surveyor will clarify that requirement for the laboratory, offer resources to facilitate the compliance. The goal here is to get the lab to do the right thing. Then the laboratory has the opportunity to correct the problem. If all else fails after several attempts, CLIA does have an armamentarium of sanctions that can and will be imposed against laboratories based on the seriousness of the problem and the scope of the problem. They range from fines from $10,000 a day to (inaudible) to Medicare reimbursement to losing your CLIA certificate.

CLIA, however, has an unusually high success rate in that the proportion of proposed sanctions when we warn the laboratory that we will do this if they don't correct their problems to impose sanctions is about 10 percent.

Again, the CLIA survey process is very effective. It looks at outcomes, meeting test results. It's interactive. We talk to the personnel in the laboratory who do the testing, who manage the laboratory. We observe testing throughout all phases of testing and review records as well. The QA program of the laboratory, which does encompass all of the quality standards, is the pivotal piece that really tells us that's the clue to how well this laboratory is doing.

Now Thomas Hamilton will address the answer to the question that you've all been waiting for today.

MR. HAMILTON: Let me begin with the question that Dr. Tuckson posed. Is there a problem? I have to confide in you that I'm probably not the best person to pose that question to because the Survey and Certification Group, we're the Grand Central Station where reports of medical misadventures from all over the country arrive daily. So we have a very distorted view of the American health care system. We're responsible for the onsite surveys of just about every type of Medicare-certified provider: hospitals, nursing homes, dialysis centers, hospices, and so on. Everywhere we look, there's a problem. So it's not so much is there a problem but rather what are the most effective ways to go about identifying and addressing the problems that do arise.

As we looked at the topic of whether or not there should be a regulation establishing a new genetic testing specialty and put a fair amount of work into that, when we take a rule through what's called our clearance process, it's an internal deliberation process involving the major agencies in the Department, and we ask ourselves a number of questions, we are obliged to establish positive answers to make the process a little simpler, three questions.

First, is there an absolute benefit to this particular rule? We might ask is there a problem for which the proposed rule is a remedy? Is it a significant problem? Does the rule, if it is a significant problem, effectively address that problem? And how strong is the evidence that suggests that the proposed rule will indeed effectively address the problem that's identified? This is where we first run into problems in terms of this particular issue on the regulation. To what extent is there evidence that there are problems that are not only soluble by a CLIA but currently unattended by CLIA?

When we look at this, one of the strongest arguments I think is the argument in favor of proficiency testing. A genetic testing specialty will not magically make proficiency tests available, and the way that CLIA is set up, CMS is not directed, authorized, funded to go out and create these tests. So I see statements in various communications saying that CMS has not established a test and is falling down on the job. The way the CLIA law is structured, it's the professional societies, the professions that establish those tests and come forward, and CMS approves those.

So right now, if there are more than 1,000 genetic tests, there are only a few proficiency tests available, as Judy described. We ran into this problem, and this will illustrate the issue well, I think, in the 1988 version of the CLIA program. Cytology proficiency testing for gynecological examination, Pap smear screening, was required. It was not until 2005 that CMS was actually successful at getting that mandated nationwide. Now, why was that? The reason was that nobody made the investment and came forward with an approvable Pap smear screening proficiency testing program, and there was a fair amount of controversy over this when we did implement it.

Basically, we found ourselves in CMS at the mercy, if you will, of the private sector coming forward with an acceptable and approvable test that met the requirements of the law, and there has been a fair amount of controversy. Ironically, we haven't heard a whole lot from the advocacy organizations. I

don't think this advisory body took up that issue, but for the first time in history, in 2005, 12,000 cytotechnologists and pathologists were individually tested for proficiency in reading Pap smears. We think that that was a very significant advance and very much needed when we began to look at the results.

When we got those results in, we found that individuals had, by regulation, up to four opportunities to pass the test. Approximately 7 percent of the cytotechnologists failed to pass the test on the first try, or put in reverse, 93 percent passed and 7 percent did not. For those who took the test the second time, only 3 percent failed. So overall, those results weren't too bad. Seven percent failing is still a problem but not overwhelmingly so. However, when we looked at the failure rate of pathologists who work without a cytotech, the failure rate on the first test was 33 percent, and on the second test it was 29 percent. It did not go down very much. We think that is a problem, and we've devoted considerable energies to addressing the educational and the testing aspects of this so that improved performance can be achieved going forward. But in the process, we had significant opposition to that. In fact, one house of Congress passed a bill that would have, if it had been passed by the other side, suspended the testing.

So I raise this as an example of an area in which there has been a significant problem, there has been assertive action on our part to try to rectify the problem, but you can see the gap in between 1988 and 2005, the gap that persisted because no organization came forward with a statutorily approvable proficiency test for Pap smear screening. So we could establish a genetic testing specialty, but it simply does not make those proficiency tests appear.

The second burden of any proposed regulation is not just the absolute benefit but how does the benefit compare against the costs? Do the benefits exceed the costs, and do the benefits outweigh alternative approaches that might be less costly, more effective, or faster to address the problem?

When we look at this area, one of the issues is laboratories are already covered by the Laboratory Improvement Amendments, and that includes genetic testing laboratories. There's also some objections we received as we looked at this because there's an existing set of specialties and subspecialties, and the genetic testing would need to be teased out of that. So that was a concern to some people, and we also acknowledged that going through the rulemaking process is a long endeavor. We first propose the Notice of Proposed Rulemaking according to the Federal Administrative Procedures Act, we have to solicit and respond to every comment, and only then does the final rule become published.

So we asked ourselves what can we do that would be faster and what could we do that may be just as or more effective. But those are the three major tests that any proposed rule would have to satisfy, and that's where the genetic testing proposed regulation runs into problems. If you think otherwise, we certainly invite your comments, your thoughts, and your evidence with regard to each of those issues. What we have been doing is going back and trying to identify how the existing CLIA regulations and law can be used as effectively as possible to address any issues that show up, and there are issues. We found some laboratories doing genetic testing did not think that they were subject to CLIA, and we've been screening those, identifying those. We've been working with the FDA and CDC to pool our collective surveillance. Whenever we find a laboratory that does not have a CLIA certificate, or has a CLIA certificate but not for the genetic testing, then we direct the state survey agencies to get out there, and we've got numerous examples of where we found some of those laboratories and have gone out on site. If they refused entry or refused to apply for a CLIA certificate, we threatened them with the appropriate sanctions and have moved forward.

We also have benefitted from some of the reconnaissance and discussions that have occurred. The Genetics Policy Center at Johns Hopkins, for example, did a survey. We looked at that survey, and the survey found that 8 percent of the laboratories that were not doing proficiency testing were also not doing the alternative quality control. The portion of the regulations that Judy was citing that do apply to

genetic testing is the requirement that every lab have a quality control system. Under 42 CFR 493.801, it says for those tests performed by the laboratory that are not required to have proficiency testing, basically, a laboratory must establish and maintain the accuracy of its testing procedures. The responsibility is on the laboratory to make sure that it has appropriate internal controls to assure the accuracy of the testing. Another part of the regulation goes on to say at least twice annually, the laboratory must verify the accuracy of any test or procedure that is not subject to proficiency testing, and it can do this through various methods such as sample exchanges with other laboratories.

To the extent that genetic testing laboratories are not fulfilling those responsibilities that are required right now in the regulations, we want to identify those laboratories and make sure that they are brought on board into full compliance with the regulation.

The third burden that we have to satisfy is even if a regulation is important in its own right, even if it has comparative advantage compared to other regulations, how does it fit in the overall scheme of priorities as we look at all the different regulations? We're in the process right now of trying to get out the patient rights regulation for all hospitals, millions and millions of people and struggling to meet the new timeline that Congress established before all regulation disappears, the three-year limit that Congress established.

So when the Department and CMS is looking at all the potential regulatory changes that we could effect that we've been studying and developing, the agency has to make a set of prioritization decisions. When CMS has gone through the process of looking at the evidence, looking at the urgency, and looking at the extent to which we might be able to address whatever issues are there through current regulations, then the final decision on the part of the agency was that we would put our efforts into applying and strengthening as much as possible the existing regulations and, in contrast to a proposed regulation, those actions can be done immediately.

So I hope this is useful in terms of some of the logic and the thought process that CMS engaged in as it considered this question of a genetic testing specialty. It's not that we didn't think the issues were unimportant. It is that we go through this process of looking at the available evidence, making the priority decisions, and then identifying alternative strategies that hopefully can get to the same or a better ultimate destination.

The next slide provides an example of some of the things that we've been doing, and we're very open and interested in whatever suggestions you might have for what we can do. But there are quite a few tools in the existing regulation that are quite useful.

I think at this point Judy was going to pick up on the conversation about the direct-to-consumer testing. But let me pause at this point and just see if you have any questions related to what I've just covered, because I know that this was a topic of great publicity, if not concern.

DR. TUCKSON: Thank you for that.

Let me just ask from a process point of view, Judy, what are you going to do with the remainder of your time again?

MS. YOST: Very little. I'm just going to provide the update on the GAO investigation on direct-to-consumer testing and the subsequent hearing that took place this summer, and a brief overview of the New York State Genetics Program under their state law.

DR. TUCKSON: Okay. So the New York State law thing, I'm thinking that maybe we ought to just deal with the questions that are on the table and come back to the New York State deal and the GAO deal. So I think you're right. Thank you for that.

So, my colleagues, I think it's time for you to ask the questions, and I think where I'm still struggling and I'm looking for lights to start coming on and hands to start going up here, because you all

will make this make sense -- where I'm caught still here, first of all, there's one thing that I think is important that, Judy, I think you were very wise to put a dichotomy out there. I don't think this committee, and I know I'm not interested in regulation for regulation's sake. I am not interested in having more regulations. That doesn't interest me personally, just as a person.

What I think we're just trying to figure out is does there need to be regulation, not should you just have more regulations. But I don't think anybody likes regulations. So the question continues to be, with what FDA does -- Steve, come on up, by the way. You should be up here. There are some laboratories who produce things that are done to the American people, it seems, that do not have to have that thing, that test, go through the FDA process. There are some things that slide past. Again, I'm asking this rhetorically because I'm trying to understand both of your comments.

There is a set of tests that slide past FDA and go into -- and deal with people, human beings. CLIA people say that we evaluate, we're willing to evaluate how good a laboratory it is and you're going to evaluate a specialty and you're going to check to see whether there are bugs running around in the room, and that's important. But it doesn't speak, that I'm hearing, to the same things that Steve does in terms of the test itself. So it seems like what I keep trying to get from you guys is, is there a set of things that slide by both of you? You don't deal with it, and you don't deal with it, and it still goes to my mother or my kid. So there's a second-order issue here as to whether or not that is okay. I'm not dealing with whether that's fine and it doesn't matter because nobody gets hurt and nobody has ever reported anything bad, or it's another order whether or not the poor folks, the lovely laboratory people, who are working night and day for $2.22 and they can't have any more regulation on top of their head -- if they did, they wouldn't produce another test ever again, so leave them alone. That's a different issue.

Is there a set of tests that go to my kids that slide by FDA and/or you guys? That's all I want to know. I just want the answer. I mean, I've been asking this forever. Lord knows, you know. I'm asking my government.

MR. HAMILTON: There are certain things that CLIA does, particularly the analytic validity, are you going to get accurate results. That does not address the clinical validity, should this test be done in the first place, is this really the right test for this kind of thing. It's just going to focus on whether or not a physician ordered the test, then is the test being done accurately.

This came up heavily in the direct-to-consumer testing. There are probably five or six different functions you can look at there, the advertising of the test, the sales, the clinical validity, the analytic validity, the interpretation of results, and the communication of those results to the consumer. Of all of those functions, CLIA itself is just going to deal with one, the analytic validity.

So it's important when you ask that question and we challenge ourselves with regard to the most effective system, it's important that the system be comprehensive, and that means we all have to work together. The FDA has a role in the clinical validity piece for the test kits, but the home brews, I'll let Steve speak to that particular question.

DR. GUTMAN: Well, the answer is yes. Then the corollary answer is maybe it doesn't matter, maybe it matters a lot, maybe sometimes it matters, and maybe FDA is or isn't the right fix, but the answer is yes.

DR. TUCKSON: I'll get off the soapbox now and be just a pure moderator.

I think Debra was first, and then we'll go around.

DR. LEONARD: I kind of like you on your soapbox.

(Laughter.)

DR. LEONARD: Can I answer your question?

DR. TUCKSON: You're up.

DR. LEONARD: Yes, there is a category of tests that doesn't go through 510(k) of FDA that are called laboratory-developed tests, and the CLIA regulations are weak in the evaluation of those. So CLIA has purview, it's my understanding, and correct me if I'm wrong, over tests that are currently being done, but that premarket review of tests, if you will, making sure they're okay before you start doing them, is not necessarily what CLIA does. CAP, in response to SACGT, added a whole list of questions for genetic tests that have to be answered by the inspector. They have to look at validation data. Can that be done effectively? It depends on the quality of the inspector, the education, the training of that particular inspector whether or not they can make an assessment of the validation process that the test went through. But every two years, every test that has been brought online has to be reviewed by the inspector for genetic tests.

So in not deciding to make a genetic test specialty or a genetics specialty, I think there are things that are falling through the cracks, but it's possible that through creating general rules in CLIA that look at test validation for laboratory-developed tests, you could get at this.

Judy, you're shaking your head. Do you look at laboratory-developed tests and the validation data of those?

MS. YOST: Yes, we do.

DR. LEONARD: Because the CAP added regs to their checklist. They have basically paralleled the questions that FDA now uses for its evaluation process, because I was partly involved in the development of those.

MS. YOST: Yes, the CAP does have a specific checklist that asks questions regarding genetic testing. However, CLIA always had a requirement that for every new test, the laboratory has to validate the analytic validity. CLIA does not cover anything regarding clinical validity. That's the distinction that has to be made. But CLIA does always ask is that test accurate, is it precise, what is your reference range for that test, what is the reportable range for that particular laboratory? And if it's a new test, it has to be the sensitivity and the specificity, and we clearly recognize that in some cases our surveyors may not have the expertise to look at that data and to evaluate it.

So we have been talking with both CDC and FDA, who have graciously agreed that if we collect the stuff on site, they will evaluate it to look at it. But it's just did the laboratory get the right answer, not was that test going to diagnose any kind of disease or malfunction. That's the distinction.

MR. HAMILTON: So you could turn this around and say if we had a genetic testing specialty, could we all go home? Would all the problems be solved? And I don't think so. So we go back to the two parts of the regulations that I think provide overarching authority and responsibility for the laboratory, Title 42 of the Code of Federal Regulations, 493.801(a)(2)(i)(i), each laboratory must establish and maintain the accuracy of its testing procedures. That applies to the home brew tests as well as the test kits. So even though the FDA may not be approving the home brews, the laboratory is still responsible. When it mixes up and produces its home brew, then it's still responsible for the accuracy. Then when we go on to Title 42, 493.1236(c), at least twice annually the laboratory must verify the accuracy of any test that is not subject to proficiency testing. That also applies to the home brews. So all of the quality control requirements in CLIA do apply to the home brews to establish the analytic validity. But again, just to stress, if we're concerned about whether or not the tests are really measuring the thing that you would hope that they're measuring, the clinical validity, that is a different topic.

DR. TUCKSON: This is terrific. We're going to keep this discussion going, and we have three people in the docket.

Chira, Emily, and then Andrea, and I'll look for other hands.

MS. CHIN: I just wanted to restate that you said something about laboratory-developed tests

are not being regulated by FDA, but the process of analysis is being regulated by CLIA. So is there any way that the laboratory-developed assay be regulated by somebody?

MR. HAMILTON: Well, if the assay is not producing accurate results, then that falls under the analytic validity area and is subject to CLIA. So when we go back to the responsibility of the laboratory to establish the accuracy of its testing and we find that a laboratory has inaccurate testing, then that's a deficiency under the Laboratory Improvement Amendments.

MR. HAMILTON: But Tom, again, just where we're at here, if I understood your earlier comment, it sounds like, as we keep cutting through this, that there's this general provision that says if it isn't specifically noted, then you have to just have good procedures and processes or else we're going to yell at you, and hopefully somebody is actually checking that, but you have this obligation. Where the problem is, I think you said, is that there is no requirement around the assessment of clinical validity, and that's what you are, I think, also saying. There's no clinical validity. So it's a terrific test, you've got great processes, you're very sharp. By the way, the test isn't clinically valid, and that's what I think they are also saying.

We've got Emily, and then Andrea.

DR. WINN-DEEN: So I think we have to accept that this is an imperfect system, because if I asked Andrea or Deb how long does a CAP inspector spend in your laboratory reviewing your validation data on a new test, and I asked Steve Gutman how long does the FDA spend reviewing an IVD submission on a new test and reviewing that data, I'm willing to bet that the FDA spends more time per test and reviews things in more depth than this inspection system can support. So I think what we have to struggle with is some kind of balance between is there a system that works for low-volume tests, for brand new tests, and at what point do we say that a test is so well established that it doesn't make sense anymore to have 200 molecular labs each manufacturing their own assay, and it makes sense to have six or eight companies manufacturing the assay instead?

But because we're in a field where things are emerging all the time, we don't want to get rid of lab-developed tests, we don't want to get rid of IVDs, but we have to understand that there is a continuum, and there also is some point when those things need to change over. I don't see any way that we're ever going to bring lab-developed tests up to the rigor that a manufacturer-developed test is subjected to.

DR. TUCKSON: So as we go to Andrea, I want to keep in the minds of people to be thinking about, and somebody can start to answer it, is does it matter? Is this much ado about nothing? Maybe that's what we're going to come up to. If you can't ever get at it and it's such a thorny issue, who cares if you don't do it? Is it a big deal? We'll get to that in a moment, but those who know the answer to that should start to help us with that.

DR. FERREIRA-GONZALEZ: I thank all of you for your presentations.

Judy, I was taken by a part of what you said about the proficiency, both of you, Thomas Hamilton and you, about the proficiency testing for cytology that took so many years and taking that as an example. But I look at it a different way. Now when I go to have my Pap smear done, I feel very confident that somebody, if I have a cytotechnologist at this point, that the results will be more accurate or the appropriate result. Before that, results from this proficiency testing, even though it took so many years to come along, we didn't have that confidence. At that same time, now we have addressed issues that we need to go back and continue education in a section of these individuals providing this testing.

So I think we have learned a lot of new things about testing that is being done very broadly that has taken so long to come up with a proficiency testing program. I agree with you that there is a major issue, but it's not because it isn't easy that it shouldn't be done.

The second question that I have, or comment that I have, is that we discussed a lot about

processes and quality control, pre-analytical, analytical, but I want to see if you'd mind elaborating a little bit more on specific requirements for individuals performing genetic testing, and specifically inherited disorders. If you are a high-complexity CLIA-certified laboratory director in microbiology or chemistry and so forth, and you decide today to start offering an FDA CLIA product for cystic fibrosis carrier screening, could you do that under CLIA the way it is today, with all the quality control? Is there any specific person and requirements that will assure that the proficiency testing for cystic fibrosis carrier screening will be interpreted by somebody with the adequate training that will assure me of the valid interpretation within a clinical context?

MS. YOST: Currently, the way that CLIA is structured, because there are not specific requirements for genetic testing personnel, the laboratory director obviously has the overall responsibility for hiring the right people to do the job. So that's the part of the process, and in that case, if you're going to add a test where it takes a very specific expertise to do that, then the laboratory director is responsible for either retaining on a contract or hiring individuals who can perform and oversee that particular type of testing and be sure the information that's provided to whomever the authorized person is is accurate and reliable. So there's a responsibility there. There may not be a specific requirement, but there's clearly a responsibility, because we say CLIA personnel requirements are essentially minimal. Even for the type of test you're describing, we're talking about a physician or a Ph.D. with board certification, a number of years of experience, plus specific training. So with all of those three things, you then place in that individual the responsibility to ensure that they hire the right people to not only do the job but to oversee the job. So if you need a technical supervisor to help with the interpretation of those results, then that laboratory director is responsible for making sure that that does occur.

DR. TUCKSON: Is that good enough? In other words, every doctor that's graduating from school, every professional in the business, you're supposed to do right. Is that enough? Does CMS believe that that's enough?

MS. YOST: I have to say that what we do, we have a very strong practice. Our practice is that if we find quality problems in the laboratory such as this, you have a test and you don't have the appropriate individuals with the appropriate training or experience to be able to perform the testing, guess what we do? We cite the lab director, and that gets their attention. Trust me, it gets their attention, because they know that they are ultimately responsible, and if not, that laboratory can lose its certificate to do testing.

DR. FERREIRA-GONZALEZ: But what is appropriate training? I take a class in undergrad in genetics? I've been going to the genetics clinic? I've learned how to do this? I mean, that's what I'm going to.

MS. YOST: I mean, CLIA is a package deal. You saw that it's a series of checks and balances. You need to do your quality control on a regular basis to make sure that the test results are correct. You also need to have the right people to manage and do the testing. You've got to have an audit system, a record-keeping system to follow the process throughout the entire thing. You need to do the proficiency testing such as Thomas described, whether it's a formal proficiency testing or whether it's the informal. But either one is mandated. You have to do all of those pieces. Plus you have to be able to demonstrate that you're providing accurate and reliable results for all the tests that you're providing, not just your genetic tests, because there are a lot of other tests that are very complicated to perform and interpret, and you've got to be able to provide that information. You have to look not at the narrow scope but at the broader scope of everything a laboratory can do.

Someone said this morning 2,000 tests that a laboratory could possibly do. I put 1,000 up there just as a conservative estimate of how many tests are on the market that a lab might possibly perform.

Qwest can tell me. I don't know. What's on your menu? How many tests? It's very expansive. So you have to be responsible for every one of those, and you have to be able to, under those circumstances. So it's not just one thing or another that's going to guarantee you that the system is going to work. It's all those pieces working in concert.

DR. TUCKSON: But now let me just make sure that Dr. Randhawa --

DR. RANDHAWA: Randhawa.

DR. TUCKSON: That's what I said.

(Laughter.)

DR. TUCKSON: I'll just make sure, though, because what you said is important. Can Qwest get a test to the American people, no matter how many zillions they've got on the thing, without going through FDA? They can? They get them out without going through FDA. Thank you very much. So they're in the same deal.

MS. YOST: Can I just add one more comment to what I was saying? It's very important to also put this in context. I'm not saying that every laboratory is perfect because CLIA is here. It's just like Steve said: we have the good, the bad, and the ugly. We truly do. Every once in a while there's a zinger that nobody could have anticipated that we all go and we say, oh my God, what have we been doing all these years, but for the most part we have that bell curve and those labs are doing a good job, as best they can under the circumstances.

DR. TUCKSON: And that continues to come back to the question does anybody have any data for those who aren't doing a good job? Has anything bad ever happened to anybody's kid?

DR. RANDHAWA: Since you called me doctor, now I'll call you Dr. Tuckson.

In the discussion that I've been hearing today, I'm not sure that even if you were in an ideal world of accurately doing laboratory tests when we think it should be done, that is sufficient to improve the public health and outcomes. So I think we're just talking about the first part, and what the downstream consequences of the test are, whether it's a more invasive confirmatory test, whether it's the harms and benefits of the treatment and how we balance that, which is really what improves or has an impact on the public health. So I think it's important for us to get a better handle on doing the tests well, but I haven't heard any discussion about clinical utility or the outcomes of testing, and that hasn't been a part of anything I've heard from either the CMS or FDA. So I'm not sure that even if you were to get everything done perfectly by the labs, that would really solve the problem.

DR. TUCKSON: Great. I think I understood what you just said, and that makes sense.

I didn't realize Debra had to go or I would have jumped her in the line. They're trying to run and see if they can catch her.

Other questions from the committee that will help out here, or any questions that are on your mind? Let me just ask the committee, if you don't have questions, do you all feel like you understand any of this so that you're prepared to make some recommendations here?

DR. EVANS: I'm confused about one thing. Is one of the problems that CLIA inspectors don't have the expertise to evaluate the in-house developed tests? Is that a problem?

MS. YOST: It's a problem that has an identifiable solution. We didn't really get to talk about the list of things that we're planning on doing, and one of those is to probably do something creative as far as looking at those tests, because we realize we may not and because most of the labs that we look at are not the type of labs that are going to do this type of sophisticated testing. So we would either create a core of folks who would go around and develop the expertise, train them and get the technical and the investigative training in place, and they could go around and look at all the laboratories in the country rather than the local surveyors, or we could have a contract with someone who already does that and

already possesses that expertise and just pay them. So there are a number of ways that we can get at this. I wouldn't take that as an irresolvable problem because it's something that can be addressed, and it's something that we've already been evaluating.

Actually, way back when in 1997, when the recommendations were made from the task force, we knew that we probably would need to look at something because the technology was exploding and we weren't going to be able to keep up with it in-house.

DR. EVANS: Is it related to the lack of a specialty of a genetic testing --

MS. YOST: Nothing at all. No, it is not. No. It's the specific technology. But that, again, is going to happen everyplace, because you'll have microarrays or you'll have other types of technology that will come into place that we can't even anticipate at this point in time, and we'll be in the same position. But don't also forget that those folks that we train, we train them with very detailed, specific investigative skills, how to collect information, how to interview people, what to look at. It doesn't matter what kind of technology they're using. Those folks can find a problem if a problem exists. They know what to ask, they know where to look. They'll have the lab explain the technology if they don't understand it. So that isn't a limitation. It's actually an advantage.

DR. FERREIRA-GONZALEZ: Well, you know, another way to get around this issue of CMS and the subspecialty -- the CDC is here? It is my understanding that the February CLIAC meeting, CLIAC is actually going to look at these specific issues on the genetic specialty. Is that correct?

DR. BRADLEY: I can't speak to that. I'm not involved with CLIAC. I'm sure Judy knows.

DR. FERREIRA-GONZALEZ: If CLIAC actually, which is the advisory to CDC and CMS, is going to look at this specific issue, maybe we can wait for them to see what they recommend with this specific issue.

The other thing that we can do is maybe appoint someone to that group or have somebody from that group come back to this committee and report on what are their recommendations and then see what that group, which are most of them laboratorians, feel about this.

DR. TUCKSON: Would you hold that recommendation for just a minute and resurface it when we get to what we want, if anything, to do as a committee? I think you've raised something that's tangible.

Let me ask, then, Judy, to finish the part where she has some important stuff in terms of what New York is doing. One of the things that I think Judy has emphasized well here that has certainly gotten my attention in this whole discussion, and it came up in the example also with Qwest, is how many of these tests are rolling down the road? So if you put every single test through a pretty serious drill, that might be an almost impossible regulatory burden. So that's important to think about. I'm thinking about it and trying to figure out what that means. New York has done some stuff that gives us a real case scenario for some of this. So can you share with us the New York thing?

MS. YOST: (Inaudible) office. They are the investigative arm of Congress. They were requested to look at direct-to-consumer testing, but also to follow up on the status of the proposed rule at CMS. Just to get back with you, they did identify a number of laboratories that were providing nutrigenomic testing, evaluation of lifestyles. As Thomas indicated earlier, most of the issues surrounding that are not CLIA issues. We do not deal with advertising and marketing and clinical validity and utility of results by a provider, but we are responsible for oversight of laboratories. That's if the test is covered. In this case, some of those nutrigenomic tests, as they're called, evaluate lifestyle. They look at your diet, they look at your nutrition, they look at whether you smoke, they look at how much you sleep, all those kinds of things. Obviously only if it's a health assessment is it covered by CLIA and thereby subject to CLIA requirements.

In this case, these are clearly laboratory-developed tests. Trust me. So in that case we are closely monitoring. I think it's important for you to know the labs that have been identified plus a whole pile of others, because once you find one, they're like little bunnies. They multiply, because they're all associated with one another. They're all in cahoots with one another. That's the only way I can describe it. So you find one, and there's another. One is marketing for the other, one is doing the test, one is interpreting the test. One is in London, one is in Denver, the same lab. It's just incredible. So you just have to un-weave the web constantly to identify these facilities, and we are doing that. We are working very closely with CDC and with FDA on this process.

But let's go on to the New York program, because it's probably the penultimate in oversight of genetic testing, and I have to say that clearly they are overall in New York the most stringent state laboratory standards in the United States. They also have a wonderful infrastructure to share. So it's the difference between the economy in CMS, where we're self-funded, and a laboratory program that has very high fees, very good resources and revenue to support it.

Under this program, there are two types of tests, FDA-approved or cleared, and then everything else, the research only, the investigative use, the in-house developed ASRs and so forth. In those cases, those tests must be approved by the laboratory program before the lab can offer the test. Currently, Steve, you're correct that it's about 12 tests you've approved, genetic tests. So everything else under the sun that's a genetic test has not been approved by the FDA.

Just a typo on this. Actually, they had done up to 450 reviews overall, not just this year. But their review includes both analytic and clinical validity. They also provide the laboratory guidance on the information that they need to provide in order to do this review. But there's an interesting factor here in that all the reference laboratories in the country probably have a site somewhere in the State of New York, because if you understand New York's program, it has tentacles, because any testing on any New York resident, regardless of where it takes place, is covered under the New York State law, and they thereby must submit their tests to the state in order to be approved.

So if you extrapolate that, considering that all the major reference laboratories are there and the major facilities that are there, it is estimated that probably 75 percent of the genetic testing in the United States is already subject to New York State oversight.

The program in New York -- and there's a representative here from the program, so she'll be happy to jump up if I say something off, and she's provided all this information, so I didn't make it up -- but it's broken into two segments. There's cytogenetics, and then all of this information, the clinical information about test selection and interpretation, patient consent, confidentiality, specimen retention, turnaround time, very, very prescriptive, very detailed requirements of all the information that needs to be submitted. In addition, there are requirements for reports to be signed by a cytogeneticist and that there be an interpretation suitable for a non-geneticist, which is just fantastic.

Also, prenatal and preimplantation outcome verification. We're even looking at utility here, and of course the lab is subject to the New York State PT program. The same thing for genetic testing, very similar requirements, as you can see. Again, very detailed QC, clinical and analytic validity, confidentiality and so forth. Now, in this case they have the same thing that CLIA does, essentially, because where there is not PT material available, particularly for rare diseases, then the laboratory is subject to external PT if there's PT available, or the twice per year just as in CLIA.

It's also interesting to note that even though there is a very detailed definition of genetic test under the state law, there are also tests that are disposed through the laboratories, just as in CLIA. There are some tests in microbiology, immunology, chemistry, hematology and pathology. So not everything is all collected into the one area.

That's basically a summary of it, and this affects about 173 facilities. The cytogenetics piece has been in place since 1972, and the genetics piece since 1990.

DR. TUCKSON: Well, thank you very much.

First of all, I want to really thank Steve, Thomas and Judith for not only their presentations but for putting up with my pain-in-the-neck questions. I really appreciate the way you've handled all of it.

As the committee now tries to think about this as to any next steps that you may decide, or you may just let it lay here, I wish I had never brought this thing up. There are some things that, it seems to me, you take for granted. When it comes to clinical interventions, whether they be diagnostic or therapeutic, one assumes that there is a government that is appropriately looking out for your interests, and you just sort of take that for granted. I do hope that that is the case here, and maybe it is.

I also know that you sure don't want to be piling on needless regulation on the backs of industry that would therefore result in extra health care costs that deny access to the very life-saving diagnostics and therapeutics that you started out with in the first place, and you definitely don't want to pile on a bunch of regulations onto the poor laboratorian in an academic center who barely gets an indirect cost provision from their dean to keep the lights on. So you darn sure don't want to do that.

So somewhere in the middle of all this is a right answer, and I'm trying to make sure that there's sort of an ethical obligation this committee has for having raised it, or our predecessor has for having raised it. Shame on them, except I was on that committee, too. You know, once you raise it, you'd better doggone well deal with it some kind of way, because if at the end of the day it means that people's health could be compromised because of a lack of vigilance, then that's a pretty bad thing to have happen and just decide that it's too complicated or whatever and you just walk away from it. So I really regret ever having asked the question.

So with that, you need to figure out what you want to do and how you want to do it, and you need to determine, I think, first here is there a problem? Is the problem significant? Do you know enough to answer either of those questions? And if you don't know, then what do you want to do, if anything, to find out the answer to is there a problem or if the problem is significant? I look now for wise guidance.

Matthew?

MR. DAYNARD: Is the New York person available?

DR. WILLEY: Yes.

MR. DAYNARD: Well, I think you'd be a great place to start to answer Reed's question, namely what has the response been and the effect of the New York law on industry and consumers, to your knowledge?

MS. BERRY: And if I could amend that, too, what is it that prompted New York to act in the first place?

DR. WILLEY: I'm Dr. Ann Willey. I'm the director of policy for the Wadsworth Center, which is the public health lab in the State of New York. I've been responsible for the cytogenetics oversight programs since 1979, and for the implementation of the genetics program in 1990.

What prompted New York State? There's a New York State statute that dates to 1964, predates CLIA in 1967, which requires the State of New York to oversee the practice of laboratory medicine for the testing of all specimens derived from the human body for all purposes. So when cytogenetics, the examination of human chromosomes, became a practice of laboratory medicine, it was an area that required oversight. When biochemical genetic assays for enzymes or PKU or DNA markers for genetic assays became the practice of laboratory medicine, it was required that we establish appropriate good science-based standards for laboratory practice.

The statute requires that all tests performed by a permitted laboratory must be either generally accepted -- by definition, FDA cleared is an in vitro diagnostic device -- and approved by the Department. That means technically we can say no to a test the FDA said yes to. I don't know that we've ever done that. But for any test that is not cleared by the FDA, so as not to limit availability of this general practice of lab-based test development, we had to have some basis by which we would approve those tests that didn't go to the FDA.

Our process for validation review of non-FDA-cleared tests is not unique to genetics. It applies to any laboratory test. It could be clinical chemistry, it could be microbiology, virology. Genetics is only one area. The standards are that the laboratory has to submit adequate data, and for genetics that's usually very small numbers of cases because for most of the tests it's going to be small positive patients, if any. So their validation data and their clinical validity. There must be some known clinical association with the genetic marker.

So, for example, a lab that says they can find SNPs, analytical validity is absolute. They can find every SNP in the human genome, they can print out your CD SNP profile for $1,000; if they cannot establish clinical outcome associated disease state for each SNP, they cannot offer that SNP in New York State.

What's the response been? Consumers are not well informed about how we oversee laboratory tests. Physicians are only slightly better informed. Many of them are told where to order their tests by the insurance that's ordering the services for the patient. So the laboratories themselves, 95 percent or better of all labs are good labs. As I think it was that Steve said, if you don't know that the test you're offering provides good results, what are you doing offering the test? And 95 percent or better, that's going to be the case. If they forgot to submit their validation package, hopefully it's already on the shelf and they can correct the deficiency within a matter of days. If they send us the package, we review it.

We're slow. There are only two technical persons on the staff who actually review all of these submissions. I review all of the cytogenetics, the (inaudible) assays that are ASRs that require individual probe review. All of the genetic testing is reviewed by another individual who is a geneticist. We get behind, and that's the biggest objection from industry. It takes time. They've done the work, and we have to do the reviews.

It's also an educational process. We'd like to streamline it. We'd like to see every application come to us with the table of contents and everything on the same page. That's not the way it happens. But it works.

In the meantime, if a laboratory had a critical clinical need to offer a test for a clinical referral reason, we will issue what we call a non-permitted lab approval for that patient, for that purpose, for that time only, and we tell labs that when they get to 50 requests, we begin to get really unhappy.

Our surveyors do not attempt to review the technical data at the time of survey. They go in and ask the labs what tests you offer. If it's a home brew test, it's not FDA approved, there's no package insert that says it's an IVD, they ask to see the letter of approval from the department of health. If the lab can't produce the letter of approval, then the lab is cited for offering a test without approval, and the deficiency is corrected by submission of the validation data.

There are labs out there offering clinically useless tests that are having dire consequences for fetuses and patients.

DR. TUCKSON: I have been waiting for three hours to hear somebody say that.

(Laughter.)

DR. TUCKSON: Now, first of all, thank God for what you all are doing in New York. Given what Judy Yost told us so clearly about the interconnections between New York and the rest of the

country, would a lab have to submit to you and then to other -- I mean, wouldn't this be burdensome for labs to have to jump through your hoop as well as the CLIA hoops and the FDA hoops?

DR. WILLEY: New York State is CLIA exempt. For those labs located in New York State, by meeting New York State requirements, they do not have to meet CLIA requirements. For labs outside of New York State, they will get their CLIA certificate from their local state entity. However, to my knowledge, nobody else is reviewing the actual validation data. CAP may be at the time of survey onsite would not discourage that, and they may find things that we don't find. I mean, the more times you look, the more helpful comments, the more constructive criticisms we can offer. Right now, we're not in competition because nobody else is doing it.

DR. TUCKSON: How much money -- oh, I'm sorry. Cynthia has her hand up.

Matthew, by the way, you had the floor. Did you finish your question? And then Cynthia is next.

MR. DAYNARD: Well, I did. Thank you very much. I'm just wondering what do you do about these labs that are offering tests that are hurting people?

DR. WILLEY: Well, for New York State, we simply tell them they must cease and desist, and if they continue we can charge them $2,000 a day.

MR. DAYNARD: Are they operating in other states even if --

DR. WILLEY: New York State has no jurisdiction in any other state. I'm an attorney as well as a geneticist.

MR. DAYNARD: Right. I'll be in touch.

DR. TUCKSON: We have Cindy, and then Emily.

MS. BERRY: What I think I heard was that there wasn't a particular problem that prompted this. This was a statute that existed a long time ago, wasn't specific to genetics or pharmacogenomics or any of that, and so because of the regulatory scheme in New York State, genetics fell into it, if I'm interpreting it correctly.

DR. WILLEY: There was a terrible problem in the early 1960s when, if you sent the same specimen to two different chemistry labs, you got two different answers. The hypothesis was that there's the same potential problem in every area of clinical laboratory medicine if you don't put appropriate oversight in place.

MS. BERRY: So what I'm wondering, then, is that maybe there are things that New York does that could be done at the federal level with some tweaking or whatever, but I'm not totally convinced that genetics is unique, that whatever these problems are could apply to many tests and many labs. So I'm struggling a little bit with why is it we need to focus on a genetics component to CLIA or whatever, because it seems to me there are other things that could fall through the cracks.

DR. TUCKSON: Well, given that you're going there, in your opinion and with your experience, and we appreciate you stepping up and helping us here, is there a special need? We wrestled with this question of genetic exceptionalism, and it's on our menu of activities for all the things we're supposed to be doing. Is there a special need for genetic exceptionalism here, or is this just diagnostic laboratory medicine?

DR. WILLEY: I'm a geneticist, but I have a personal bias. I believe this is good for all of laboratory medicine, and the success of the New York State program is because it does not treat genetics differently. It makes no exceptions for genetics, but it simply holds it to the same standards.

DR. TUCKSON: Emily, and then Andrea.

DR. WINN-DEEN: I had a question regarding FDA-cleared tests. Once they're cleared, is there any incentive for New York State licensed labs to switch over to a cleared assay, other than the fact

that they don't have to prepare a dossier for you?

DR. WILLEY: It is of concern, I believe, to some of the vendors of IVDs, that if they go to the trouble of producing an IVD and getting FDA clearance -- this is true in genetics; I can't speak to other areas -- that a lab will use an FDA-cleared IVD as their gold standard against which they will validate their in-house developed assay perhaps because the in-house assay is cheaper. So, yes, there would still be an incentive for a lab to do a home brew, home-developed assay if they thought it was cheaper than the IVD cleared.

DR. WINN-DEEN: But the state doesn't have any mandate that says that in order for a test to be available at this level, you have to --

DR. WILLEY: No, but it is probable that if there's an IVD-cleared assay, that is the standard against which we're going to expect the lab to validate, and that may put them at a high standard that they won't be able to meet.

DR. WINN-DEEN: And I had a quick question for Judy. I actually was sort of distressed to look at the CAP molecular surveillance panel and to see that they're just genomic DNAs and they're really not full process controls. Is there any plan to work with CAP to develop full process controls for genetics?

MS. YOST: Not specifically, no.

DR. FERREIRA-GONZALEZ: What do you mean by that?

DR. WINN-DEEN: Well, it doesn't go through the isolation purification part like a clinical sample would. It just comes as a purified genomic DNA.

DR. FERREIRA-GONZALEZ: For the proficiency testing?

DR. WINN-DEEN: Yes, for the proficiency tests.

DR. FERREIRA-GONZALEZ: There are major issues of how you manufacture and have a license --

DR. WINN-DEEN: Yes, I understand that. I just didn't know how it met CLIA's requirements.

MS. YOST: Actually, because they're not required. That PT is not approved by CMS. The only PT we look at when we approve proficiency testing providers are for the 83 analytes that I mentioned that are in the regulation. Everything else is voluntary for the laboratories to perform, or in the case of certain accrediting organizations where they require every analyte to have formal PT. One of the difficulties, again, is the fact of the shortness of materials. There are not materials available that are easily transportable, or in the case of a rare disease it's just that there are so few materials that it's impossible to create PT the way we're used to seeing traditional PT. So there are limitations to what can be done with that, and I think that's part of the process.

DR. FERREIRA-GONZALEZ: And that's the problem you have with cytology, too?

MS. YOST: Yes, it was only one. It was one of the problems we had, that there were not enough slides available.

DR. FERREIRA-GONZALEZ: There are significant efforts through the CDC to develop controls and materials that could be used for genetic testing for a significant amount of different things.

MS. YOST: Yes, there are.

DR. FERREIRA-GONZALEZ: So maybe that could be a venue for different professions for materials that could be used to have the enforcement. I strongly believe that there's got to be some enforcement for PT for the laboratory.

MS. YOST: You're absolutely right, and there have been major efforts by CDC in that area, both in PT and QC, for genetic tests, and we have been working with the CDC to support those efforts, because I think we're paying for most of them anyway under CLIA. But it's important to know that in

addition to working with them, we hope to develop educational materials for genetic testing laboratories that would encourage the use of those types of materials then. So we would get at it from that direction. We really didn't go through my list in detail, but that's one of the things that we had talked about doing.

DR. FERREIRA-GONZALEZ: A question for the New York -- the New York lady, I'm going to call you. You mentioned that when you have FDA-cleared IVD products, that when the laboratory brings them online, you don't have to submit for your review before these laboratories start using them.

Now, if you use an ASR, you're still doing a laboratory-developed assay, and then you have to submit for the review by the New York State Health Department. Is that correct?

DR. WILLEY: I'm sorry. I didn't hear the second part.

DR. FERREIRA-GONZALEZ: When you use an ASR --

DR. WILLEY: ASRs, yes. When you use an ASR as a component of an in-house developed assay -- and we greatly appreciate the FDA's recent clarification that when you buy a single component, you're buying an ASR. So when you put them together -- you know, your control probe and your target probe and you're making up an assay -- then, yes, all in-house developed assays using ASRs require departmental approval, whether it's genetics or microbiology.

DR. FERREIRA-GONZALEZ: I think at the core of some of these issues that we come back and forth, certainly to genetic testing, is just that within CLIA there is no need to show clinical validity of the testing that we bring it. This is not just for genetic testing. It's for all laboratories. So we've tried to fit a 9 foot into a size 6 shoe.

(Laughter.)

DR. FERREIRA-GONZALEZ: You know, this is at the core. Who does the oversight at New York State or sending it to the other agencies? You know, the problem is that the current CLIA regulation does not include demonstration of clinical validity.

The CAP Molecular Biology Checklist has a significant amount of questions now put into that program to deal with this issue. It's three days. Like last month, they came and inspected us and spent three days in our laboratory looking specific about data. It's a different issue, and again, these are your peers looking at what you're bringing online.

But at the core, it will be that issue that there's not in CLIA a specific regulation for the clinical validity of the test.

DR. TUCKSON: And I think that we all get that what that means, as you described, Dr. Willey, is that there could be or there are in some cases people who are purchasing a test, people are paying for it, that may not work. It may not tell you any information that would be useful or it could be that a clinician is using that information to make a diagnosis that leads to a therapeutic intervention that may not be appropriate. That's where the importance of the question mark arises, if I understand the discussion.

DR. RANDHAWA: This is a question for my CMS colleagues for my clarification. Is the reason New York State is exempt from CLIA is because they already had a program equal to CLIA?

And the second part of that question. This is a hypothetical, sort of a dangerous question to answer. Suppose another state comes up with a program similar to New York State. Would it also become potentially exempt from CLIA if it wanted to?

MS. YOST: States have to apply in order to become exempt and then we do an excruciating review of their standards to ensure that they actually are at least equivalent. They could be more stringent, as obviously these are, but they must be at least equivalent to CLIA.

Please understand that we're talking about opposites here. This is the continuum of laboratory oversight. This is one end of the spectrum and we are the other. CLIA was put in place as minimum

standards for laboratory quality with certain caveats, again, that the lab director has that overall responsibility and that should pick up where it needs to in the event that they can, and the laboratory has a choice about who's going to inspect them under CLIA. They have the choice of either the state department of health, who use the CLIA standards, or an approved accrediting organization, many of whom also have more stringent standards than CLIA, because it just is equivalent. It doesn't say identical.

That's the way the program was developed. It was developed also that it would essentially dovetail into FDA because they didn't want duplication of effort. CLIA would look at is the answer right, and FDA would decide if it was a useful test. So it makes sense if you put all the pieces together.

DR. TUCKSON: All right. So here we are, 15 minutes left.

Dr. Ann Willey, you are just terrific, and I just can't thank you enough.

DR. FERREIRA-GONZALEZ: Can I add one monkey to the wrench?

DR. TUCKSON: Well, first of all, what you get to do is, you get to add one monkey to the thing, but what you also get to do is to start to formulate the beginning of a consensus of what, if anything, we want to do. You need to do two things.

DR. FERREIRA-GONZALEZ: I'm not sure about the second one, let me tell you that.

(Laughter.)

DR. FERREIRA-GONZALEZ: As I commented this morning, I'm a member of the IRB for VCU. As a member of the IRB, we review a lot of protocols that actually are clinical trial protocols where some of the clinical trial protocols propose to do, for example, pharmacogenetic testing on individuals to be placed in a specific arm of a clinical trial, and then certain drugs are given to that patient.

But I was talking to and asked my IRB members and said who is doing the testing for these clinical trials? And somebody looked at me and said what does that matter?

I started bringing the issue of research testing that is being used to make decisions on how a patient is treated in clinical trials, and my understanding is this is under CLIA purview, but it seems to me there is some disconnect between what actually IRBs in different areas of the country are knowledgeable about these specific issue.

So one of the concerns I have is also the research laboratories. How are they regulated for these private tests?

DR. TUCKSON: All right. Let me try this.

Thank you, by the way.

Let me give you an option to shoot at because I'm looking for somebody smarter than me to say it or figure it out. What I'm thinking is is that we say to the Secretary in a letter that we've had a chance to discuss this, learn a lot about it, and that we have certain principles that we have come to understand.

Principle number 1 is that the public should be protected or there should be oversight. Not even protect. That's negative. The public should expect that there is appropriate oversight in place for the diagnostic and therapeutic interventions that they receive.

Number 2, that this transcends genetics but because our focus, our mission, is on genetics, we recognize that genetics fits into the larger continuum of clinical care, and that we come at this from the point of view of specifically looking at genetics.

Number 3, that we as a principle understand that inappropriate regulations do no good and we have a report that's already out around our concern about access to genetic technology that could be compromised by unnecessary, burdensome rules and regulations that are not helpful. We put that as a principle as well so we clearly get on record as not looking to be a bunch of irresponsible nuts running

around talking about regulate everybody and everything.

Number 4, that we've heard good testimony from his -- in this case, because he's a man -- own agencies that leave this committee with some questions as to the adequacy of oversight of genetic testing.

And that finally, because of the potential implications of a lack of adequate oversight on the health of the public, that it would behoove him to bring his people together -- FDA, CDC, CMS -- and they should report to him and give him an answer as to whether or not there is a significant problem and what the remedies might be to be able to address it, and hand him the transcripts of our testimony, a synopsis of all that we've gone through, and simply say, you know, this is on you. I mean, this is what you get paid to do and all these smart people in government get paid to do, and the FDA, that's all they exist for, and CLIA, that's all they exist for, and the CDC, in part that's what they exist for. Figure it out.

I just put that out there for you all to shoot at.

MS. BERRY: Hasn't that already been done to an extent? I mean, Thomas, you went through kind of the laundry list, the thought process or the approach that you take when you analyze is there a problem, and if so, is the proposed solution necessary to correct that problem? You know, the whole thing that you outlined for us. I mean, was that done just at CMS? Was that done with input from FDA and others? I'm wondering if we've already done what Reed has kind of outlined.

MR. HAMILTON: Well, again, we weren't looking at the entirety of genetic testing in that. We were looking at the question of a proposed reg that would establish a genetic testing specialty. So it was a narrow focus within CMS. We obviously discussed it with CDC and the FDA, but our clearance process was within CMS.

DR. TUCKSON: Kevin?

DR. FITZGERALD: I'm just wondering if we could be more specific in the letter to try to give the Secretary a bit more concrete focus and mention that in this process which you mention, with these principles that you mention, one of the things that came up that Andrea also mentioned is this fact that there is a difference between a plan like New York's and what is currently federal regulation, and it focuses around clinical utility.

So the question is to say not that the federal has to be the same as New York, but, as we heard, New York is at one end of the spectrum. Should we move more in that direction and, if so, then how and to what extent? So I'd say you could break it down into fairly specific sorts of issues.

DR. TUCKSON: Joe?

DR. TELFAIR: Yes, I would agree with both you and Kevin, but also take into account, I think, what has been said. Mine is real simple, hopefully. I think it seems like the issue is broader and it's bigger than just our committee as a whole, and it seems like what we can do in terms of the strongest thing we can do is to hear what is the bigger issue of clarity, and then determine based on, well, even what was just presented, and also I think because there's a committee coming up, to say this is our piece to the bigger solution and that's the most we can do, okay? That would be a thought.

DR. TUCKSON: Thank you.

DR. FERREIRA-GONZALEZ: What we heard earlier from CMS is that genetic testing is currently regulated under CLIA. Our thinking is a specialty will produce more strong or more defined criteria for this testing, but I think maybe letting CLIAC come out with their recommendation, specifically if there is a need to increase oversight of genetic testing by the creation of a subspecialty or specialty within CLIA might not be a bad idea, and just wait for that group to look at this and report back to us before we make our final recommendation.

DR. TUCKSON: When are they meeting?

DR. FERREIRA-GONZALEZ: February.

DR. FITZGERALD: Andrea, one quick question, though. In that process, will even the issue of clinical utility ever come up? Because it wouldn't normally, right, even with a new specialty?

MS. YOST: My guess is it will.

DR. FITZGERALD: Your guess is it will come up. So this would be a first.

MS. YOST: No.

DR. FITZGERALD: You have clinical utility for other --

MS. YOST: It's been coming up in that venue also.

DR. FITZGERALD: Oh, I see.

DR. FERREIRA-GONZALEZ: So this might tip it over the edge?

DR. TUCKSON: Andrea, first of all, the committee needs do it with the consensus, and I think we've got to keep raising consensus.

My concern -- and I think, first of all, we've gotten extremely frank, well-meaning, and good testimony from Steve, Thomas, and Judith, and clearly they are honorable people serving the public's interest -- at the end of the day, the natural tendency, inevitably, for people in government agencies has to be to tell us that things are moving along and doing fine. I think we need to put it on the Secretary and ask him, in the quiet of his own deliberations, whether or not this is going as it should, because I think there are things that can be explored in private that can't be explored as well in public. That's just a bias.

DR. FERREIRA-GONZALEZ: Well, that committee will report to the Secretary.

MS. BERRY: I just think whatever we send to the Secretary should more clearly define what the problem is because we're hearing that 75 percent of the labs are regulated by New York State. We also know that health plans to a large extent tell doctors which labs to use so that something is reimbursed and kits are regulated by FDA. Is that correct? So if some consumer just on his own gets something -- so he or she is protected to a certain extent.

So I want to hone in on what is the actual problem? What is it that's the problem? Who's unprotected? What are the gaps? And I'm not certain I have a good understanding of what that is.

DR. WILLEY: Can I just make one technical point? Seventy-five percent of the testing is regulated by New York State. That's because the very large commercial labs are all regulated by New York, and the reality is the majority of tests are still done by those large labs, not 75 percent of the labs.

DR. TUCKSON: And, by the way, you may want to, Cindy, again, in this section in the briefing book on page 8, there is a set of one, two, three, four identified gaps which are part of it.

So the challenge we have, based on what Cindy has said -- and I was sort of expecting that that's where we also are here -- is that there are still, despite the information we've gotten, some unclarities in the basic database in the background.

So let me just ask you your preference here, Cindy, based on what you said. You could postpone writing a letter to the Secretary and try to discover some more of these things and make it more clear what you want to write in terms of the problem and the issue. We could come back at it in the next meeting. You know, work on this in the interim between the meeting and then finalize it at the next meeting, or you could just simply say we've had all this stuff, we're uncertain, and we urge you to take a look at it. So it's really a matter of sequencing as to how you think you may want to proceed.

MS. BERRY: I mean, I've read the briefing book. I just, from today's discussion, don't know precisely are all of these problems real problems? What is the scope of these problems? Is there agreement, universal agreement? Are there others that were not mentioned here? I don't have any objection to, if people know what that is -- and this is not my expertise, so there are others here who deal with this on a daily basis who would be able to articulate much better than I what the problems are. If there are truly concrete issues and problems and gaps, I just think we should identify it in a letter, and I

don't object to doing a letter right away if we're able to put our arms around the nature of the problem immediately. If not, then I would suggest that we postpone the letter until we can get that nailed down.

DR. TUCKSON: Other points of view as we try to determine what your wishes are in this regard?

DR. FITZGERALD: Just a quick question, and again, if you would help maybe clarify this a little, and perhaps we can look at it this way. Rather than listing, perhaps, all the specific problems there might be, my question would be is there an approach or solution that would pretty much address all that list of problems; i.e., clinical utility?

DR. WILLEY: I don't think there's one solution, but I think there are many options. One is greater use of the FDA option. One is changing CLIA's authority for all testing to include clinical validity, heaven forbid. One is something specific for genetics. I mean, there isn't one solution.

DR. FITZGERALD: No, I'm not saying there's -- maybe I didn't phrase that properly. What I'm asking is there's a whole list of things that may be wrong. Is there a solution? Not one solution. Is there a solution? Or maybe there are several different solutions, all of which, as you mentioned, could address the list of problems.

It's the list of problems I'm trying to get at. Do we need to list all the problems or are there a set of solutions that would pretty much take care of all the problems, whether it's one in the set or many?

DR. WILLEY: I don't have the list of what you've identified as the problems.

DR. FITZGERALD: Okay.

MR. DANNENFELSER: I guess I would want to know how rigorous it is to determine the accuracy of the test, and then what is told in terms of to the patients how accurate the tests are in terms of is there a percentage of accuracy and how certain can we be and how accurate that assessment is.

DR. WILLEY: Accuracy of a test has a very specific scientific definition. It's not hard to establish accuracy. That is, if you have a specimen that has the target, how often do you find the target or how often do you get a negative answer when you should have gotten positive and positive when you should have gotten negative.

I don't think that's the accuracy you mean. I think you mean the predictive value in the particular clinical circumstance of that patient. That is much more difficult.

DR. TUCKSON: Marty, is that what you mean?

DR. WILLEY: So in a laboratory, I can tell you that cytogenetics laboratories, their accuracy rate is 99.9 percent. One out of 1,000 cases would get the wrong answer, right? That doesn't mean much to a patient where the predictive value depends on why the test was ordered by that physician in that circumstance. I, the laboratory, can't tell you that without knowing exactly the clinical reasons the physician ordered the test.

MR. DANNENFELSER: Can you do studies after the fact to determine if the --

DR. WILLEY: In New York State, we ask laboratories to confirm prenatal and preimplantation genetic diagnosis results for all pregnancies. That's the only way that lab can do quality assurance on outcomes, but that doesn't give them predictive value, again, in the clinical circumstance. It gives them test accuracy.

MR. DANNENFELSER: Well, here's a hypothetical. A number of pregnant women are told the child has Down's syndrome, they give birth, and then there's a determination how many of those were actually accurate. If 40 percent of the children did not actually have Down's syndrome, can you then conclude that perhaps that test is 40 percent inaccurate or does that give you reason to think it might be?

DR. WILLEY: No, it wouldn't give you analytical accuracy. That wouldn't be how you'd establish analytical accuracy. That's how you would establish predictive value. They're two different

measures.

DR. TUCKSON: By the way, Steve, would just remind us again of this postmarketing surveillance that we're getting at here? Again, who handles that again? Just so we have the right information.

DR. GUTMAN: Well, I can't speak for New York State. At the FDA, there obviously is an entire program. Actually, it's being reenergized. There was a report out I think last week about the new contours of that program.

We in Devices are sort of responding to the issues in Drugs, which is that not New York State, not CMS, not FDA looking at a premarket package can predict the future when you extrapolate it to the huge universe of use. So it's always sort of an estimate, and the reason you want to track tests is to see the truth.

DR. TUCKSON: All right. Thank you.

So we're back to decisions, and the decision is standing between you standing in the lobby being picked up to go to dinner. By the way, at 7 o'clock, you're supposed to be in the lobby, and if you're late, God help you, because you won't eat for free.

MS. CARR: It's not --

DR. TUCKSON: It's not even free anyway.

(Laughter.)

DR. TUCKSON: You won't enjoy each other's company. That's it.

So you have two choices here. Cynthia has -- oh, great, Phyllis. Save us.

DR. FROSST: I'm sorry. Never get between a committee and it's dinner, but I do have a third option that's somewhere between a letter to the Secretary saying there's an issue that he needs to get his smart people working together on and between doing what sounds a bit more like a short report really highlighting the issues that are at stake here, and that would be to write a letter, but including an illustrative example that highlights a gap that an individual could fall into. It seems to me that that might be a way of getting a busy person to notice that there's a real personal element here that he can make an effect in.

DR. TUCKSON: That's actually a very cogent recommendation, and if the committee were to adopt that, you would have to have a few people who would volunteer to sort of put that together, and then we would float that by the full committee in time to send that forward.

So what you've done, Phyllis, because obviously you're an active listener, you have summarized the three options better than the chairperson ever could.

So, committee, which of those three options that have been laid out do you enjoy first? So which of those seem to make sense?

Phyllis, start with the first one. Raise your hands for those that like 1, 2, and 3. What's the first one again? You did great.

DR. FROSST: The first one is suggesting that the Secretary get his wise heads together and try to address the problem that we superficially highlight.

DR. TUCKSON: Good. Then the second one was?

DR. FROSST: Similar to Option 1, but to include sort of a case study, and example, if you will, highlighting an example that would demonstrate the gap that we've discussed today. A gap that we've discussed today.

DR. TUCKSON: That was the third one.

DR. FROSST: No, that was --

DR. TUCKSON: Here they go again. Just so we've got them. See, I'm active listener, too.

The first one was you send a letter to the Secretary saying get your smart people together and figure this out. Number 2 is you do something that's essentially a report where we put together and really go through some of the things that were implied by Cindy's very good recommendation. The third is you send the letter soon, but you indicate in there an example of somebody falling through the cracks because you want to illustrate what's going on.

DR. FERREIRA-GONZALEZ: Let me throw a monkey.

DR. TUCKSON: Go ahead.

DR. FERREIRA-GONZALEZ: I have a fourth one, to wait until CLIAC reports in the specific issue of the genetic specialty and see what the Clinical Laboratory Improvement Advisory Committee has to say on this.

DR. TUCKSON: Right. Now, you're assuming on that fourth one of waiting for the CLIA folks to meet, that whatever they come up with is actually the solution to the problem or are you just saying it would help inform your situation?

Okay. So we're going to do it in reverse order. All those -- I'm not good at counting.

DR. FROSST: One point of clarification. A sense of when input from the CLIAC would be forthcoming?

DR. FERREIRA-GONZALEZ: February.

DR. TUCKSON: February. Good for you. That's the right question to ask.

DR. McGRATH: We could also include in either of those three options a statement about the CLIAC meeting that he then could follow up on that himself with his wise heads.

DR. TUCKSON: So we would build that into an assumption for whatever --

DR. EVANS: And one could also take one of the other three after the CLIAC recommendations, right?

DR. TUCKSON: One could do that as well. God, I love you all.

DR. FERREIRA-GONZALEZ: Do you have enough monkeys there?

(Laughter.)

DR. TUCKSON: This is a sense of the committee, including the ex officios, because you've all worked hard and you deserve the right to vote. So we're going to ask you with a sense of the committee -- you raise your hand -- Number 1, that we don't do diddly-squat until February after the CLIA folk meet. So how many of you all like that idea?

(Show of hands.)

DR. TUCKSON: So we've got one, two, three, four, five. I love this.

The next one is you're going to send a letter to the Secretary today and say get your smart people together and figure it out, knowing that the CLIA people are meeting in February and yadda, yadda, yadda. Who wants that one?

(No response.)

DR. TUCKSON: All right. That's out.

(Show of hand.)

DR. PAREKH: I'll be the lone hat.

DR. TUCKSON: Good for you, man. The courage of your convictions.

The next one is --

DR. TELFAIR: Letter plus scenario.

DR. TUCKSON: Letter plus scenario. Right. So letter plus scenario. Who's for that?

(Show of hands.)

DR. TUCKSON: Two. Three. One, two, three, four, five. Oh, don't give me a tie.

(Laughter.)

DR. PAREKH: You know, Reed, you really should count my vote also for the letter plus the example because the key here is the letter, and maybe I shouldn't vote because --

DR. TUCKSON: Six to five.

DR. PAREKH: But yes, I would count my vote there.

DR. TUCKSON: So he's with the last one.

DR. TELFAIR: No, the point of voting is, you know, pick one.

PARTICIPANT: You can't vote for more than one.

MS. AU: Mine is wait for CLIAC, but start working on the letter with examples, so you can get it out quickly.

DR. TUCKSON: Okay, this is fine. This is great. We're almost done.

You've got two choices. It's all down to two.

MS. AU: (Inaudible.)

DR. TUCKSON: Which one is that?

MS. AU: Wait for CLIAC --

DR. TUCKSON: Wait for CLIAC --

MS. AU: Wait for CLIAC while working on the letter with examples, so you can get out right away. Hurricane preparedness.

DR. TUCKSON: So here we have a compromise. Are people excited by that? Those that did not vote for wait for CLIAC, would be happy to jump on the bandwagon of wait for CLIAC and start writing the report? That sort of makes everybody happy? Who's upset with that?

DR. McLEAN: I'm just wondering if getting the letter out now might help influence the CLIAC meeting, and that's why I'm wondering if getting the letter out now might be a good thing.

DR. TUCKSON: We've got two hands up, but we've got an interesting point of view here, which is nice. This is simple. We can do this.

So do you send out the letter now, therefore juicing up attention around the CLIAC deal?

DR. PAREKH: My very humble advice, you all have identified clearly a very important issue, and a potential gap. In whatever form you all feel comfortable, get a letter out. Get a letter out. Whatever in addition you do, that's wonderful, but don't lose the momentum and don't wait for the perfect thing. Get a letter out and let work continue.

DR. McLEAN: And is there anything that CLIAC may give us that may materially alter what we want to say? We'll get a curveball? I don't know.

DR. TUCKSON: So we're going to revote. Let me phrase the consensus options. Number 1, get a letter out, get it to the Secretary so they can start working it. In your letter, allude to the fact that CLIAC is going to be meeting in February, among other things that are relevant for the Secretary's staff to review.

Option 2 is wait until CLIAC meets in February and simultaneous to that continue to gather information and fact find and so forth, such that by the time you come back after the February CLIAC thing, you've got some work done.

Now, we're going to now show hands again. Option 1, I want to see what you feel for sending a letter to the Secretary now that tells him there's an area of concern and, among other things in that letter, noting CLIAC's meeting in February.

How many want to do that strategy?

(Show of hands.)

DR. TUCKSON: And we've got one, two, three, four, five, six, seven, eight.

The alternative, how many for wait until CLIAC meets and simultaneously begin to do some fact finding?

(Show of hands.)

DR. TUCKSON: And we've got one, two, three, four, five, six. So it's 8 to 6.

Let me ask the outliers, would you be terribly unhappy with doing it the other way? Are you violently opposed?

MS. BERRY: I would be opposed if we're just going to send a letter that just skates on the issue and really doesn't clearly identify the specific problems. Not only identify the problems, but how are genetic technologies different from all complex tests?

DR. TUCKSON: Got it.

MS. BERRY: And I feel we need to really nail that down, and if we can, then I don't object to sending a letter, but I'm not sure we're there yet.

DR. TUCKSON: Good. Well, how about we'll do this then? Joseph, are you in that ballpark?

DR. TELFAIR: I'm in this ballpark because I think I agree you need to have as clear and as strong evidence and information.

DR. TUCKSON: All right. What I would like is volunteers for the letter-writing effort who would put something together and would work not as a permanent subcommittee, but just as a single issue, non-bureaucratic subcommittee to put something together which we'll circulate to our colleagues with the expectation that we will have sent this letter to the Secretary on or before January 1.

So are there some people who would like to help to try to draft such a letter with the Cindy Berry modification? Who would like to help out on that, other than me?

DR. FERREIRA-GONZALEZ: I can't take the lead, but I can review whatever you write.

DR. TUCKSON: So we've got Andrea with that. Scott is in on that. Cindy's on it. Cindy writes well.

PARTICIPANT: I'll be part of the review.

DR. TUCKSON: You'll be part of the review. We've got Phyllis, and did Ann leave? Ann's gone? I think we might want to consult with Ann. We'll certainly consult with FDA and CMS on that as well. So we've got a committee.

Let me just tell you, first of all, again, Judy, Thomas, Steven, we owe you a debt, especially for putting up with the irritable Reed Tuckson. You are terrific.

Committee, good work. We are in the lobby at 7 o'clock, and feel good about the fact that you guys can reach consensus on such complex issues. The hotel lobby, 7 o'clock.

(Whereupon, at 6:31 p.m., the meeting was recessed, to reconvene at 8:30 a.m. on Tuesday, November 14, 2006.)