SECRETARY'S ADVISORY COMMITTEE ON GENETIC TESTING

FOURTH MEETING

Thursday, February 24, 2000
Polaris Ballroom
International Trade Center
1300 Pennsylvania Avenue, N.W.
Washington, D.C.

IN ATTENDANCE:

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P R O C E E D I N G S (9:05 a.m.)

DR. McCABE: Well, good morning, everyone. Welcome to the fourth meeting of the Secretary's Advisory Committee on Genetic Testing. The public has been notified of this meeting through an announcement in the Federal Register on February 8, 2000, and a posting on the SACGT's web site. We appreciate the public's interest in our work. I am going to take a few minutes to review events since our last meeting as well as our agenda and major goals for this meeting.

Over the course of the next two days, we will have discussions that will allow us to complete the assignment we were give last June by Dr. Satcher, Assistant Secretary for Health and Surgeon General. Dr. Satcher asked us at that time to assess the adequacy of oversight of genetic testing, in consultation with the public, and he provided a framework of five central questions around which we were to organize our analysis. Dr. Satcher further asked that if, based on what we learned from the public and after considering all of the issues, we find that further oversight measures are warranted, we are to recommend options for that oversight.

At our last deliberative meeting in October, we discussed the importance of reaching as broad a spectrum of the American people as we could, including members of diverse communities who may have particular issues regarding genetic testing, and members of the general public who have not yet experienced genetic testing but are likely to face decisions about these tests in the future.

We agreed on five mechanisms for gathering public perspectives: The Federal Register, a targeted mailing to interested individuals and organizations, a web-based consultation, an analysis of scholarly literature on oversight, and a public meeting. We agreed that the public meeting was especially important because it might be our best chance to reach members of the general public, especially members of diverse communities, and to engage the public directly and hear first-hand their hopes and expectations about genetic testing and its oversight.

To provide a framework for receiving the input we developed a document called a "Public Consultation on Oversight of Genetic Tests." The document provided background information about genetic tests including their current limitations, benefits and risks, the provisions for oversight now in place, discussed the five main issues that Dr. Satcher asked us to address, and requested feedback on those issues and a number of related questions. We also developed a summary of the consultation document in English and in Spanish.

We formally launched our 60-day consultation process on December 1, 1999. We have been enormously impressed with the effort that people have made to participate in our public consultation process and believe that the recommendations that we make about the oversight issues will be enriched substantially by the views, opinions, and perspectives of the public that they have shared with us.

A total of almost 400 comments have been submitted in response to the consultation. The comments have been compiled into three volumes, known already as the green books, and they are available at the registration desk if anyone wishes to see them. They will be on permanent file at the SACGT offices as well. The comments have been tabulated and summarized by the staff in the documents that appear in Tab 3 of our briefing books. Staff have also provided a draft analysis of the literature on oversight and a summary of the international efforts in this area. These analyses appear in Tab 5.

We held our public meeting on January 27th in Baltimore. The meeting gave us an opportunity to engage the public directly in the issues and we were enormously gratified by the level of public participation and

the many perspectives we heard on issues of oversight of genetic testing. We also heard an overwhelming affirmation of the importance of better information and enhanced public and provider education in genetics. A summary of that meeting appears at Tab 4 of our briefing book.

The meeting, as you all know, was held at the University of Maryland-Baltimore on January 27, 2000. We were very lucky with the weather because a snow storm had paralyzed the city and closed the institution for the two days prior to that. The meeting was a tremendous success, thanks in large part to our colleague Dr. Joann Boughman, who provided the venue and a great deal of meeting support. We also owe a huge debt of gratitude to the Steering Group that planned the meeting. The group was chaired by Judy Lewis and composed of SACGT members: Pat Barr, Ann Boldt, Joann Boughman, Mary Davidson, Victor Penchaszadeh, Michele Puryear, and Reed Tuckson, and thirteen ad-hoc advisors.

Our ad-hoc advisors contributed enormously to the design and conduct of the meeting, and I want to thank them each again publicly. These are: Maricela Aguilar, Adrienne Asch, Sylvia Au, Thomas Bleecker, Vence Bonham, Mei-Ling Chang, William Freeman, Jane Lin-Fu, Ilana Mittman, Robert Murray, Donna Olsen, Pilar Ossorio, and Gisela Rodriguez. I believe SACGT is in agreement that the January 27th meeting was very effective in gathering public input and we hope to be able to use this form of public consultation again in the future.

We have a very big job ahead of us for today and tomorrow. We are going to spend much of the day considering the public comments that have come in through our various outreach mechanisms. We have organized the discussion around the five major questions that we are tasked with addressing. Our report, as you all know, is due on March 15th as a draft, with then two months for response to that draft. So we are going to try our best to take careful stock of the public input and then begin mid-morning tomorrow to formulate our own answers to the five questions. We are committed to developing recommendations that reflect the broad range of perspectives on the oversight of genetic testing that we have heard.

After lunch we will have a presentation from Dr. Robert Martin of CDC's Division of Laboratory Systems on the outcome of yesterday's meeting at the CDC of the CDC Genetic Consortium-Laboratory Working Group. We have provided time, as we do at each meeting, for public comments.

Our one scheduled commentator at this time is Dr. Penelope Manasco from GlaxoWellcome, Inc. You will recall that Dr. Manasco presented to us in October on the ethical, legal, and social issues of pharmacogenetic research. Her presentation raised a number of important questions that were taken back to Glaxo and thought through very carefully. Dr. Manasco will discuss the ways in which Glaxo has reconsidered these issues. Because the pace of research in pharmacogenetics is intensifying, it is important for SACGT to keep abreast of developments in this area. We have therefore allotted additional time for SACGT to discuss these issues, and we will invite Dr. Manasco to join us for that discussion.

Later this afternoon, we have presentations on some very important developments regarding Federal efforts to prohibit genetic discrimination. One of the principal fears about genetic testing is the risk of socioeconomic harms that could result from the misuse of genetic test results by health insurers and employers. This issue is a high priority for SACGT and it relates in important ways to the issue of oversight of genetic testing.

As you all know, on February 8th the President signed an Executive Order that prohibits every Federal department and agency from using genetic information in any hiring or promotion action. His action was

historic and it will go a long way toward ensuring that health information resulting from genetic tests cannot be used to discriminate against Federal employees. Importantly, the President also urged passage of pending legislation that would extend these protections to private sector employers and to individuals purchasing health insurance.

This afternoon we will have an opportunity to learn more about the implementation of the Executive Order as well as prospects for passage of broader legal protections. I have asked Francis Collins to moderate the discussion in recognition of the critical role he and NHGRI played in advancing this issue forward. Francis will begin by describing the historical background and initial policy efforts in this area. We will then turn to EEOC Commissioner Paul Miller for a discussion of the scope, provisions, and implementation of the President's Executive Order prohibiting genetic discrimination in Federal employment.

Our third presenter, Ms. Cybele Bjorklund, Deputy Staff Director for Health Policy, Senate HELP Committee/Minority Staff, will discuss the status of efforts to pass Federal legislation to extend protections against genetic discrimination to private employment and health insurance sectors.

We will take ten minutes after the three presentations for discussion.

Following the genetic discrimination session, Dr. Michele Puryear from HRSA will brief us on the recommendations of the Task Force on Newborn Screening. The task force was organized by the Health Resources and Services Administration and the American Academy of Pediatrics and supported by CDC, NIH, and other organizations. It met in May 1999 to review many new challenges and opportunities facing State newborn screening programs.

Before we get started, I wanted to take just another moment to express the committee's thanks again to Joann Boughman and the University of Maryland for the immense support that they gave us in holding the January 27th meeting. In addition to providing the venue, Joann assembled a team of key staff from her immediate office, the Office of External Affairs, and the School of Nursing to work on meeting plans and preparation. She also mobilized members of the faculty and student body. The meeting would not have been possible without such support. And we want through this Certificate of Appreciation to show our immense gratitude to Jo and the entire University for their tremendous effort.

Jo.

DR. McCABE: Joann also mobilized the snow clearing crews in Baltimore so we could get there. Thank you very much.

DR. McCABE: With that, and before we get started with the review of public comments on issue one, Sarah Carr needs to review the conflict of interest rules with us.

Sarah, please.

MS. CARR: Thank you. Before each meeting of the committee, you are asked to provide us with information about your personal, professional, and financial interests. This information is used as the basis for assessing real or potential conflicts of interest or even the appearance of such conflicts that could

compromise your ability to be objective in giving us advice. If you are found to have any conflicts, waivers can be granted because the need for your advice outweighs the potential for a conflict of interest created by your interests.

The information you have submitted to us before this meeting was reviewed by authorized staff to assess whether any of your interests might affect your ability to provide objective advice. Ethics counsel waived the potential for conflict of interest and is permitting you to participate in matters of a general nature that might involve your interests. If a particular matter comes up that would affect those interests specifically, you must recuse yourself and leave the room while discussion of the matter takes place. All of your financial disclosure documents are kept confidential and are seen only by properly authorized staff.

If you have any questions about rules of conduct or of conflict of interest, Ms. Brenda Farmer, who is responsible for committee management responsibilities, can address them. You all know Brenda. Okay, that's it.

DR. McCABE: Thank you, Sarah.

With that, we are going to now move forward. We have the next roughly hour and ten minutes or so to review the public comments on Issue 1. Just to remind you, that issue is: What criteria should be used to assess the benefits and risks of genetic tests? We are going to look at a staff profiling of demographics of the responses and summary of comments by Dr. Susanne Haga and Dr. Alan Stockdale.

A critical part of our assignment to assess the adequacy of current oversight of genetic testing was to consult with the public. We will be spending almost half of our meeting carefully reviewing the public input that we have received. We have organized this review around five major questions that frame our assignment. These questions, as you already know, are:

As I said, the first is, What criteria should be used to assess the benefits and risks of genetic tests?

Number two, How can the criteria for assessing the benefits and risks of genetic tests be used to differentiate categories of tests? What are the categories and what kind of mechanism could be used for assigning tests to the different categories?

What process should be used to collect, evaluate, and disseminate data on single tests or groups of tests in each category?

Number four, What are the options for oversight of genetic tests and the advantages and disadvantages of each option?

And number five, What is an appropriate level of oversight for each category of genetic test?

We will want to assess how the public responded to each of these five questions as well as to the subquestions that we identified as related issues. We will want to determine whether and how the public's answers to all the questions affect our individual and collective perspectives.
Staff have done a tremendous job of tabulating and summarizing the public comments for us. Dr. Susanne Haga is a SACGT staff associate, and Dr. Alan Stockdale is with the Education Development Center, the firm that designed and mounted our web site consultation effort.

The summary tables that Susanne and Alan prepared are at Tab 3. As we begin our discussion of the public input on each of these issues, we will first turn to Susanne and Alan for a brief oral sum-up of what the public said about the issue. After we have taken careful stock of the public comments, we will begin, hopefully by mid-morning tomorrow, to formulate our own recommendations on these issues.

So let's get started on Question 1. Alan and Susanne, which of you will be summarizing the demographics and the input on Issue 1?

DR. HAGA: I'll be doing Issue 1. We will both summarize the demographics because, as you can see, the comments came from different sources, whether they sent them into the office or whether they were submitted via the Web site. For comments that were sent into the office either by fax, e-mail, or regular mail, I received 199. That is not counting the ones that you received late, probably an additional ten more.

As you can see, I had a lot of comments from professional organizations and large patient advocacy organizations.

I would classify the public comments if they had no affiliation or did not disclose their degree or work as general public. There were a number of the comments that were from the public who are effected with genetic disorders or who had family members that were effected with a genetic disorder, and a number of academics with advanced degrees.

I also had a number of State health departments, Missouri, Washington, Illinois, Texas, Michigan, and in addition you have New York and Minnesota in front of you as late comments; a number of industries; and some religious groups. That was through the office.

Alan has the Web site sum-up.

DR. STOCKDALE: Yes. There were 171 total comments to the Web site. Significant features of the demographics on the Web site:

There were a large number of women commentators to the Web site; 125 of the commentators to the Web site were women.

There were not a large number of people commenting from diverse communities to the web site and I think that may have been a function of this particular mechanism. Even though there was a lot of attempt to outreach to those communities to respond to the Web site, there was not a lot of actual response through the Web site from those range of communities.

There were a lot of comments from the general public and particularly patient consumer advocacy groups, particularly a lot of comments from parents or individuals with a genetic disease.

Another large block of comments came from people affiliated with hospital/health care institutions or academic health centers. A large number of people who commented had training in some type of genetic specialty or were working in genetics research. A particularly strong response from genetic counselors; 53 people who responded had some type of training in genetic counseling.

So that's really the major features of the Web site responses.

DR. HAGA: Okay. So what we tried to do yesterday when Alan and I got together is to combine the two sets of comments that we individually analyzed to come up with what the top responses were. That was a handout that should have been on each of your desks this morning and that will be up on the overhead as I'm going through them. They are each bulleted under each sub-issue or the main question. Normally, the top bullet will be the number one choice that was the most popular answer unless I say otherwise.

In general, people responding to the overall question of Issue 1, What criteria should be used to assess the benefits and risks of genetic tests, the most popular response was treatment and prevention, followed by them agreeing with the selected criteria or the discussion that was in the public consultation document. The third answer that appeared was it should be done on an individual basis, that each test needs to be analyzed in the context of that individual and that individual's circumstances. That it is just not possible to have just general benefits and risks, that it really depends on the individual.

On Issue 1, so the related questions.

1.1. What are the benefits and risk of having a genetic test? Overwhelmingly, the popular answer was accurate and proper diagnosis of disease, identifying those at risk, early diagnosis. And a very close second would be prevention, medical intervention, increased or decreased surveillance. The third response that was more through the Web site than through the office was that the information would be valuable in making reproductive decisions or life decisions.

The risks associated with having a genetic test? Again overwhelmingly, it was disclosure of genetic information and discrimination. That came through everywhere it seemed. Second was psychosocial implications to the family, to a group, to the individual and stigmatization. And third was misunderstanding and misinterpretation of test results.

1.2. What are the major concerns regarding the different genetic tests that are currently available?

Again, discrimination was overwhelmingly the favorite. It was just a major concern who the information was disclosed to, who had permission to look at that information, and how it was used. Another major concern was the accuracy of the tests. And third again was physician understanding, potential for misinterpretation of test results. Fourth was the cost of the test, insurance coverage. You see that in Alan's comments through the Web site that many were concerned with insurance not covering genetic counseling or the genetic test itself.

I should have mentioned this earlier, we are not specifically addressing Issue 6 but we have tried to integrate the questions that were associated with Issue 6 that the committee came up with into the five major issues. A lot of people overwhelmingly put down patient and public understanding and education as a major concern. They would either put it with Issue 1 or stick it with Issue 6, which was, What other concerns do you have concerning genetic tests? Another one was gene patents that was probably second, at least in my analysis from the group of people that sent in comments to the office. And third was newborn screening, having uniformity for newborn screening. There were more or less complaints that different states had different things. There was a push for tandem mass spectrometry to be used for newborn screening. That was definitely on Alan's and then mine.

1.3. What expectations do individuals have about genetic tests?

High expectations. Many admitted that they were unrealistic expectations that they had of genetic tests. They want tests to be highly accurate and reliable and that test results should be useful in making important health or life decisions.

1.4. In deciding whether to have a genetic test, does it matter whether treatment exists for the condition being tested for? Is the information provided by the test important or useful by itself?

A strong response here. No, it does not matter whether treatment is available or not, the information is important by itself. There's two questions here, it is important and is the information important by itself. Treatment is an important consideration and people would emphasize that, but it was not the only consideration when one would evaluate whether to have a genetic test or not.

1.5. Do concerns about the ability to keep genetic test results confidential influence an individual's decision to have a genetic test?

Overwhelmingly, this was the most popular response on the Web site. Yes, confidentiality does matter. It strongly influences an individual's decision to have a genetic test. Persons with family members or themselves who are effected with disorders were not as concerned about confidentiality for diagnostic tests. There were several strong statements through the Web site statements about families with young children who were potentially affected with a genetic disorder that diagnosis was the most important to them and that would override confidentiality in their situations.

1.6. Are genetic tests different from other medical tests such as blood tests for diabetes or cholesterol? Should genetic test results be treated with more confidentiality than other medical records?

This question was split almost in my responses. Still the favorite was genetic tests are different and should be treated with more confidentiality. The second was all medical tests should be treated with confidentiality across the board. There should be no special considerations given to genetic tests over other tests. All medical information, all medical records should be treated with the highest confidentiality. The third was genetic tests are not different from other medical tests.

There was a significant minority for the latter two responses, that either all medical tests should be treated the same, or that genetic tests are not different than other genetic tests and therefore deserve no special confidentiality treatment. Two-thirds of the responses say they are different, one-third say that they are the same. Of course, comments I am receiving are different than those received by Alan, so I have a lot more professional organizations and people associated with academia and higher degrees than Alan did. So that was probably where a lot of the push came that they are not different or that they should all be treated the same.

Alan, did you have anything else?

DR. STOCKDALE: No.

DR. HAGA: Okay.

DR. McCABE: Thank you very much for that, Susanne and Alan.

First, I am going to begin by asking Wylie and then Barbara to give us your assessments of the public input. Other possible questions for discussion that people should be thinking about before the presentations are: Will this discussion change the three major criteria we discussed in the consultation document? Do we need to modify the weight we have given to the three elements?

So, Wylie?

DR. BURKE: I think the first point I would make in terms of public comment about Issue 1 is how much the word "accuracy" came in and how much emphasis people put on accuracy. There was, as you just heard, some comment about whether expectations may be unrealistic. But it is very clear that as people see value to genetic tests, they see value because genetic tests are accurate and reliable. And it seems to me that this simply underscores our concern about clinical validity.

To some extent, it does pose the question of how accurate is highly accurate. I think that is a tough issue. But there is no question that tremendous weight is being put on accuracy and that people tightly link the benefits to be derived from genetic tests with their accuracy.

The other important points that I would make about the comments are, first of all, the issue of confidentiality. Clearly, confidentiality is an extremely important concern. What I saw in reading through the public comment was a perhaps misunderstanding, perhaps confusion, perhaps uncertainty about the whole issue of confidentiality within medical records. That is, I think a lot of the push that says genetic tests should not be any more confidential than any other medical test comes from a point of view that says we already have fairly strict confidentiality protections, sufficiently strict confidentiality protections and that is how medical records should be, and obviously genetic information within medical records should come under that same umbrella.

But at the same time, there clearly were a few comments that were getting at something that we have seen generally in public comment about genetic tests, and that is the idea that genetic information perhaps should not be seen by the health insurer. That, obviously, goes contrary to how we handle medical information, which is that medical information is potentially known by the health insurer because the health insurer pays for the health care that generates that health information. But I think what is really being said there or what is being expressed is a concern that genetic information should not be used in decisions about health care coverage.

So I think it is very important to separate the issue of, on the one hand, confidentiality such as we assume to be present in medical records generally, and certainly expect to be present in medical records generally which would cover genetic information, and the secondary issue that I think people are getting at when they talk about confidentiality, and that is what would genetic information be used for, and, in particular, would it be used for health insurance decisions.

The two other points are points where there is a difference of opinion within the public comment and I think we just need to acknowledge those. Does it matter whether treatment is available? Some people said no, it does not matter, others said it did matter. As I read the comments, I think there is a clear understanding that genetic information that leads to definite preventive or definite curative treatment has a tremendous value, has a value that probably is greater in the larger sense than genetic information that simply provides people

with information that they can use in life planning.

So I think we have to assume, yes, the availability of treatment influences how we think about a genetic test. Perhaps that influences how we think about it in clinical practice as opposed to whether we would release a test for use. In other words, a test that is highly accurate and one could imagine ways in which it would provide useful information to people might be an appropriate test to release for use but would be used differently in clinical practice than one that leads for treatment.

And the other place where we heard difference of opinion was are genetic tests different from other tests or are they the same. I think this really gets back to that confidentiality issue. As I understand it, it really gets back to what can people use genetic information for, people other than health care providers I should say. What agencies might use genetic information in ways that we don't want them to use it; i.e., how do we prevent discrimination. I think that is the issue that drives some people to say genetic tests are different.

DR. McCABE: I wonder if also part of the confusion might be a confusion between confidentiality and privacy and that that might be something that perhaps the public was not clear on.

Barbara, sorry to put you on the spot. We hadn't warned Barbara we were going to call upon her. But I think one of the reasons why we did that was that you have been very vocal in our previous meetings about the social impact of genetic information and the impact beyond medicine really, and that is why we wanted you to comment.

DR. KOENIG: Yes, I think I'm really not prepared to make any formal comments. I just have one concern perhaps to lay out about how we think about the public comments, which came to me as I was reading the summaries, which is, and this is just putting on my social science hat, that the whole issue of how to deal with the most frequent comments is complicated when you're not -- I mean, this isn't a sample that was organized in any way. So just to keep in mind that we really probably have an obligation to look at the whole range and that it isn't just an issue of frequency. So as I was looking through the summaries, I was a little confused by how to deal with that dimension.

DR. McCABE: Yes, please, Judy?

DR. LEWIS: I would just like to pick up on something that Barbara said. When you talked about the public I thought it was also interesting that at one point you ferreted out students and sort of made them a subset of the public as I was reading through the categorization of the comments when they came in. But it would be real interesting for me to have a sense of whether or not the responses were different whether they came from professionals, or whether they came from people who had personal experience with genetic conditions, or whether they were the general public who were just talking as educated members of the public with sort of what are the overall concerns.

Because I think those are three very different populations and I think we have to pay attention, and maybe this is what you're trying to say, Barbara, but I think we need to pay attention to where the comments are coming from as well as what is being said, because I think that professional communities may have a very different perspective and part of what our goal was was to reach out to those people who are the users as opposed to the providers.

DR. McCABE: Do you, having looked over this very thoroughly yesterday, Susanne or Alan, do you have

any response to that, a feel for that?

DR. STOCKDALE: We didn't really have time. The analysis took a long time to do. We were doing it right up until yesterday. So we didn't really have time to sort of break it down into those kind of categories. It is probably easier for me to do that on the Web site responses because we actually had the opportunity there to collect detailed demographic information and to actually have people click on categories so that we could classify people. I think that would probably be much more difficult for Susanne to do.

DR. HAGA: I have tallies of who say what. And if you specifically want to know the person or the group that said it, I have it. Like for Issue 1, it was primarily the people that are affected with genetic disorders or who had family members with them that came out with prevention and accurate proper diagnosis as their answer. And there were only three professional organizations that had that. That wasn't their question of choice to answer. So there are some differences that I can point out if you ask and can definitely tell you who said them if you want the specific group or person.

DR. McCABE: Okay. Pat?

DR. CHARACHE: I had the same type of question in terms of whether each person or society was equal in the tabulation. In other words, whether a given person would be one hit as would the American College of Medical Genetics be one hit?

DR. HAGA: Yes, they were. I would have wanted to give you percentages. But people picked and chose what they wanted to answer, and someone with a burning desire to say one thing that may have not had any question that we asked would just say it and I tried to put it in the right spot. But as you can see from the numbers, Issue 1 was probably the most popular question answered. Either they just ran out of gas by the time they got to Issue 6 or –. Or that was what they wanted to get across, that genetic tests are important to me for this reason, and that's all they said. So it was difficult to give you percentages and to say that 37 percent of professional organizations wanted this when only 7 of the 25 answered one question and then 21 of 25 would answer another question. But I can tell you who said what if you really want to know.

DR. CHARACHE: Thank you.

DR. McCABE: Ann, and then Muin.

MS. BOLDT: This is a little different line, but when I was looking at these answers, it underscores I think how benefits and risks really got tied into the health care professional and the competence that they have in providing that. And that really is tied in, as you see, in accurate early diagnosis.

That is something that we have to go through, the limitations and the risks and everything. I know we have somewhat tabled that discussion, that we thought we could address that after we come up with a report for the genetic tests. But I think we have to remember that this is really a process and the pre-test and post-test counseling is vital. And I think we do need to discuss ensuring that the health professionals that are involved in ordering these tests are specially trained in genetics.

So I just think it really shows the risk misunderstanding and misinterpretation. And I can talk about many examples of that being done when it is not involved with the genetic counsellor, geneticist, nurse person.

DR. McCABE: Yes, and we'll get into a little bit more discussion of that later because that deals with one of the other questions. But, certainly, education is a major and consistent theme that we kept hearing.

When you are done with your mikes, if you could turn it off. It changes the settings up there apparently.

Yes, Muin?

DR. KHOURY: First, I would like to commend Dr. Haga and Stockdale for the tremendous amount of work that they have done. I have been drowning through the three or four volumes we got last week and they have done a great job.

I would like to caution us a little bit and sort of echo what others have said about a detailed, quantitative evaluation of these responses. The first thing that comes to mind is this is not a representative sample of the U.S. population. So we need to be careful on how we quantitate those responses in terms of frequency, et. cetera, et. cetera. If we want to do that, then a stratified analysis by group, and by age and gender, and education will have to be done and this is probably not the right forum to do it. So my advice is take this as a qualitative way, and maybe you were trying to say the same thing, and a bit more of an in-depth analysis of the range of public input rather than a quantitative way of doing it.

DR. McCABE: Pat?

MS. BARR: I think that raises the question that the committee addressed, which is that we wanted to make some incremental progress. That is that we wanted to reach more people than a simple Federal Register announcement would have reached. And I guess, not having a lot of experience with Federal Register announcements, if Sarah could comment or you could comment about the strength or the number of responses, did we make that progress in this effort?

DR. STOCKDALE: Yes, I think the response rate was actually quite good. Particularly, a number of people who commented, when they got to Question 6 one of the comments they would put down is how exhausting or how awful it had been to go through all 28 questions on the web site submitting answers. When I first mounted the thing in the Web site, a survey person that I work with from my company said, "Oh, you're never going to get a big response rate given how demanding this process is. They're going to have to read a 30-page document and then submit comments to 28 questions that also include various subquestions as well." So I think the fact that we got so many comments, what was it, 300?

DR. HAGA: It was 370.

DR. STOCKDALE: Yes, 370 comments plus additional comments that have come in late, that that was actually an extremely good response rate.

MS. CARR: I think I would just add that if you compare what came in as a result of this request or this public consultation with what came in to the Task Force on Genetic Testing when they sought public comment on their draft principles, Kathy, you might have the exact number, but it was around I'd say between 50 and 75, if I recall. So that is one example. On the other hand, the proposed rule on privacy I think received about 40,000 comments. And I read something about how they weren't really even accepting facsimile or maybe not e-mail, I'm not sure. So they were very precise about what sort of form they would take with those comments. So I'm not sure that tells you.

DR. McCABE: I think the fact that we got so many responses to the different modes suggests that they were complimentary. And certainly the demographics fit with that also, that they were complimentary. I was impressed by the number of students. I think it is a tribute to the staff that the background document has been so useful. A number of individuals have told me that they were going to use it in classes, and it already apparently has been used. And some of our responses came from college students, very thoughtful responses from college students about this. So that one of the things that we're doing is not only getting responses from the public, but I think that we are helping to educate the public. And that is certainly one of the issues that we will be discussing.

Muin, did you have a comment?

DR. KHOURY: I wanted to say that all the students are from the University of Maryland. Just kidding.

DR. McCABE: No. Actually, Father Baumiller, who has been very involved in genetics, had this as a class project. But it wasn't just Father Baumiller, it was a number of other classes.

DR. STOCKDALE: There were quite a few from Simmons College in Boston as well.

DR. McCABE: Yes, Elliott?

MR. HILLBACK: I would kind of like to get back to Wylie's comments on the content. There were some things that were very striking to me when I looked at the tabulations and I am curious why she started off with the accuracy issue. When you look on page 2 at Question 1.1, when people were asked about the risks -- and I got fancy with my different colored markers overnight, I had nothing else to do in the middle of the night in the Marriott in Washington -- if you add up discrimination, psychological implications, confidentiality, family implications, stigmatization, that is 120 out of 158 checks. Those are the things that people comment on as the major risks. The other large one was misunderstanding and misinterpretation results which may be accuracy or it may be back to the education of the physician and the education of the public. And I get down to four comments on test errors or inaccuracy, four on the risk of amniocentesis is what I take that next one, and then issues about lack of treatment or financial burdens.

To me, this was an overwhelming comment. And it surprised me that discrimination, I know it is a big issue, we have spent a lot of time in industry as the rest of the people in this room on that issue, and we are glad the President did what he did, but this was a huge commentary there. And I don't see the accuracy issue on the risks page. And so I wondered why Wylie came to that conclusion.

There are a couple of others that surprised me as well. The strength of the response on the information being important not of itself, I would have expected a more split decision there. And back to the confidentiality again being a huge problem on the Question 1.5.

So I found this very interesting data. I know there are all the cautions about how we can interpret it, but I would like to sort of come back to Wylie's point and see if we can get into what do we think this means. Because I think as we start going forward and trying to draft something, figuring out what this means, what people are saying to us, we may agree with it all, we may not, but I would like to get into that.

DR. BURKE: Just to respond, I think we are talking about two parallel streams; that is, what are the benefits

of genetic tests, what are the risks of genetic tests. My reading, I didn't do the tabulations, I didn't have different colored markers, but my sense is that even when the word "accuracy" was not used it was implicit. That is that when people talked about the benefits of genetic testing it was finding out information that they could use for treatment or for planning their life, and implicit, and in a number of occasions explicit, was saying that that information had to be reliable or had to be accurate, had to provide a diagnosis, had to provide information.

I think that really is a starting point, that is sort of a major starting point that these tests have to be reliable. People can't use them really unless they are reliable is what I take from a lot of that. And I am undoubtedly putting some interpretation of my own in that, but that is how I read people's descriptions of what the benefits of tests are.

So I think this whole other, I agree, very overwhelming commentary about concerns with discrimination is there as well. I think we have been hearing that for a long time. People are tremendously concerned about stigmatization and discrimination on the basis of genetic information. As I mentioned, I think that feeds some of this concern about special confidentiality.

And to some extent, the misunderstanding issue I think is very complicated. Misunderstanding could occur because genetic tests aren't as accurate as we would like them to be, and clearly that happens. Misunderstanding can occur because physicians explaining the results to patients don't understand the tests, and that clearly happens. And then there is a different kind of problem that you could call misunderstanding which might have to do with an insurer, let's say, or an employer believing that the test has more predictive value than it has. In some cases, as in the Sickle Cell trait issues, that certainly gets to the point of absolute out and out wrong discrimination. But in other cases, there may be a sort of giving more weight to a predictive test than it should.

So I think that whole area of the risks of genetic tests is complicated. But I agree, I think we heard people saying we are really concerned about this, this is an important issue to address.

DR. McCABE: I am going to make a comment there also. I have had a couple of calls from individuals who would not send anything in to us because they were concerned about confidentiality. Specifically, I asked if perhaps the relative who had had a problem would e-mail me, and they wouldn't do that even because they didn't want anywhere for there to be a record. So I think this confidentiality and discrimination, we certainly heard it in Baltimore at that meeting, we have heard it individually, we know it is a major issue in the press. But I was struck by the people who would not respond other than by voice to me because they didn't want any record of their identity. And there's a problem, and serious problems, with breech of confidentiality with information being given out inappropriately to other family members and those sorts of things. Very serious problems.

Jo, then Judy. I'm sorry, Elliott, you wanted to respond to that.

MR. HILLBACK: Could I just respond for one second. I think one of the reasons I asked the question, and now I think I understand a little bit better where you're going, we have used various terms here. Accuracy has been a term we have used as in clinical accuracy, meaning in the lab performance, and I guess I assumed that is where you were going. What I read out of this is people want information that is useable and that they want to know that there is some way to use it that makes sense. And I think we need to be very careful with terms, because we've used analytic validity, clinical validity, utility, now we have accuracy. What is

accurate? We're going to get into that later I'm sure.

So I think what people do want is something they know they can use and that it is useful information. And that is the strong message. If that is what you were saying, then I totally agree with you. And they don't want it to be used by anybody else against them. I mean, those are the two fundamental messages I thought we got.

DR. TUCKSON: Can I just ask, about how many calls did you get? More than two?

DR. McCABE: No.

DR. TUCKSON: About two?

DR. McCABE: Yes.

DR. TUCKSON: Thanks.

DR. McCABE: No, it wasn't a lot. But I wonder, if those people made the effort to get through to me, I wonder how many others are out there. And I can tell you this is also an issue, Paul Miller will talk about this, the Commissioner for the EEOC, they are interested now in looking at some of these discrimination cases and actually bringing them forward and they are having a hard time getting that to happen because people are unwilling to come forward because of concern about additional repercussions. So that I think that while again it is one of those issues I don't know that we can do it by the tally as much as to tell us that this is just the bare tip of a much larger problem.

Yes, I have Jo, Judy, and Ann. Okay.

DR. BOUGHMAN: I'm going to grab the floor for just a moment and actually make two or three comments. First of all, I was really impressed by the depth and breadth of the comments. And when we think about them, I would hate to count the number of years sitting around this table of lives spent thinking about these issues over time. And so I saw many of these comments as a reality check, if you will, from people who have not spent days or years of their lives thinking about these issues and trying to keep our feet on the ground as we go through this.

And I think Elliott brings out a good point in how we are going to interpret some of these. I didn't go through it issue by issue, and I will probably come back to this a couple of times, but with regard to Issue 1, when we put the accuracy as a benefit and then the discrimination on the risk side, which is the way it tallies, we also have to remember then in other responses there was clearly the assumption of accuracy before individuals went forward. So given that then what are the risks, they would remove it from a possible option in their multiple choice.

On the accuracy, I also thought that it was interesting and valuable to me that more than one person, and I've actually highlighted a couple of ways that individuals worded it, that the accuracy was really important in genetic tests because of the nature of the results that would not change over time versus many of the other clinical tests that, in fact, you wanted to change over time, for example, cholesterol, and that that was actually noted and understood by some of the individuals, which I thought was interesting.

Secondly, in the confidentiality issue, I think that that related to the discrimination is going to be more of a difficult kind of thing to tease apart because we're talking discrimination in insurance, in employment, and then at another level, that I was also slightly surprised about reading here, in the concept of why genetic tests might be different.

In the responses from individuals who have had genetic testing, have family members or they themselves have a genetic disorder, in fact they were able to articulate the weight of that information that they had and their own personal obligation and challenge to share it with other individuals in the family. They felt that that result was different for some reason, which comes back to the issue of counseling and information versus a doctor talking about a high cholesterol level and the implications that might have for all your family members as well. It may be that genetic information is more inextricably linked.

Then in both the discrimination and why genetic tests might be different, I was also impressed with people understanding the concept of the stigmatization as it relates to larger groups. This did not come out only from a few or one or two kinds of groups that we tend to lump together and talk about screening that population. It was, in fact, the weight once again of some genetic information that individual members of the public out there understand that now they know something that might have slightly broader implications and comes back to this results of mine personally now makes me or now informs my recognition not only of what gene I have or genes I have, but in fact what groups I might be a member of that I had not identified with before. The words weren't put quite that way but in fact it came out in three or four comments.

And those kinds of contextual comments I think helped me believe that the structure that we had given and the complexity and the inextricable nature of the questions we haven't gone overboard on because in fact that is the way the public thought is going as well. And so, in fact, that reality check I think is really an important one for us.

DR. McCABE: Judy, Ann, and then Mary.

DR. LEWIS: One of the things I wanted to comment on earlier when Elliott went through and commented on how frequently we heard some of the same responses, I want to caution us again not to pay attention to the frequency because, one of the things that struck me a couple of times, to look at this you would think that hereditary hemochromatosis was the most common genetic illness in the world because that group really mobilized well in terms of responding. And so I think we need to pay attention to where the comments are coming from, but also not just to pay attention to raw numbers because some groups were really politically active, or whatever the right word is, in terms of being able to get a lot of responses. Other groups we heard from once or twice but I don't think that that necessarily means that the concerns of those people are any less valid.

So I want to help us focus on, as Barbara said earlier, the range of responses and not necessarily if everybody said something it must be right. Because we also have to pay attention to the people we heard in the public meeting whose comments you didn't summarize because they came in through a different medium and we all heard them, to the literature review pieces that we read, and to all the other places that we're getting information, as well as the people who for one reason or another chose not to respond or weren't aware of the opportunity to respond. So I think that is an important piece.

And the other issue that came out for me that we didn't really talk about, I know it will come out in other issues, was people really needing to have fully informed consent as to what this meant. If the information

you're getting on the input side in terms of counseling or informed consent is faulty, then your sense of what is accurate and what isn't accurate is skewed by that. So I think the whole idea of giving people information so that they can even decide what the risks and benefits are is a piece that we have to pay attention to as well.

DR. McCABE: Ann?

MS. BOLDT: I guess in terms of Elliott's question, too, I was thinking that the current system right now, individuals that are having genetic tests are having them through a genetic counsellor, a genetic specialist. So that, to me, is really indicative to some degree though that that's why the benefits are what they are, is because they have had the genetic counsellor or geneticist go through and actually talk about the "what ifs," the limitations, the accuracy. And that is why we have the risks being more broader in terms of discrimination and confidentiality. So I think that is because the current system is that there is genetic individuals and specialists involved in that.

DR. McCABE: And yet, one of the things I was struck by were the number of examples where they weren't and some of the problems that that led to. I can tell you in the couple of comments I alluded to before that was a problem in terms of information.

MS. BOLDT: But then I think that ties back to the misunderstanding and misinterpretation.

DR. McCABE: Right. Right.

MS. BOLDT: Exactly.

DR. McCABE: Mary?

MS. DAVIDSON: Yes. I just wanted to throw in another piece of qualitative information and mention that the concerns that were voiced consistently about the safety and discrimination and privacy issues is certainly consistent with our experience on the Help Line, just to pick up on that. And your comments, for example, we have people who will call and certainly not give us their name and will choose not to use any e-mail Help Line access for that same reason. So I think that is really something to take really very seriously.

The other piece is I wanted to echo some other comments about the importance of public and provider understanding and how that links to both the utility as well as the safety of the information for users. This ties in also with informed consent because informed consent really works at providing the patient and family has the context, the vocabulary, some understanding of that process. And so I thought that was a very useful comment that came up, not only with Issue 1 but in a number of different places, was the importance of education in the broad sense.

DR. McCABE: Yes, Reed?

DR. TUCKSON: Let Pat go first.

MS. BARR: I'm actually responding to the frequency of the hemochromatosis group, because I think there was another reason, not just that they could mobilize but why could they mobilize. And I think they could mobilize because there is a test, it is accurate, there is an intervention, and if you don't get the intervention

you get very sick.

And so what they were really commenting on is the other end of the spectrum; which is, when we know it works why can't we get it to move out there, and what can we do in our thinking

about this to get things that work out. So I read it differently than just that they were well-mobilized. They were able to be well-mobilized because of the circumstance.

DR. McCABE: And I think they were also motivated by some of the discussions of diagnostic odysseys that they had been through, the misdiagnosis. And their feeling, to reiterate what you've said, is that if this genetic test was more available, it could have saved me years and a lot of frustration and I could have gotten therapy sooner.

Yes, Wylie?

DR. BURKE: I apologize. I know there is a line of people that want to talk. But I just want to comment quickly that I found that aspect of the hemochromatosis commentary also a little bit frustrating. There definitely was some misinformation or misunderstanding of the role of a DNA-based test versus a readily available measure of serum iron status which has been around for a long time. I think, just to get back to points that have been made about education, the ample documentation we now have of long delays before diagnosis in hemochromatosis I think can be attributed to a lack of considering the diagnosis on the part of physicians, people going to doctors for three to five years, going to an average of two to three doctors before they get the diagnosis, not that the diagnostic strategies haven't been readily available.

The result of that is that I think they mobilized. And I think their comments were actually very reasonable. But to some extent they were concerned about things that they didn't need to be concerned about.

DR. McCABE: I have Reed, Michele, and Barbara.

DR. TUCKSON: I think I just was trying to get to more of a summary understanding. I think, something that Joann said earlier that the people around this table have spent a lot of time thinking about these issues, we had a sense when we formulated these questions of what it was that we thought really was important to focus on for this section. The comments we got back from the public have pretty well solidified that I think.

I think when it all boiled down at the end of the day, it says that the concerns that we were concerned about are concerns of the public. I think we do have to be careful about the statistical representation, whether it is the hemochromatosis community or not, or organized professional associations mobilizing people in mail-writing campaigns. At the end of the day, I think the way we categorize in our report that this was not a scientifically statistically significant sample but what it was was a vigorous process through a variety of mechanisms that now tell us that we can speak fairly authoritatively that the American people are concerned about these kinds of issues and we think they have credibility because we're concerned about them.

And so I think as this gets to the summary point --

DR. HUDSON: Or the other way around.

DR. TUCKSON: Or the other way around. Yes, depending on your gold standard. But I think the point is

that I think that we've gotten to a good place and I think we can worry more later about the actual language of how we report it. But I feel at least comfortable that these are legitimate and it has been validated and that we can feel good about moving to the next step.

DR. McCABE: Michele?

DR. LLOYD-PURYEAR: Hi. I have a question for Susanne. What were the demographics in terms of ethnicity for the public comments? I know for the Web site. Do you have that?

DR. HAGA: I don't, unless they came out and actually said it in the comment that they sent in. But Alan has more if they checked off that box.

DR. LLOYD-PURYEAR: Yes, I see that. Because I know we worked very hard to achieve broad public input, but the demographics on the Web site show no people of color, a few, essentially none. The majority of comments were received from actually white women. So if that is also reflective of the meeting in Baltimore, we have a long way to go to actually getting broad engagement of the public.

DR. McCABE: Reed?

DR. TUCKSON: So I think one of the things that is going to be key I guess would be as we report this or write this in the final report that we would combine the Baltimore session, which did have a heavy input from people of color, and also the Advisory Council and Committee people and that process in with this so it is all of a whole. We have several pieces that lead to the conclusion from the public in this area.

DR. McCABE: Barbara?

DR. KOENIG: Now that I've had a few minutes to get on East Coast time, I have maybe a few more sensible things to say. We haven't had a chance really to talk as a group about what our responses were to the Baltimore meeting. I just wanted to make one point that the thing that really came to me and which was confirmed in the material that I read was the importance of genetic tests as a way of reducing diagnostic uncertainty and resolving. It was just the way in which those interesting stories of people who had these long periods of dealing with this incredible level of uncertainty. And I hadn't really I think appreciated that. So in that way, it was a very useful.

The other thing that I read some of the public comments for, I have a couple of things I want to say. One is we had the presentation on the whole question of genetic exceptionalism and how should we think about the issue of are genetic tests different. And it seems to me that the one thing that the comments do say qualitatively is that, perhaps it is just the fact that we asked the questions in a certain way, and that in a way this whole committee is an example of genetic exceptionalism, but nonetheless, the comments that we get really do seem to suggest that people do experience this particular domain of medical testing as different, as somehow different than others.

So I think that perhaps argues in some way against the more philosophic arguments that we had that in a purest sense perhaps you shouldn't think of these as different.

I also wanted to comment on this issue of information being valuable in itself and that being something that came out so strongly in the public comments. I think it is related to the relief of uncertainty, to some extent

it is related to the accuracy and reliability. But just as a reminder, I think that if you ask someone, and this is an issue in terms of interviewing, almost anyone will say in an American context, this isn't true across the world, is just knowing something will it make it better, is it good, it is such a fundamental cultural good in the United States and our culture that people will say yes. So I think that is basically what people are responding to.

But then what any genetic counsellor will tell you is that then that kind of a knowledge is good kind of belief, not for everyone but for a large percentage of people, in the context of really having a very specific knowledge about a particular test will change, and change substantially. So just to keep that in mind that the whole issue of how you think about what information is good in and of itself.

And then the last thing I wanted to say is that the one thing that doesn't come out, and it is perhaps because we didn't ask it, is there wasn't much about the issue of the value of not knowing, which is the other side of this. In a way, I sort of wish we would have made it more possible.

I think one of the reasons the discrimination comes out so quickly and so easily in people's comments about this is because it's a category that is readily accessible to people in terms of understanding their relationship with government, and with other people, and with health insurance. Everyone has an experience of having been denied something that they want. So is that really the most important concern or is that just sort of an easily accessible way of sort of putting a whole bunch of concerns in one category.

DR. McCABE: Kate, and then Reed.

MS. BEARDSLEY: Yes, I wanted to just pick up on one thing that we're seeing here. I agree with Reed that basically what we're seeing here is a lot like what we saw in our document. But one thing that is here that I don't think we see in our document is the comment about the cost of tests and insurance coverage. I wanted to pick up on that because I think we also very much heard a lot about access at the public hearing.

Those two issues seem to me to be the same issue and really important. It may be that that's an issue that is way broader than we can deal with in this committee. But it is certainly something that we need to reflect I think our very real concern for.

DR. McCABE: Reed?

DR. TUCKSON: That's actually I think a very important point that just got made. I just wonder before we do come to that sort of summary of this session that is there anything else that sticks out like access that was not in our report that the public did say. I can't think of anything off-hand. But I just think that's a good way to look at it is is there any one big thing that we got back in these responses that we did not have as a list. And so, i.e., what new thing do we need to say in our report is that, you know, gosh, we were forced to pay attention to this issue.

The other thing I am just troubled, I don't think I am satisfied with an earlier comment I made regarding the issue of minority participation on the e-mail surveys. I was sort of thinking well let's make sure we use the session from the Baltimore session. But I'm worried that that may not have given us enough specificity as I think back on that session to answer these kinds of questions and give that kind of input to it.

I wonder, Judy, whether or not we should ask, if it is appropriate to ask the Minority Advisory Committee

to either respond to the survey in the same way that others did, if they have not, specifically asking them to do that, or have representatives of their constituencies to do that so we are on record with written comments from that area.

DR. McCABE: We'll take Judy, and then Ann.

DR. LEWIS: One of the things that I think we might want to look at that would be helpful is several members of the Steering Committee actually offered e-mail responses of their perception of the meeting. I don't know if we included those comments.

DR. McCABE: Yes, they are included in the materials that we have.

DR. LEWIS: Okay, because I think that is maybe what you're looking for, Reed. But several people who are on the Steering Committee took their best attempt I believe already at looking at some of this stuff and giving us a response to what they thought were the key issues. And maybe that is what you're looking for.

DR. TUCKSON: Yes. And let me just be even more transparent. Again, my experience on these sorts of committees does remind me that there will be folk who will pour through the database upon which we use to make our conclusions. There will be people who will look to see the evidentiary file and they will ask the very question you asked about that sort of participation. So I just think I'm looking for a place to have it gathered that is inseparable from the e-mail process, because that is where people are going to really focus. So I just want all of a whole so tight and identifiable.

DR. LLOYD-PURYEAR: I have a suggestion, and that is to, if we can, engage the Secretary's Committee on Minority Health to take a look at what we're putting forward and to make some comments.

DR. McCABE: At this point in time, I would remind everyone we will have a document March 15th but that will be a draft document with some time to respond. So that would be the mechanism that I think we ought to engage the Steering Committee as well as other individuals. Certainly, I'm sure that we have a way of trying to get back to the people who have already responded so that we can let them know about this.

I haven't forgotten you, Ann.

Yes?

DR. KOENIG: Just a bit of follow up about this issue of the demographics. I think it just needs to be stated very clearly that the Web site consultation is the only place where we collected the demographics and it is totally skewed by the fact that 53 out of 175 were genetic counselor and all it does is reflect the demographics of the genetic counseling profession. If we just say that in the analysis, that's really what is driving those demographics.

DR. STOCKDALE: A lot of parents commented, particularly mothers. Like the hemochromatosis group that sent in, there were a lot of people, mothers who wanted newborn screening. I had a big group of those who were organized around an e-mail list together. So there were about 18 mothers that basically said the same thing, tandem mass spectrometry. So there was that kind of skewing.

DR. McCABE: Ann, and then Pat, and then Victor.

MS. BOLDT: Just really addressing Reed's question if there are any other areas we should talk about. And really building on Kate, there's not only the issue of cost of medical tests, but reimbursability of genetic education and counseling.

DR. McCABE: Yes, Pat?

MS. BARR: And I'm also responding to a general issue that I saw, and that is that those who communicated to us in the morning session were dealing with what we have come to think of as the most straightforward of genetic concerns and they had such a broad experience of discomfort, unhappiness, poor treatment. We need to talk about, as this gets far more complex, the emphasis on trying to provide good information to providers. It is the education, but I was just struck by how complex the situation is when you've got a gene that is definitive versus the situations where they are not going to be definitive.

DR. McCABE: Victor?

DR. PENCHASZADEH: Yes, that was actually one of the points I wanted to make, and that is that most of the comments and many of the issues that were raised in the Baltimore conference were dealing essentially with Mendelian conditions. And when people talk about accuracy and they talk about the value of information by itself and so on, they usually think of confirming a diagnosis to knowing for sure that you have a condition or something like that. That is certainly not the case and will not be the case for many years for most of the complex diseases that we are starting to grapple with.

And the other issue is the issue of access. I completely agree that this is probably one of the major lessons -- I think we kind of knew the issue of access was a significant one. At some point, we will have to deal with the question of insurance coverage for genetic testing. And I want to also echo all the comments that were made talking about the whole process. It is not a test, it is the whole process of health care delivery that has a genetic test in the middle.

I can't help to always remind myself when people say the health insurance industry pays for health care, that's not true. We pay for it. The American people, the citizenship pays for health care. And probably the way something is covered versus not covered should not only be determined by the health insurance industry. So that's another thing.

But I just want to add all the cautionary things that have been stated already to the quantification of the responses. I think the responses gives us a range. We have an idea of what are the thoughts and what are the concerns in the field. But certainly we cannot pay much attention to quantification because of all the facts that have been already said.

DR. McCABE: I want to just reemphasize the issue about access and remind everyone that the Surgeon General spoke to this in Baltimore. It is one of his major concerns is differences in health outcome and the contribution of access to that. So that I think this also fits well with the feelings of the individual to whom we report directly. I think it is important that that has come out here and was also discussed by many of the people in Baltimore.

I have heard from many of you around the table but I haven't heard from everyone. I just wonder if anyone who I haven't heard from has anything to say, because we are going to take a break in a few minutes.

Pat?

DR. CHARACHE: I'll just expand briefly on that access issue. I hope as we address it we will look at the full range of access factors, and cost would be one. One of the speakers at our first session pointed out also the importance of the development of tests that pertain to specific patient populations, the reimbursement schedules by HCFA where you can't do predictive testing. And there is a whole wide range of access issues in addition to the cost of the test.

DR. McCABE: Any other comments before we take our break?

(No response.)

DR. McCABE: I think this has been a useful discussion. I think that we will see some of the themes that we've discussed under Question 1 resurfacing fairly consistently throughout our discussions.

Okay. Let's take a 15-minute break. So we will resume at 10:40 a.m., back in this room.

(Recess.)

DR. McCABE: I just want to remind the Advisory Committee that we looked at factors that we would consider under Question 1. Those are in our original document, the background document to the public comment. These were clinical validity, clinical utility, and social implications. I just want to remind you of those three. And tomorrow as we're discussing where we're going to go and how we're going to craft the final report, one of the things I want you thinking about is whether you feel that those criteria really capture the feelings from our public consultation. So please be thinking about that as we prepare for tomorrow.

We're going to look at Issue 2. Let me just remind you: How can the criteria for assessing benefits and risks of genetic tests be used to differentiate categories of tests? What are the categories and what kind of mechanisms could be used to assign -- note that there is a typo here -- could be used to assign tests to the different categories?

And we're going to start off again with the staff summary of the comments. So how are you going to organize this? Alan, are you going to go first?

DR. STOCKDALE: Yes. Well, to the question that you've just read, general responses were that categorization should focus on the type of test. This was primarily from responses on the Web site. The answers to this were quite complex. People would say focus on predisposition or presymptomatic versus other types of tests, or prenatal versus other types of tests. But a lot of responses were focused on the particular type of test.

Another frequent response was focusing on the availability of treatment or prevention measures as a consideration.

There were also comments about taking care on estimating risks or getting into some type of risk assessment because risk assessment was subjective or that it was highly contextual. There were several commentators noted that the committee should be careful making broad judgments about risks for those reasons.

There were comments also about the high risk/low categorization being rather crude and not very useful both in the Web site comments and the comments that were mailed as well as the Baltimore meeting breakout sessions. You can see the summary of the breakout sessions under Tab 4 if you go to page 27 and 28.

For Question 2.1. Do some genetic tests raise more ethical, medical, and social concerns than others and should they be in a special category and require some special oversight? If so, what tests or type of tests would fall in such a category?

The common response was predisposition, predictive, or on presymptomatic tests raised a lot of concerns. A number of people also raised the issue of prenatal tests. There were comments from a couple of people who were associated with Little People of America and another one that comes to mind was a woman who had albinoism who were concerned about the uses of prenatal testing to select against certain conditions. There were a number of other people who also raised disability issues and issues of diversity in regard to the use of prenatal tests.

For Issue 2.2. Are there some genetic tests that raise no special coverage and therefore need no special coverage? If so, what tests or types of tests would fall into this category?

Diagnostic tests was listed by a lot of people, also tests for treatable conditions. But there was also a significant minority of people that said that all tests should have some sort of oversight.

DR. PENCHASZADEH: Is "coverage" the right word, or "concern"?

MS. CARR: I think it means oversight.
DR. McCABE: Yes. I think it was coverage by oversight. It is the term that we have. I think it means different than the vernacular coverage in medical jargon. But it is really coverage by oversight I think is what the term means there.

Susanne?

DR. HAGA: I would like to point out on my analysis several groups had some very detailed ideas of how to categorize tests. On page 5 in Tab 3 of just the analysis of comments received through the office, Emory University, comment number 40; UCSF, comment number 64, categorizing tests by risk or complexity of the test. Ohio State had a very elaborate comment, comment number 70, on how tests should be categorized by the weight of practical clinical test application rather than on high or low risk. And some organizations also had ideas of how to categorize. The American Society for Clinical Laboratory Science, the American Association of Bioanalysts, and the American Academy of Pediatrics, their ideas were have a high, moderate, and low risk category. So that was the first.

The second was classify according to treatment options. And the AAP said again by the type of test, diagnostic, presymptomatic, predisposition, or carrier testing.

DR. McCABE: Susanne was just looking at the landscaped pages and that is where the comments are numbered.

DR. HAGA: I'm sorry. Also in the upper right-hand corner of Volumes 1 and II of the green books there is a number. That is the comment number when I received them in that order. The bottom right-hand corner is just the page number. So you can refer to that also.

DR. McCABE: Anything else, Alan or Susanne, before we move on?

(No response.)

DR. McCABE: Okay. So then let's discuss this Issue 2 and what our thoughts are on this, again keeping in mind whether we feel that the bulk of evidence suggests, and, again, bulk not necessarily being quantitative but also just the types of responses, but whether we feel that categorization is feasible.

And as we start this, Wylie, do you want to comment?

DR. BURKE: I just have a couple of comments. The first is that I think the public comment on this issue was useful in elaborating more different kinds of categories of tests than we had really outlined in our report. I think that is useful to capture.

I also thought that the comments that made a distinction between diagnostic tests well-accepted and already within the standard of practice are different from tests sort of coming down the pike, and particularly if those tests are predictive. So I thought those were useful sort of elaborations that I think were consistent with our basic approach but provided more detail.

My main other comment is that we are clearly getting into an area in the comments on these questions that I think we are going to have to think a lot about when we get to how we approach oversight, and that is the question of how tests are used versus whether or not a test should be available. That is, I think the simple regulatory question is a test ready for commercial use basically, is it ready to be disseminated into clinical practice. But what these answers are telling us is that when you think about oversight it becomes very salient to think about how the test is going to be used.

That really has implications for what kind of oversight should be there in terms of using tests under certain circumstances and not under other circumstances, or using a test only when appropriate, therefore well-defined, pre-test and post-test counseling is available. So to me, the comments here raised that as a major question that I think we will have to address later. And that is, what kind of oversight should we be proposing that has to do with how tests are used.

DR. McCABE: Other comments then from the committee? Yes, Ann?

MS. BOLDT: I guess I just would add one more category of preimplantation. There were a few comments that weren't added on our list, and so I don't see it here either. So maybe just to put that on too.

DR. McCABE: Yes, Judy? And then Jo.

DR. LEWIS: One of the comments that I heard at our Baltimore meeting was from a gentleman who was talking about the difference between germ-line and genetic tests that are genetic in nature that might be used for disease progression and monitoring disease. And I think that this comes back to the point that Wylie was making in terms of the intended and off-label uses or other uses that tests get put to.

If a test gets approved, it may be approved for one particular use, but once it is available for use it may be used for other uses and it may also provide information other than the primary information that's sought. So I think those are the pieces we need to pay attention to, is whether the test is being used for a particular purpose versus whether a test is available and then we dream up all sorts of wonderfully creative other things to do with its use and with the other information we get secondary to the primary use.

DR. McCABE: Jo?

DR. BOUGHMAN: In my context of reality check, I think one of the important points that was made in a variety of ways was the reminding us about the speed with which things are changing and whatever structure we might give to the categorization, that unless there is some underlying reasoning that will remain stable even in the face of rapidly acquired knowledge about a variety of things, that it would turn out not to be a terribly useful categorization. And that gave me pause to go back and reread the way we in fact had written our first document. I would urge us to think about that. I thought that was a useful contextual comment made by several people.

MR. HILLBACK: Can I just ask for a clarification of what you meant. I am sorry to jump in. But are you just saying that categories might be stifling? Is that really what you're saying?

DR. BOUGHMAN: No, it was actually the opposite. That it is not going to be useful to in fact have a set of categories where one test might be used one way in the year 2000 and then when we gain a great deal more information it would flip-flop in categories, that we would be so busy recategorizing tests that it wouldn't be useful.

DR. McCABE: So you're saying that the categorization should be on the use of the test not necessarily on the test per se.

DR. BOUGHMAN: Well, that was the approach, and I was really making the comment trying to pull out my impressions from several different kinds of comments. I think several people did come at it that way, as Wylie pointed out, but there were others in the aspect of whether in fact you may be thinking that predictive versus symptomatic really is the use of the test. I guess that's where I am right now. We have to be very careful about how we use the words and what the meaning of our categorization really is, whether we are talking about the use of the test, the use by one person and not another person, off-label/on-label, however we are doing that, but to keep in mind that that structure needs some stability.

DR. McCABE: Just to follow up on that. I think it brings an important point. And one of the things that we have begun to discuss at UCLA having to do with IRB and the fact that our IRB is

very good at reviewing projects at the very front of the project, but we're beginning to develop mechanisms now for more thorough review of amendments. I know this has nothing to do with what we're talking about here but I think it says something about us almost culturally. And that is that we are very good at gate-keeping but we aren't very good at monitoring the process. And whatever we come up with I think we have to recognize the dynamic nature of the field and that the process has to monitor that dynamism as we move forward.

So do you think that is capturing it somewhat?

DR. BOUGHMAN: Yes, yes.

DR. McCABE: Okay, Victor?

DR. PENCHASZADEH: On the same line, I think that it is true that we should not pay so much attention to the technology of a particular test but, again, to the process by which and for what it is used and essentially the different type of uses that particular test may have. In that regard, I found many of the responses very useful besides to help us realize that for many tests that are used for confirmatory purposes for a specific diagnosis, they are really becoming standard of practice and probably those are the tests in which one might say that there is not much difference between the genetic test and the test not based on DNA testing. I suppose the best way to categorize testing, in my view, would be the type of use that test will have.

DR. McCABE: Pat?

DR. CHARACHE: I would second that, particularly that categorization probably should be independent of technologies because they change overnight. But I think it also emphasizes the complexity because what is diagnostic for hemochromatosis in one patient is predictive for the family.

DR. McCABE: I want to come back to your point though that should be independent of the technology, and I understand completely your point there. But I would also urge us or the process that we may decide upon to look at the technology and what an optimal technology is.

And I come back to newborn screening, where I've spent my entire career, and there are many states that are still using the Guthrie test which is very inexpensive, not very quantitative. One can argue forever about how that really compares with some of the newer tests. But I think that if a technology does surface as being a much better technology than a traditional technology, I would hope that then there could be recommendations for the technology per se as a better functioning approach to the use of that test information or developing the test information.

Pat?

DR. CHARACHE: I'd like to amend my statement about technology. There obviously has to be a balance between the cost of the procedure and what's going to be used for screening versus definitive diagnostics. But I do agree there should be something in the document that emphasizes that the technology must be appropriate to its use.

DR. McCABE: Other thoughts? Yes, Mary, and then Jo.

MS. DAVIDSON: Yes, I'm kind of giving a collective answer based on just a dialogue that we've had within our group with our member organizations, but also last night I read through in particular the various consumer responses all they way from affected individuals to consumer advocacy organizations. I think, in particular, and this relates to Issue 2 but to some of the others as well, there was real concern about the balance between quality and oversight and access. I think it really relates to this issue about categorization of tests.

This is kind of a different take on the hemochromatosis group, and what I've heard from them and different places is just a real panic that there may develop a gate-keeping that is well-intended but that really could impact the ability of people to have access to tests. So I go back and listening to this discussion, thinking about categorizing tests in terms of how they are used rather than the state of the technology right now I think makes good sense.

DR. McCABE: I think we've discussed from the outset the balance of the information and the importance of that information with ensuring the accuracy of that information, whether it be analytic validity or clinical utility. I was also struck by those comments from the Hemochromatosis Foundation but was hoping that that would not be the role of this group or any process that we came forth with.

I think that the goal would be not to have information misused. If tests are determined to be valid both in the laboratory and in the clinical sector, I would hope that by adding some credibility to that utility or validity that that would in fact help with the dissemination of the tests. So I would hope that that would be one of the things that we could very strongly support in the document, that we need to ensure the accuracy of the information, but once that information was determined to be accurate, that there would be some encouragement of dissemination with access across the board to the public in that.

Is there something relevant to that comment?

Yes, please?

DR. BURKE: I just wanted to sort of follow up and say I think it might be very useful for us to keep that hemochromatosis example before us, particularly as we get to Issues 3 and 4. I am not sure I could imagine any way that we could do anything that would really be in keeping with the concerns that were expressed. But at the same time, it is very possible that we might as a result of what we do push for more pre- and post-test counseling for hemochromatosis genetic testing than is currently occurring.

So I think because treatment is available, and because the concern that the diagnostics be available is a very valid concern, this may be a useful touchstone for us to keep coming back to as we consider regulatory possibilities.

DR. McCABE: I think the hemochromatosis is a nice example, because it also says that the gene test per se may not be the definitive test, that there may have to be multiple tiers. And this is where we would have to work with the professional community as well as the public to understand the appropriate use of the mutation analysis together with more functional clinical measures. So I think it is a good test to keep in the forefront.

I think from my own perspective and my own knowledge of this field at this moment in time, that to use the mutation test as a broad screening strategy and then build therapies solely on that would probably not be the best use of that test. But, again, I'm still continuing to be educated in this field.

Joann?

DR. BOUGHMAN: One of the useful impressions I got from especially some of the groups that put so much thought and discussion into this I think, and this will come back to us in some of the other discussions of options, but in fact a few terms kept coming forward. One of them was standards of practice. And I think

that in the context that we're talking about now that could be standards of the laboratory or testing practice and then standards of clinical practice.

There were also some comments and discussions about guideline principles or best practices models in fact which might turn out to be different, and especially as it related to the consortium idea, which we will come back to later, rather than regulatory but determination of these standards of and best practices.

You talked about tiers. But if we talk about the accuracy of the test or the results, I would encourage us to in fact think of that in levels of complexity as well. It is one thing to have the lab report have an accurate result on it, another thing altogether for the practitioner to interpret that in an accurate, let alone complete, way. And then beyond the interpretation is the understanding or the documentation of the understanding of that result and its implications. So, once again, I found these comments about standards of practice and best practices models actually very useful and provocative.

DR. McCABE: Pat Barr, and then Francis.

MS. BARR: I just wanted to suggest that Wylie's notion of bringing a particular disease forward and examining it in terms of what we project should be a system would be very wise for us to do with a number of them. If we walked through them as a check, then we could also present them to the public this is how we imagine this would work.

DR. COLLINS: Just a comment on hemochromatosis. A cooperative group met the last two days at NIH, funded by Heart, Lung, and Blood and the Genome Institute, to embark on a pilot project to screen 100,000 or so members of the general public for hemochromatosis and, hopefully, over the course of three to five years, get some answers to the questions that you were raising about what is the most effective way to identify those who are in need of interventions without unnecessarily labeling people who don't need interventions.

I think this points out very clearly the sort of difficult position we will find ourselves in over and over again where there is some strong interest in having this kind of testing available in many circumstances and yet we're very much in a research phase of trying to figure out how to do it in other settings. This committee will wrestle with that over and over again.

DR. McCABE: And I think it brings home again the concept that the transition from a research to a clinical test is not quite the bright line that we used to think it was.

DR. COLLINS: Right.

DR. McCABE: And that any process that we come up with will have to recognize the fact that there is a gradient between research and clinical. And that in the past has been a brighter line than I think we can recognize it now. And that by the very nature of these tests, and this was brought home recently with the rotovirus vaccine in pediatrics, we will have to have post-marketing analysis as it were, the terminology used in the drug industry. So that I could conceive of this test being done on 100,000 people in the general population but then I would hope that there would be some monitoring for the next 500,000 as well because things might come up as we move forward that might not be recognized in the initial cohorts.

Yes, Muin?

DR. KHOURY: I'm glad the NIH is funding those studies because they are extremely important to come up with answers to these questions. As you all know, we started a pilot project on hemochromatosis to collect the already existing data as new data becomes accumulated, I will talk about that a bit later.

But the thing that I wanted to mention right now as part of this is that a test is not the same for everyone. And the consortium that we put together will examine sort of three facets around hemochromatosis testing. The one is the question of general population testing for 20-year-olds or 40-year-olds, sort of asymptomatic people. The other question is around symptomatic people with various kinds of symptoms who have come in either diabetes or arthritis or liver testing. And the third context of testing is what do you do with family members of people who already are diagnosed with hemochromatosis.

So these parameters of analytic validity, clinical validity, and clinical utility will vary by the context of testing. And this is the kind of model we tried to put together in coming up with the existing body of information as new information gets gathered through original research on 100,000 or maybe 1,000,000 here and there in different communities. So this is very important.

DR. McCABE: Yes, Wylie?

DR. BURKE: Just a quick follow up. It is interesting that it wasn't on your list to consider newborn screening for hemochromatosis. I think that fits with the general consensus in the U.S. that that would not be appropriate. But it is worth mentioning that at an international conference last May on hemochromatosis that idea, the idea of detecting hemochromatosis families by newborn screening actually got a lot of play in some other countries.

I mention that because I think that gets us back to using examples and asking about use of tests; that is that use of tests may actually get us to the oversight issues that we're most concerned about. And I'm guessing that we are likely very uncomfortable with the use of newborn screening for hemochromatosis but that it probably ought to be on the list as part of the discussion.

DR. McCABE: Other discussion on this issue? We're really talking about how we can categorize these tests. We've talked about that there are more categories than we had originally listed in our document, and I think that's been very informative to have this information.

I don't know if it would be possible, for Alan and Susanne, for you again to just run through the additional categories that came up as you read the information. You were talking about that at the outset, but I think it would be good to come back to that, the different approaches to categorization that you got from the feedback from the public.

DR. HAGA: Well, looking at Ohio State's recommendations or comments, they suggested categories should be based on clinical validity and clinical utility and looking at the weight of the practical clinical test application rather than on risk assessment. They came up with three groups of categories: Clinical, diagnostic, and preventive tests would be one; the second one would be predisposition and clinical research tests; and the third would be laboratory research tests. And they had some elaborate discussion about what tests would be in which categories that we can all look at in comment 70 from Ohio State.

Another group would be medical versus nonmedical, nonmedical did appear in a proportion of comments;

diagnostic versus predictive; and treatable or preventable versus nontreatable was another three categories that tests could be categorized in.

And a more common one was diagnostic would be one group; predisposition, presymptomatic would be another group; and carrier testing would be a third group.

And there were people that did agree with the risk categories though some did suggest having a third category of moderate risk. So it would be low, moderate, high risk categories. I think a comment did not like the term of "risk". It was risk to who are you assessing? Is it risk to the individual, is it risk to society, which risk would you be basing your categories on? They suggested the term "complexity" instead of "risk".

Other categories: I said nonmedical purposes. Tests for germ-line mutations. This is as opposed to testing for specific tissue samples, more a prognostic testing; behavior patterns, testing for conditions/traits that would fall into that group; paternity testing; testing for workplace hazards, there were several groups that commented on testing that would be used in the workplace and the potential negative consequences of that; testing for gender was raised several times; testing of minorities, and for diseases of late onset was a concern; and carrier testing, as I mentioned, is another group. I did not have newborn testing as a category, surprisingly, in the set of comments received through the office, though Alan had some.

DR. STOCKDALE: I have a couple others to add to that list. One was the medical risk of the test, presumably prenatal tests, the risk to the fetus. The other one that came up in response to one of the questions in Issue 6 as well was testing of children or minors.

DR. McCABE: Yes, the testing of children is an interesting issue and has been raised particularly if there is nothing that can be done. And knowing that information is frequently not remembered properly for periods of many years, a couple decades, it gets to the issue of would you do a newborn screen for something that has no influence on that individual until much later in life.

Hearing the first groups of categories there, if we think back to the 1975 report on genetic screening, I think it still holds up very well. There were three categories within genetic screening and at that time they were referring primarily to newborn screening but they did keep it open and didn't just use it as newborn screening, called it genetic screening. And those were, for Category 1, was where it made a diagnosis in the individual being tested. Category 2 was where it might tell about a relative. It was talking about predictive. But there are two types of predictive that I heard here; one is predictive for the individual, predictive for a family member. And then Category 3 was where we really have no action at this time but where we're gathering information. It was really the research category within that.

So I think that a lot of that document has held up over the past twenty-five years. I think it is still possible to fit a lot of the categories that we heard into the context of that document.

I saw some hands. Ann, then Judy.

MS. BOLDT: Well, as I'm listening to these categories, I think if we're going to categorize them by use of the test and the complexity of the testing, I see us making recommendations that the more complex the test, the more that we would want to see genetic pre-test/post-test counseling being performed by a genetic specialist. I guess at this point the current demand and supply is okay. But I know that we have concerns

that that is not going to be met in the future.

But maybe this should be a task, and I'm just looking at the issues and this is probably the best place it ties in, is that is there a need for us to do a needs assessment of the current workforce and then try to determine if we need to also make a directive to train more genetic professionals in the future as well if we don't think we're going to meet the demand for the complexity of these tests and they are not going to have the genetic specialists to do that.

DR. McCABE: Let's hear some discussion of that.

Judy, is this relevant to that?

DR. LEWIS: The point I was going to make was very similar but it was coming at it from a different tack. It was going to be looking at do we need to categorize tests by the complexity of the information that the test reveals in terms of who would be the best person or the best place for where the person could get the test.

And there are two ways to do it. One is to educate more professionals in genetics. The other way is to look at how many of these tests we can take and provide the education to the primary care provider. So that we move them and we save the highly specialized people for the highly specialized tests that have really complex counseling where some of the tests and the issues become more straight forward and some of them are more complicated.

So what my perspective was going to be is maybe what we need to do is categorize the tests related to the complexity of the information that needs to be transmitted to the patient. And newborn screening is a wonderful example of stuff that can be done in a primary care setting and a lot of that information can be given to parents in a primary care setting. And then when you get to some of the more complicated stuff you go to a more tertiary setting. So that whole primary, secondary, and tertiary care setting idea.

DR. McCABE: Just a thought I had on hearing you that perhaps we won't have a single list but perhaps a matrix. Because you could think in terms of the categories falling out of the National Academy report of 1975 with that modification of Category 2 being predictive for the individual or for a family member, and then even within these categories one can have levels of complexity of the information. So that we might want to begin to think in terms of matrices as opposed to simple lists.

Jo, and then I'll catch the people over here.

DR. BOUGHMAN: I had used the term "standards of practice" before. Maybe we need to think from a slightly different angle and talk about standards of care and those who are providing the care at these various levels. Which gets back to a few of the professional organizations' comments about certification, recertification, ongoing educational opportunities and so on that would apply in a lot of different areas.

I also wanted to flag one comment that hit me pretty much between the eyes. I am not sure if this is an official group of any sort. It is response number 112. It has several names on it, a Boston group, but professors from U. Mass., Wellesley, Brandeis, and several from Harvard, basic scientists, ethicists, and so on. The committee is pretty much admonished here by saying "The document does not sufficiently emphasize the probablistic nature of most genetic tests." It then goes on to make some other useful

comments. But being from the statistical genetics world, my hands were slapped pretty clearly by that. It was a pretty impressive group that reminded us of that very clearly.

DR. TUCKSON: Which number is that again?

DR. BOUGHMAN: It is number 112. It is page 337, Volume 1.

DR. McCABE: Yes, I was struck by that also because I hadn't seen that we had left that out. And I would comment to everyone there is an emerging concept even in the single gene mendelian disorders and that is that they are not simple. That at the phenotypic level, they are not simple mendelian traits, they are really complex traits. And so the one-to-one correspondence between genotype and phenotype that we had all hoped would be there isn't going to happen. And that is going to be important even for the simple mendelian trait. So I think that is something we have to bring out in the final report, that we have to recognize the complexity of all disorders and the probablistic nature of any information that is passed on. Thank you for pointing that out.

I have Pat Barr, Pat Charache, Wylie, Elliott, and Muin.

MS. BARR: I think when we get to our work tomorrow the other thing we have to be very sensitive to, which was discussed briefly earlier, is that a test that is appropriate on the market for one thing may not yet be for another but that will not prevent it from being done. As our experience with off-label use of drugs is, we know that some of those off-label uses of drugs are very effective and useful.

So it again looks at the system of do we want to gather the information for the off-label use, do we want to have review later, do we want to prevent it through something, which means we'll never get the information. What are the trade-offs there? So there may be and I am sure that tests that could be used any number of ways, companies will look at the easiest way to present the data to get the test out on the market, which is their right and is appropriate. So that is just an area that as we do our matrices we also have to think about moving from one to another outside the system.

DR. McCABE: Yes, I think that is very important especially given the nature of genetics. That frequently -- being a pediatrician, I am very familiar with off-label -- ampicillin is off-label for use in kids. And that we have to recognize that there were incentives in the industry not to do those tests. Now incentives are being developed to do that testing. And there are ways of incentivizing the industry to look. And what I'm thinking here is that we would want to be very cautious not to have the testing done only in the majority population, recognizing that there will not be a majority much longer in this country. And in children, the disincentive was you didn't want to do it because if you found it might behave differently in children that could threaten the marketing of that drug.

And yet you also make the important point that some important information has come out of this. If we didn't have ampicillin for use in kids, it would have been a very difficult situation for a common disorder. So it is a fine balance but we have to recognize that as well.

Pat Charache?

DR. CHARACHE: I wanted to come back for just a moment to the comments made by Ann and Judy. There were two components to Ann's thinking, discussion. One was that certain categories of tests should

require more counseling. The second was a resource question, do we have or will we build enough counselors. And I wonder if as we go through these thoughts we can capture the concept of where added resources may be required. Certainly, the educational resource comes out right here as well for the clinicians. So that when we finish, perhaps under Issue 6, we can ensure that we have made the point of what resources are required so the recommendations of this body are implementable.

DR. McCABE: Thank you.

Wylie?

DR. BURKE: I also am following up on comments of Ann and Judy. I think it is going to be very important for us to separate the concept that certain tests because of their complexity require pre- and post-test counseling from who does it. The issue of tests requiring pre- and post-test counseling is an issue really of crafting something that is enforceable. And I think that is a tough question, how do you construct that and in essence create a practice standard that requires that?

The issue of who does it is an area where I think we have to be careful not to be too prescriptive. If we're too prescriptive, I think certainly anybody in the genetics community that gets involved in being too prescriptive can be accused of self-interest. But I think the much greater concern is that it is an access problem. That is, to the extent that we are prescriptive, we are first of all saying we don't think all our efforts at genetics education are going to work, but secondly, we're just really cutting off access in a very real way and I think more than we want to do.

So I think it is important to keep those issues separate, and each one of them obviously carries problems with it.

DR. McCABE: Elliott?

MR. HILLBACK: There are two comments. One, I think at a much earlier meeting a number of people raised the issue of education both of the practitioners and public and that we fundamentally have deferred that to another session after we finish with whatever happens the 15th of March in the next little law. Because I think there are a lot of issues, the practical issues of so we do a good job of defining a great oversight mechanism that ends up with lots of good tests being available in the right way, the question is, who is there to use them and how will they be used? And I think we have a huge task ahead of us there that is as big as the task we have taken on here. So I think the issues you raise we should note and we should be ready to deal with. I don't know whether they change the oversight, sometimes they might, but I think we should note that.

The other point I wanted to come back to, Ed, was your point about the matrix. I guess when I think about oversight, to me, the simpler we can make an oversight mechanism the better. And so the reference you made back to the 1975 categorization of diagnostic, predictive, and maybe screening.

If we're really trying to define ways to look at what are the risks of the test, is there enough useful information to make this available in some way, the simpler we can do that and not layer in a multiplexed matrix that starts to look like five dimensions, I can't think past three unless you can draw it for me, so five dimensions gets too difficult. I think we end up back where some comments from Joann and you about we spend all our time categorizing and fighting over what the category is instead of saying, look, this is a

diagnostic test in this context, let's figure out what that means versus predictive.

Realizing that's a little simplistic, but we get our job done and we get at 97 percent of the issues. Maybe we can't get at 97 percent of the issues with that simple categorization. Then we have to debate it. But I get nervous when we start talking about matrices and multidimensions in terms of practical, something that will work in the real world.

DR. McCABE: Yes. My thought there, just to come back to it, was if you go by the categories, even in the predictive there are going to be tests that are simply predictive. There is the test that 100 percent of individuals who have this will develop this by such and such an age versus the predictive test that is much more complex in its interpretation. That was my only thought there. I agree, I have a hard time thinking in multidimensions. And this may not be the way to go. But it is one way of dealing with some of the greyer areas perhaps.

Muin?

DR. KHOURY: I guess I forgot why I had my hand up.

No, actually I just wanted to catch up on Joann. I think the comments from the New England group were particularly resonating with me, too. This comes back to what Ed and Elliott have just said. The way I think about genetics, and most of the public input we got here does not reflect this point of view, is that we are talking about genetic information in relation to disease. And the single gene aspects of this, which are complicated by themselves, are going to be only 5 to 10 percent of all human disease.

And so years from now when we're going to use the predictive tests, which I don't think they will be predictive in any good sense, they will have a very complicated likelihood function; depends on age of the person, whether he or she takes Drug A or Drug B, or drinks alcohol, or takes a vitamin C. The clinical validity for coming down with a specific disease will vary by those strata. Even simple things like hemochromatosis, the clinical validity of the DNA test will vary whether you take iron or not, or whether you are on vitamin C or not.

So the whole concept of gene/environment interaction, and we will probably hear from the pharmacogenomics people a little bit down the road, will be probably the rule rather than the exception in the years to come. So whatever system we come up, I think this will be inherent under the concept of clinical validity.

So clinical validity especially for those predictive things are going to be a very complicated function. The more data we collect along the way, because the data will not be available at the outset or there will be only limited data, the more we will be informed both as consumers and health care providers.

The other comment I wanted to say is that once we get into that complicated area, then those functions will become less of the characteristics of the test, per se, but more of the function of the complexity of the genotype/disease association. So you can have a wonderful test that picks up all the mutations of 100 percent analytic validity, but the clinical validity component, especially if not used in a diagnostic setting but in a predictive setting, will have nothing to do with the lab or will have very little to do with the lab but will build on the clinical relationships that are very complicated.

DR. McCABE: Yes, Ann?

MS. BOLDT: Just to respond to Wylie's comments, and I think her points are very well taken, I think we have to try to assure some minimal level of competency though in individuals that are doing these tests because we don't want to have access be a disservice to the patient because they don't understand what it is all about.

DR. McCABE: Yes. And certainly there were comments to that nature.

Yes, Wylie?

DR. BURKE: I agree with that. And I think when we spell out what pre- and post-test counseling should involve, which I think for many tests of high complexity it is important that we do, I think that is implicit. The question is how do we create the oversight to ensure that to happen. I think that is an issue we need to really think about.

DR. McCABE: Yes, Kate?

MS. BEARDSLEY: I guess I'm listening to this discussion and I'm getting confused a little bit. And maybe this is a comment that belongs tomorrow and not today. But in any event, let me just throw it out. That is it seems to me we have heard a lot of different ways that you could categorize tests. And presumably the reason we're categorizing tests is because we think those categories have something to do with levels of oversight. It seems to me that in a lot of ways all of the categories that we are talking about are both sort of under inclusive and over inclusive.
And I guess my comment is I just wanted to note that we didn't really ask the question here does it make sense to categorize tests. And I hope that that is the question that we will be able to answer or at least think about, even though we didn't ask that question of the public, because I think that is a really real question.

DR. McCABE: Some of the public did respond to that.

MS. BEARDSLEY: Did they?

DR. McCABE: And there were a number of responses that gave us various categorizations in addition to the one that we had given. There were other responses that said you can't categorize tests, that this would be not very helpful, that there are too many different ways of doing it to come up with a way that is really going to be effective.

So it might be good to discuss that because we've sort of assumed that it made sense to categorize. I think some of us went in with that bias. But why don't we discuss that for a few minutes, and especially is there any discussion among the members of the committee that there should not be categories, that there might be another way of doing this other than by category, that there is no different level of oversight for one type of test than for another type of test.

Yes, Elliott?

MR. HILLBACK: Well, I think inherent in the conversation you and I had a second ago, if you put all the predictive tests in one category, you're going to have probably in the long term, to take Muin's comment,

90 percent of the genetic tests are going to be in that one category. And so now you've uncategorized.

The things that are truly diagnostic, in the traditional sense of the word "diagnostic," are going to be a very limited number. And the things that are at the other end of the scale, carrier testing is carrier testing I guess, but the great unwashed is going to be the majority of everything else. And if you start getting into predictive and start breaking that down, then I think you get lost and I think you just get caught up in bureaucracy rather than in action.

So I think you in effect have a de facto very limited categorization if you do the simple version you talked about and I talked about.

DR. McCABE: Pat Charache, and then Barbara, then Pat Barr.

DR. CHARACHE: I'm struggling with two things. First, I do think that if there is no categorization, if there is no focus on the group that have the greatest challenge either in terms of performance or understanding or use, that it will become impossible to come up with an oversight that can be applied in an effective way without being stifling. So I think we have to do some categorization.

I think how things are categorized probably cannot be just by predictive value versus nonpredictive value versus screening. Among other reasons, because of the knowledge base. If you have a very broad knowledge base and you have a predictive test like sickle cell screening, it would not need necessarily the same oversight as if you had one which had a very complex penetrance in expression of disease as a result of the test. So I think the challenge will be to come up with something for which oversight is reasonable, which is simple enough to understand, but which addresses the key features of where we want to put emphasis and then not get into something that then has to be changed every year as information gets progressed.

DR. McCABE: I have Barbara, Pat Barr, Victor, Judy, and then Joann.

DR. KOENIG: I appreciate the fact that we're bringing to the table the issue of asking the more fundamental question of should we categorize and what are the pluses and minuses. And I definitely agree with Kate's comments about all the categories are going to be either too inclusive or include nothing. And back to what Pat Barr said earlier about the off-label use issue, to make it into a shorthand.

Whenever I start sort of spinning it out with one example, if you take something like cancer susceptibility gene and you think about the multiple ways in which the same technical test could be used, you could imagine using the same technical test for preimplantation genetic diagnosis, for straight forward prenatal diagnosis, for testing in adolescents, for testing people after they have been diagnosed to help make treatment decisions. There are so many different ways in which the same -- I'm not sure. Then the whole question what do you do with that. So it is not clear to me that categories help. But maybe there is something I'm not seeing.

DR. McCABE: Pat Barr?

MS. BARR: I actually think categories help but we may be thinking of them at the wrong time. It seems to me that tests get out on the market, that's one question, period. And tests get out on the market because there is some use for them, that's simple. I think the challenge we have is how can we have a system that

incentivizes the collection of data when it is being used for other reasons so that a body of knowledge builds and so that that group that would be doing standards of practice or standards of care has the evidence they need to make good decisions.

So it may be that it's much more looking at the categories after it is on the market and what are the things we can do to be sure that they are examined correctly once they are on the market based on the use they're being suggested. That's a thought.

DR. McCABE: Victor, Judy, Joann, and Wylie.

DR. PENCHASZADEH: Well, I still think that some categorization will be required, otherwise we will have just a blanket thing about genetic testing. And we will probably be vulnerable to a lot of comments saying you can't simply talk about genetic testing in general, there are different uses, there are different complexities. Perhaps complexities is not the major factor, but think of what Pat just said. Okay, if a test gets into the market, it is because ideally there will have been already valid information analyzed by an oversight mechanism and it will be on the market for a specific purpose. I can't imagine a test being on the market just to be on the market. So that purpose probably should be the degree or type of categorization that we can think of.

It is different if you talk about doing a test in an individual for whatever purpose, let's say predictive, diagnostic, whatever, than if you say this is a test that the standards would recommend be applied to the whole population, in newborn screening, or in reproductive tested screening, or whatever.
I realize that categorization may be endless but there are some broad categories; individual clinical use versus population use of some sort, confirmation versus predictive, are you talking about the diseased individual or an asymptomatic individual. These things may change over time for a particular test as knowledge and technology evolves, and of course categories should not be fixed in time, but there are some broad purposes of genetic testing that I still think have an oversight side in it. And I think we have to really grapple with where we should try to come up with the things that make most sense.

DR. McCABE: Judy?

DR. LEWIS: I think my comment follows nicely on what you were just saying, Victor. It seems to me that we probably need to have some categorization, but I think we're trying to deal with the specific and we need to step back a couple of steps and look at a higher level of abstraction. And maybe it is the individual versus the population. But I think we have to spend some time talking about what are those basic axes before we start talking about what are the categories within the axis. And I don't know what they are but I think we are being too specific.

I think we need to step back and be a little more abstract before we get to the specifics because we're all trying to fit everything into boxes without thinking abstractly enough about what the realm of possibilities are. And I don't know what they are but I think we need to step back a piece.

DR. McCABE: Joann?

DR. BOUGHMAN: Rather than actually becoming more abstract, I might suggest that we get real practical. And that is, in fact, as we move into the next questions ask who can do what realistically. There were several comments about the FDA is going this far, it could use or implement further authority. CLIAC, in

its new suggestions, are a step in the right direction. Several comments about best practices.

If, in fact, we took that approach and said what can those agencies who have some oversight currently, we've already raised the issue of the CDC role and it came back to public health and that sector again the moment you start talking about groups or populations, so that in fact would expand a CDC type role I would think just in my first blush at this, and then ask the question what would we gain further by making suggestions to or about the professional organizations, and what might be gained by some sort of consortium which would be a relatively new and different kind of approach. But if we ask the question who could do what, then things might fall out differently.

DR. McCABE: So what you're suggesting is look in terms of where the resources currently exist, what needs to be done to improve those resources, but then looking at coordinating those resources perhaps better. Then getting to the consortium issue, saying there may be resources in these various silos at this time but maybe they shouldn't be silos, maybe they should be coordinated. Is that a fair comment?

DR. BOUGHMAN: That is in fact a part of what I am saying. I actually I think am also saying let's look at Questions 3 and 4 and then come back and see how number 2 falls out with regard to that. And then coming back to some of the previous comments, then let's give ourselves a test and use a couple of examples and say how would this play out. Rather than starting from those cases, let's start with in fact what we've got. And there are some standards out there, there are some oversight mechanisms. We aren't starting from ground zero, and that was one of the admonishments we've gotten throughout this. Genetics may be a little special but in fact there are a lot of people who have been in this business for a long time.
DR. McCABE: Yes. So one of the things then I will charge people with thinking about tomorrow is that as you begin to think of categorization or recommendations, also think of them in the context of some examples. I think that is what you are suggesting also.

So Wylie, Francis, Judy Yost, then Reed.

DR. BURKE: I think this follows to some extent from what you just said, which makes a lot of sense to me. I think we do have to understand from the outset that the way in which a test is used will be an important factor in determining risks and benefits. And so it is entirely possible, and I think we should think about it practically in terms of how this could be done, that a test might initially be released only for certain uses, even recognizing that there may then be off-label uses. So that once it has been released for perhaps a limited indication, then there is an intense effort to see what happens.

The other point is that the use of tests, in part because it determines the benefits and risks, will also determine or be a major consideration in developing best practice standards. So we have to think about how tests are used as we think about what those best practice standards would be. And that is a question of who and how.

The thing I think I would throw out for us to just have in mind is that that process of developing best practice standards has to have two elements to it, possibly they should be separated. Element number one is an objective assessment of the evidence, what we know about clinical validity, what we know about clinical utility, using established criteria for evaluating the evidence, what we know, what we don't know. And the second is making recommendations. So as we answer your practical question, we have to ask I think who could do those tasks and to what extent they could be done by existing bodies or need new bodies.

DR. McCABE: Pat just added collecting data that we want to that.

DR. BURKE: Absolutely.

DR. McCABE: Francis, Judy Yost, Reed, and then we're going to break for lunch.

DR. COLLINS: I want to associate myself with Joann's exhortation that we get practical and try to prepare ourselves for the eventuality tomorrow afternoon of having some specific recommendations of not only what needs to be done but who can do it.

I want to amend those slightly the way you presented it because it made me slightly uneasy that if we come at this from the perspective of who has what capacities and then try to apply them to the problem, we might end up with a solution that doesn't quite fit. I guess I'd rather see us figure out, okay, what are the things that need to be done, and then look to see who has got the capacities and how can we get this done, who has the authority, who has the expertise, how can they step into the breech and take on the responsibility. So that was the comment.

The question I would have, and maybe this is one the FDA can help us with, is how much should we be worrying about this off-label use business? If a test were in fact adjudicated, reviewed, considered to be appropriate for a specific clinical application, take an example that APOe4 is decided to be appropriate as a diagnostic test in the evaluation of someone who has dementia but it is not approved for the use of predictive testing or, God forbid, prenatal diagnosis, to what extent, based upon experiences in other kinds of oversight of this sort, does this specific approval for a specific use serve as a deterrent for off-label use, because presumably those who are doing that face some liability if things don't go well.

DR. McCABE: Steve, Dr. Gutman, would you like to respond to that?

DR. GUTMAN: Yes, I actually would. It has always been a problem. Off-label use is a colorful and interesting problem. It has been probably codified a little bit by the Modernization Act which in fact to a certain extent makes it more of a problem. The Modernization Act clearly indicates that we are bound to the four corners of the label and that we can look at the claims and that we in fact in general can't look at off-label use or predict or worry about off-label use. So it may be more of a problem and it may be something you want to address in the recommendations that you make.

We, in fact, when we interact with companies, contrary to popular belief, are very anxious to get new technologies out. And one of the most common suggestions that we make for exciting new products is that companies in fact maintain a narrow focus and a narrow scope and limited claims so that we can help them get the product out, recognizing that there is a danger to that. I think our existing regulatory scheme is one which would have difficulty addressing that.

DR. McCABE: But perhaps one of the ways of doing this, because, again, I remember what Pat Barr said and it is important that we not be so limiting that we impede progress, but one of the ways that this is done in the drug industry, again thinking about another regulated industry, is with the package inserts. So that the package inserts specifies what that is used for and those who use it off-label use it at their own risk in a sense in terms of liability issues. But again this gets back to information and how we inform the public and the professional about what the appropriate use of that test is without being so restrictive that we can't move forward.

Also, there might be a way that you could, if people are using it off-label, and again I don't know if there is a precedent for this, but if it is being used off-label, that there is some obligation to collect data on that off-label use.

Steve?

DR. GUTMAN: Yes, let me interject, because you're absolutely on target. The one thing that we probably can rightfully be criticized for is we are absolutely obsessive and compulsive about labeling that we're not even sure is ever read. And that when we do recognize that studies haven't been done in particular populations, say a pediatric population or a pregnant population, we'll put it in big bold letters.

And as we've seen more fascinating technologies that have potential for off-label use, one thing that we can include is a requirement of approval for products that we review is we can require educational programs, we can require videos, we can require brochures, we can require patient information, we can do everything possible. You can take a horse to water, you can't make him drink. But we'll try and get the horse to the water and make sure that it is real clear what is going on.

DR. McCABE: Again, recalling that we don't want to make things so expensive that that also impedes progress.

Judy, Reed, and then I see some other hands up. It will be detracting from digestive time.

Judy Yost, yes?

MS. YOST: Hi. I just have a brief comment and, again, it follows all of the other discussion that has gone on as far as practical and simple, because I think that is something we truly do advocate, and also to hint, I guess in the same vein as simple, to not take up this committee's time excessively, to again go back to the comment about what are things that at least are in existence so that you don't have to go back and reinvent or redo someone else's work. For example, at least in the context of analytical validity and the accuracy and precision of tests, there are CLIA requirements that are minimum and basic. But the CLIAC has spent a tremendous amount of time coming up with recommendations that you will see very shortly in a Notice of Intent that do address genetic testing where it was felt that CLIA was not strong enough. That is already in place.

So at least that is a cut for maybe where we need to go, and that is in the area, what I heard through all these meetings, is in the area of clinical validity and clinical utility. And in that case, because there is a lot of work to be done in that area, particularly for the type of home brew tests that are not currently regulated by the FDA or not particularly overseen by the FDA right now, or anyone else for that matter, that's the area where I think we have to have some kind of striation or strategy to address them, because where do you start and where do you end and make some decisions about what is your priority.

And so that is all I am suggesting is to at least focus on the areas that need the work and some of the rest will take care of itself. Not saying that the CLIA is perfect or that it will be perfect when this is done, but a lot of work has been done in that area.

DR. McCABE: Reed?

DR. TUCKSON: In the interest of time, the first half of Francis' comment and the last comment made made my point.

DR. McCABE: Pat, brief comment?

DR. CHARACHE: Just something to think about. Should off-label use return a project to IRB oversight for that use?

DR. McCABE: That is definitely something to think about.

I want to thank Alan and Susanne. I know we're going to hear more from you, but I while I am thinking of it now I want to thank you for having taken the time to help us digest these comments. Thank you.

We're going to take an hour now for lunch. Food service is available in the building; there is a food court. The staff at the registration desk will also have suggestions regarding restaurants. And we will begin back sharply at 1:00 p.m.

(Whereupon, at 11:58 a.m., the meeting was recessed for lunch, to reconvene at 1:00 p.m.)

AFTERNOON SESSION (1:00 p.m.)

DR. McCABE: Let's get started again, please.

Bob, one of the things I'm going to ask you also, so you can be thinking about it, after I introduce this topic is if you would comment on the Notice of Intent on CLIA regulations, too, Bob. So if you could make a note of that as well.

We are now going to have a report of the CDC Genetic Consortium - Laboratory Workgroup, Dr. Robert Martin from Division of Laboratory Systems, CDC.

At our meeting in October, we heard from a panel of representatives from four organizations, three private sector organizations in the State of New York, about the roles that they play in providing quality assurance of genetic testing. The discussion that we had at that time with the representatives was very productive and I asked them as a group to continue to explore how their organizations and others with an interest in genetic testing might help address the need for additional oversight.

Dr. Bob Martin volunteered to take the lead in organizing a meeting to explore whether a public/private consortium could provide additional oversight of genetic testing. A public/private consortium is one of the oversight options that we had discussed in our consultation document. The goal of the meeting was to provide some greater sense of whether a consortium approach would be a workable solution.

CDC originally scheduled the meeting for January 25-26 to take place in association with the SACGT public meeting. Unfortunately, there was the snow storm in the mid-Atlantic region at that time which

caused cancellation. But there were people who had already arrived ahead of the snow storm and Pat Charache was able to organize things at the hotel so that a smaller group of individuals was able to meet and discuss the issues, though nothing conclusive did come, nor could come from that meeting, despite the report in the blue sheet that you've seen. The meeting was rescheduled for February 23rd, yesterday, and Dr. Martin is here today to report about what occurred yesterday.

Bob, if you would please.

DR. MARTIN: Thanks very much.

Actually, this topic comes at a very good time in your discussions because some of the comments that were made just a few minutes ago before lunch by Dr. Collins and others referred stepping back for a moment and taking a look at what already exists in the regulatory framework and within the professional groups to determine to what extent those existing pieces might fit the niche that we're discussing now.

The other thing that I noted, I hadn't seen the comments, obviously, till this morning in the handout, and noted a number of the comments that referred to the possible value of a forum or a coalition to address some of the issues that we're about to address now, and also many comments that were received with regard to the strengthening of CLIA. So those are some of the issues that we'll be taking a look at.

Now the other thing I'd like to say at the onset here is I'm going to use a different word than Dr. McCabe used when he described this group, and this is for a reason to try to diffuse any confusion about a consortium or the use of the term "consortium." Needless to say, that term can refer to a variety of groups not just our group. And so to not cause confusion with what Dr. Khoury has been talking about for some time with this group, I am going to be calling this the report of the CDC Genetic Forum-Laboratory Workgroup, again, just to separate these issues out a bit.

So as Dr. McCabe said, the challenge or the charge that we received, I should say, after the meeting last fall was can a public/private forum contribute to the implementation of genetic tests or contribute to the oversight process.

And the answer to that was a resounding yes, from the group that met yesterday. Many of the members of the forum are present today sitting around the table and in the audience. And I don't think I'm misrepresenting that at all. They felt that this could be a very important contribution to what is going to be dealt with in genetic testing.

The purpose of our forum, we wanted to identify that up front, and that is to assure that laboratory issues related to the quality of genetic testing are appropriately addressed. And we are defining those issues relatively narrowly. And I understand that narrowly is subjective, how narrow is a question. But, clearly, this group is the laboratory forum and those are the issues that we will be addressing, issues related to laboratory testing.

So what are some of the first steps that a group like this could take? Actually, the first step that we thought would be important would be to identify relationships with other committees and advisory groups. Obviously, the relationship with the SACGT, with CLIA, with CLIAC, the advisory committee, with the genetics panel within FDA, among other groups. There will be others that we would identify as well.

There were some operational issues that we thought important to get out of the way right up front. For example, we discussed at some length membership issues and staffing issues.

With regard to membership, it was felt that a group of approximately 20 would be a very workable group size, and these 20 individuals would represent professional organizations, the laboratory professional organizations and the Federal agencies that are involved in addressing laboratory issues. With regard to staffing, CDC will take the responsibility for staffing, the activities that would be associated with this group. We're all aware of the significant amount of effort that goes into staffing groups like this, and we will be willing to take that responsibility on.

The other thing that this group would do as a first step is begin to look at the development of a regulatory paradigm that addresses gaps, again, this is what we heard earlier this morning as well, and includes public/private participation.

Now in order to have something to look at, we in the Federal agencies have been thinking about ways in which to address genetic testing, we have proposed in a couple of different settings some models. I would just like to share those models with you, not that these are carved in stone, these are going to be the source of discussions that will take place later on within the Laboratory Forum.

For example, this was an approach that was proposed to CLIAC last September, Dr. Joe Boone developed this, in which we look at three different categorizations: Research only, single site and low volume, multiple site and high volume. Again, we recall the conversations of earlier this morning. Again, I am not showing you these because these are directions we're headed, I want to emphasize that, these are just examples of ways in which we've thought about this issue.

Another way to look at it is when a test is ready to be used for patient care, different phases of test: Development and analytic validation phase, preliminary clinical testing, clinical validation, and post application monitoring. And again, we realize there is some overlap within each of these groups that would have to be sorted out.

Dr. Steve Gutman presented a proposed paradigm from FDA for the group to think about. His paradigm is based on the purpose of the test, whether or not this would be a predictive or presymptomatic test or a test for symptomatic patients. And just quickly to go over this:

If the test was the major or sole risk determinant of high risk disease, such as BRCA1, then this would be a test that would be categorized as one requiring high scrutiny and could fall under the existing FDA oversight, or FDA could choose to contract that responsibility or grant deemed status in order to look at this.

If, in the same category predictive or presymptomatic, if this was the major determinant of low risk disease, for example, periodontal disease, then this would be worthy of lower scrutiny, existing CLIA oversight might be able to handle this, or we could go again to a contractual model as was described before.

For symptomatic, disease in patients who are symptomatic, high risk disease, for example, Alzheimer's, would require moderate scrutiny, again a contractual basis, or deemed status, or a CLIA process might work here.

And there could be low risk. For example, some of the mucalpolysaccharide deficiencies such as Hunter's,

again may be requiring a lower level of scrutiny, again contractual, deemed status, or a CLIA process might work.

So I'm summarizing yesterday's deliberations very quickly here. There was a lot of time spent; we spent eight hours in the room talking about these issues and, again, I hope I am representing them well for the group. A number of them are here and can speak to fleshing out any of these.

But the conclusions we arose at were, first of all, a public/private forum could make important contributions to the process of implementation of new tests; and secondly, the forum will be staffed and supported by CDC; and finally, we have enough information now to move on to a next meeting and begin to address possible paradigms that would function under a public/private forum, both professional organizations and the Federal agencies.

DR. McCABE: Thank you.

We have maybe five minutes or so to discuss.

Judy, then Francis, then Wylie.
DR. LEWIS: I have two comments. One would be when you talked about public/private forum, all I heard us talking about was health care professionals and Federal agencies. I didn't hear any talk of consumers. I would think that that would be an important group to consider having as a part of the forum because I think the people who are actually going to be the users of the tests would have a very valuable perspective to add.

And the second comment I have is when you started talking about high risk and low risk conditions, I think that that's a real can of worms because what is high risk for you may be low risk for me, and the other way around. I don't want to decide for you what's high risk because it may be very different given your own personal tolerance for risk. So I think that that becomes a very, very hard thing to decide because it just really gets into some core values that I'm only willing to decide for myself. I think it is really hard to decide for other people.

DR. MARTIN: I understand, and just to respond quickly. The makeup of the group we discussed at some length and there is still some visitation to that issue that will be done during the next meeting. With regard to your second issue, again, I put these up here only to demonstrate that Federal agencies have been thinking about some of these issues and none of those are carved in stone. They are just fodder for the group to deal with.

DR. LEWIS: Could I just do one follow-up on that? And that is, if you decide to add consumers and you add them after the group is already formed and working, then they don't get an opportunity to help set the agenda and set the priorities. So that it seems to me that membership becomes a real primary issue. And if you're getting to the point where, I know it's only going to be the second official meeting but it is the third meeting of the group, if you wait too long to bring other people onboard they don't have the same opportunity to set the agenda.

DR. McCABE: Francis?

DR. COLLINS: I guess I have a more fundamental puzzlement about the mission of this group. As I understood it, this was in part a response to a query based on the September meeting about whether or not

a public/private forum could contribute in some way to resolving these issues about the appropriate oversight of genetic tests. But it is, after all, the mandate of this group around the table, the Secretary's Advisory Committee on Genetic Testing, to establish what that oversight ought to be.

And I am a little worried from the way you presented this that a parallel effort is underway involving a number of Federal agencies with what sounds like an attempt to answer the same questions but in a not entirely connected way. Can you help us understand that? When you put up possible paradigms, I'm thinking "Wait a minute." I thought that was our agenda that we're going to try to struggle with today and tomorrow. How does this all fit together?

DR. MARTIN: Well, I think it fits together in the sense that was being discussed earlier, that indeed the Federal agencies are out there and have been dealing with this issue for some time as well. CLIAC was one of the groups that was charged with taking a look at the issue of genetic testing. So in that context, these have been moving forward and we see them fitting hand-in-glove with what SACGT is doing, not competing.

DR. COLLINS: Well, I'm a little worried about that.
DR. McCABE: I think we had Wylie, then Pat Charache.

DR. BURKE: Yes, I mostly actually want to echo the concern that Francis raised. It does seem to me that there is an uncertainty or lack of clarity around the table so far about what sort of decision-making process would categorize tests and then determine what regulatory pathway they would go on. That decision-making process probably needs to precede the formation or even the decision about the structure that should be put in place to make sure that happens.

I also wanted to add a comment about the high risk versus low risk. I think one of the most useful comments that we had in our public feedback, and it fits with Judy's comment, is that it may not be useful for us to try and determine high risk/low risk but rather talk in terms of high complexity/low complexity. So that it is not so much the question of what diagnosis is down the line, but rather how much uncertainty there is about the clinical validity and clinical utility of the test, and greater uncertainty leads to higher complexity and greater concern for education and care and use.

DR. McCABE: We're going to take comments from Pat Charache, then Pat Barr, and then we're going to wrap this up because we need to move on.

DR. CHARACHE: Two types of comments. First, I certainly agree, especially after the conversation this morning, that the determination of categories has to be done here.

I would add one thing to the summary from yesterday, and that is that to me the most concrete advancement and the most pleasurable one for me was, Dr. Mike Watson who was there I think expressed it best, and he said it was a setting in which it was very clear that the territorialism of these groups, both governmental and private, was being blunted and that they were enthusiastic about working objectively as a team to determine where each could fit in terms of how to do this. Some of these contractual categories were directly targeted towards some of the private groups which would be in a stronger position to have oversight with some of the

functions that were being considered.

One of the key questions and final decisions that were made addressed the issue as "If you are asked, will you serve?" because it is very demanding for a voluntary group to be willing to do so. And that was unanimously approved. So I would just add that to what you've heard.

I found it both preformed, because there was attempt made not to prejudice people in terms of what the outcome would be, and leading to that very positive concrete outcome of loss of territorial concerns and willingness to serve.

DR. McCABE: Pat Barr?

MS. BARR: My sense of the presentation actually was not that it was competitive or duplicative, it was that if we have a paradigm which we're working on, that they would be willing to take that paradigm and then think about how it applies to laboratory standards. That's my understanding, that they are limiting themselves to what they as a group feel they can handle within this process in the laboratory and that they will take direction from us in that as we progress.
So they did as much as they could do yesterday I would say by throwing out some of the sensibilities that perhaps we've already expressed, there was nothing new up there, and seeing if they could do something with it. So I think it's very helpful because I would like as much sort of off the table, reasonably, as we can put off the table. And I think if they feel strongly that they can handle the laboratory reviews and assessments, that that's a good thing.

DR. McCABE: We can continue this discussion as part of our future discussions. But I think we do need to move on.

Bob, thank you very much for your presentation.

DR. MARTIN: Sure.

DR. McCABE: We have asked Dr. Rod Howell, President of the American College of Medical Genetics, to make an announcement about an upcoming meeting.

Rod, would you, please?

DR. HOWELL: Should I go up here?

DR. McCABE: You could use the mike over here, Rod, if you wanted to, at the opposite end of the table there. Just press the button.

DR. HOWELL: There's been a great deal of discussion about the issue concerning gene patents and the provision of genetic services and access of genetic services. We discussed that here in the fall and it has been an increasingly hot topic. As most of you know, the Patent and Trademark Office has issued a new group of draft guidelines that were published in the Federal Register in the fall and many of us were asked to comment about those. Some of the large organizations that have in-house attorneys have, indeed, done that. I have read these guidelines and could not possibly comment because I don't understand them, although they're very important.

MR. HILLBACK: We're sure of that.

DR. HOWELL: We're sure of that. A number of us have been discussing this, and in discussing it with some folks last week it became apparent that my problem is fairly widespread.

And many people who are very interested in the issue would like very much to have an opportunity to get together with some thoughtful people that really understand clearly what they are so that we can then appropriately respond. The deadline for commentary is extraordinarily brief; it is I believe March 22nd, so it's coming up very soon. That cannot be changed apparently.

So a meeting has been convened very rapidly to be held next Thursday, which is March 2nd, at the Wardman-Park Hotel to which each of you will be invited. Persons present, there will be some scientific presentations, some industry folks are expected to come and comment, and in addition there will be legal experts there who have reviewed them that can discuss those. And we are expecting, hopefully, people from AMA and so forth to come.

It will start at 8:30 in the morning and will end at 2:30 in the afternoon, and it is jointly sponsored by Vanderbilt University, Dr. Ellen Clayton, who has a grant dealing with this subject, and the American College of Medical Genetics has helped try to organize this, and some funding through Ellen's grant mechanism from the Genome Institute. But it should be a lively discussion we hope. And, again, next Thursday.

DR. McCABE: Any quick questions for Rod?

MR. HILLBACK: If we could get the particulars on a piece of paper or something so we could take it away with us.

DR. HOWELL: This group should receive an e-mail invitation also that will have the particulars. But before you leave, Kathy Hudson is here and I know that she has on her PC a copy of the invitation. This has been organized shall we say with extraordinary rapidity. Thank you very much.

DR. McCABE: Thank you, Rod.

So, Kathy, is there a way that you could print? Do you have it on your PC, Kathy?

DR. HUDSON: I do have it.

DR. McCABE: Okay. Is there a way we can print here do you think? Maybe you can work with the people at the registration desk and see if there is a place where we could print it out and get it around to people.

Pat Barr?

MS. BARR: Is this something where we should have formal SACGT presence there, or this is just if individuals are interested they'll go?

DR. McCABE: How do people feel about that? We have discussed the patenting issue. It was one of the

topics for late tomorrow afternoon as to whether this was something we were going to take up in the future. So I don't know if you want to discuss it briefly now or if you want to wait until tomorrow.

DR. BURKE: I would say that our decision needs to be an informed one. And on that basis, I would certainly hope there could be some SACGT representation to bring back to this committee what is learned from the meeting. I think that is at minimum what we need to know to say it isn't on our plate, and certainly essential if we decide it is on our plate.

DR. McCABE: Francis, you're going to be there, is that right?

DR. COLLINS: Certainly, because I think this is an issue of great interest. And I am delighted that Ellen and the college have decided to put this together on a very quick turnaround. John Doll from the Patent Trademark Office is also supposed to be there and will be going through a set of examples of how the Patent Office intends to interpret their own utility guidelines which they've just issued but which, as Rod says, are very difficult to figure out if you're a mere mortal. And if we could have some opportunities to hear from their perspective exactly how they would apply this to a given patent application, it could be quite useful. And the timing, especially if there is going to be the opportunity for feedback before this comment period closes, is getting pretty short. We are down to like a month.

DR. McCABE: Okay. I am going to make one other comment and then we're going to have to continue on. That is that Sarah has just told me that if you can fit it into your schedule, and I know it's very quick, but if you can fit it into your schedule, the SACGT budget would cover you

for travel to that meeting. So if you could check your schedules and let Sarah know whether you'll be able to attend then next week. But I think that if you attend, we would like you then to report back to the SACGT about what you heard and how it might inform the entire committee.

Let's move on then. We have one scheduled commentator today. But before we begin that presentation, I would like to ask members of the audience whether anyone has any questions or would like to make any impromptu comments at this time. Is there anyone?

(No response.)

DR. McCABE: If not, then would Dr. Penelope Manasco of GlaxoWellcome please come to the podium? Thank you for coming today.

DR. MANASCO: Thank you for not only allowing us to comment, but also for putting time in your busy schedule to actually allow some discussion on the area of pharmacogenetics.

As Dr. McCabe mentioned at the beginning of the meeting today, we did present public comment in October but at that time our comments were limited. We recognized what we thought were differences in the ethical, legal, and social issues for pharmacogenetic testing when compared to testing for disease susceptibility genes or Mendelian disorders but we weren't able to really give you details as to what we thought those issues were and how we thought they were different.

And so we took that as a mission and we left the meeting and consulted with a very important ethics consultant and fourteen scientists from the genetics directorate at GlaxoWellcome with the goal of trying to

really look at the ethical, legal, and social implications of pharmacogenetics research as well as its marketing and clinical application. Elizabeth McPherson, who is our ethics and policy strategy advisor, was the one that spearheaded that effort. And the result of that effort is the written submission that we presented to the committee.

Just to mention about Elizabeth's role at GlaxoWellcome, her sole responsibility is really to look at committees such as yours and the National Bioethics Committee and to really understand what the ethical issues are in the community, not only in the United States but also in Europe and the rest of the world, so that we can be aware of them and we can take that constantly into our evaluation process for our programs.

I want to assure you that this submission that we have today does not really end our responsibilities and we will continue to integrate the systematic evaluation of ethical, legal, and social issues into our day-to-day operations for GlaxoWellcome genetics. It is our intent to work cooperatively rather than adversarially with groups outside the company to continue to identify these ELSI concerns. We anticipate the opportunity to proactively and cooperatively arrive at fruitful solutions to these real problems.

We focused this submission on the marketing and clinical application of pharmacogenetic tests. Since the SACGT is currently seeking input on the adequacy of current oversight of genetic tests in the United States, we at this time did not address the research aspects of pharmacogenetics but would be happy at any time to share our thoughts on that with you.

I just have a couple of overheads just to go through a few of the comments that we made in the submission. One, again I just want to emphasize, and it has already been emphasized today by Muin and many other people, that there is a heterogeneity in the definition of genetic testing. It means many things to many people and we only put a couple of them on there. After hearing the discussions this morning, we probably could have put many more.

But right now what we want to focus on are really the pharmacogenetics and, as we call them, medicine response tests. I want to focus a little bit on what we see as the benefits and what we see as the risks. Again, in the benefits, we think it is really important to understand that we think that pharmacogenetics promises the opportunity to truly be able to use evidence to decide what is the best medicine for a patient and not to have to use trial and error methods to be able to decide what is the best treatment for a patient. By using less trial and error, we think we will expose patients to a lower risk and be more efficient with the use of health care resources for everyone.

We also think that by understanding the genetic markers for safety and efficacy we will be able to make it safer for everybody to take medicines. Medicines that may have a safety issue, if we can identify who are the patients that are going to be at risk, it makes it safe for the patients who are not going to be at risk for the specific side effect as well as for the patients, and then the other patients will get the benefit.

We also hope that pharmacogenetics will give us the promise of a more streamlined drug development program. As many of you know, it takes about ten years for us to develop a medicine right now. That means a long time to get real answers to patients' medical problems. We are hoping that by being able to understand which of the patient sub-populations are going to respond to our medicines, we will be able to do a much more efficient and hopefully faster drug development program.

I want to again mention, and I'm not going to spend a lot of time again on the disease genetics area, but I

want to talk about what we have listed as the risks. I think probably the most important thing that came out of our brainstorming session was really that the ethical issues are probably not very different but that the magnitude of the issues may vary depending on whether you're talking about disease susceptibility gene testing, testing for mendelian disorders, or pharmacogenetic testing.

That doesn't mean there are no issues in the area of pharmacogenetic testing, but that the magnitude is probably different. We think that many of the areas have been brought up by the SACGT are still very important areas. Under testing, the issues of clinical validity and utility are important issues and are things that we will continue to address for our products. Also product information, being able to provide accurate and understandable information to patients through package inserts or whatever is going to be very, very important so we know what the tests will do and what they won't do.

One of the things that we found out by doing focus groups with consumer groups as well as patient groups is that there is a real, and you found the same thing, there is a real concern about the knowledge deficit. Will physicians actually be able to use the information that we're going to provide from our development programs to do a better job of prescribing medicines for patients. We take this as a real challenge and something that we are putting a significant effort into. Physicians and patients need to know what the tests will and will not do and that they are to predict response to therapy and not to be used for diagnosis.

We also think it is important that patients, and right now it is particularly germane, that adverse experiences and the outcome you get from a medicine is not just determined by the genotype of the patient that has it, but by many other factors, including diet, including whether the patient follows the instructions for taking the medicine. All of these will have an effect on outcome, not just genotype.

Again, we do think that labeling is going to be critical for our studies. It has to be clear that subpopulations of patients will benefit and that these medicines in some cases will not be appropriate for the whole population. So that we need to be very clear in our labeling and in our package inserts.

One of the questions that came up, and again I think at this point we are looking at whether it is risk or whether it is ethical concerns, but an issue was brought up that if a patient finds out that the medicine that is on the market is not likely, again we're talking risk here, is not likely to be effective for a specific patient, that they may lose hope and they may feel that they don't have anything to look forward to if the medicine doesn't work. I think one of the things we would like to emphasize here is that pharmacogenetic tests will not decide whether a medicine works or not, it just allows us to know that hopefully ahead of time rather than having a patient go through multiple courses of multiple medicines without getting a therapeutic benefit and all the time being exposed to potential risks.

Access to care has been brought up. We again think this is an important effort, and one that we're already working on is to begin to have dialogues with people who will provide reimbursement and will provide both prescribing these tests and interpreting them. Because it is going to be critical that everybody is onboard understanding both the strengths and the weaknesses of the tests and understanding where they should be used.

And, again, the question of whether these tests are going to be too expensive is another one. Again, we hope that the tests will be a very reasonable price and will end up being seen as being a good way to try to use our scarce health care resources more efficiently. But, again, it is something that we cannot promise at this time.

And last, but not least, is the area of stigma or discrimination due to collateral information. We mentioned when I was up here in October that we felt that there was going to be less collateral information with pharmacogenetic tests, particularly around SNPs, than are disease prognostic and diagnostic tests. But I think everyone in our group felt that at this point we could not guarantee that there would be no collateral information. So as with anything else, we think we have to consider these issues, we have to look at them carefully. We do believe that there are things that we can do around which SNPs we choose to minimize the collateral information, but we cannot promise that there will be none. So I think it is an important area.

And as in the whole area of genetics, this is moving so fast that this is a snapshot in time and it is something that we will continue to look at every day in the work that we do. Because the science is moving quickly, the technology is moving quickly, how it gets used in the health care system is moving quickly, and we need to be sure to be very aware of these issues as they develop and continue to try to put as many safeguards in as we can.

I would like to just take a last minute to say that given the important potential benefits of pharmacogenetics, we propose that the oversight should carefully scrutinize with the following questions in mind. These are in our submission but I would like to just briefly go through them. The questions for oversight really are: What are the risks which the oversight is intended to reduce? Do these risks accrue to all genetic tests to which the oversight measure would apply? And many of these you have begun to start to answer here today. Are the risks that the oversight measures are supposed to reduce mere possibilities or is there a significant probability that they
will occur? And how will a proposed oversight measure as it will actually be implemented effect the risk-benefit ratio of the technology to which it is applied? There's just a couple more. Is the proposed oversight measure the least restrictive and least costly effective alternative? Will the proposed oversight measure affect the risk-benefit ratio differently depending on which types or uses of genetic tests it is applied to? And will the reduction of risks that can be realistically expected from the actual operation of the oversight measures be significant enough to warrant its cost?

So those are our thoughts. We're happy to answer any questions.

DR. McCABE: Thank you, Dr. Manasco. On behalf of the entire committee, I want to thank you and GlaxoWellcome for taking our questions to heart and continuing to consider and explore these issues.

I would like to take some time now to discuss this with you and with the entire committee.

Joann?

DR. BOUGHMAN: I'd like to thank you also for sharing with us. I wonder if you might help clarify maybe from some of your discussions, I can imagine you got into these. I can envision a model in which having some understanding of the metabolism or the metabolic pathway and potential genetic variation as a drug is being developed might in fact make the process more effective because you would have at the end of that process your responders, nonresponders, or whatever category we might like to talk about them.

But I wonder if you might share with us any discussions you had that might inform our larger questions related to genetic testing and collection of data, including, in the pharmaceutical context, post-market evaluation. In other words, you've got drugs on the market as do other companies that probably aren't perfect. There may be some people who have an adverse reaction or are not responding as well. What were

your discussions about data collection, DNA collection, sample saving, and utilizing information from patients already in trials or in fact in the post-market and actually taking the medicine?

DR. MANASCO: So were you sitting in our offices?

DR. BOUGHMAN: No, but --

DR. MANASCO: It's like you're clairvoyant. We've actually had a number of discussions about this. I can tell you first about the clinical trial program. We actually prospectively collect samples in all of our development programs for I think almost every one of our compounds. Now we don't do it in every trial, but in every one of our pivotal trials we do. And that helps for the drugs in development because you don't know when the side effects are going to come up, you don't know prospectively where you're going to have problems. What we believe very strongly is that we want to have that information to be able to answer the questions. So for common adverse events we can do it now.

DR. BOUGHMAN: Could I interrupt there and keep me on track here. So, in fact, in a clinical trial that would collect these samples, you would have had through the IRB approval process that would be part of the informed consent?

DR. MANASCO: Yes. And we did not spend a lot of time talking about our research program here, but every one of our protocols goes through ethics committees and IRB approval. So we believe that the best is if we can prospectively collect samples. And we believe probably that some kind of method like that, again to answer questions about the utility of testing as well as looking at rare side effects, that there probably will need to be some kind of program in place to be able to allow us to look at the rare adverse events.

Post-marketing, one of our frustrations is that we don't get the samples to be able to do the analysis. That is something we are working on trying to figure out ways to be able to do. But for the programs that we have in development, we actually do try to collect that information. And in fact, for some of our post-marketing programs, for instance, for Ziagen, which is a drug used in HIV, we are actually going out and collecting samples of the patients who have hypersensitivity so that we can try to understand if we can predict who are the patients that are going to be at risk for that side effect.

DR. BOUGHMAN: So from your focus groups and your consumer groups that you have talked to, have you gotten a sense that people would be willing, if others might want to come back to them at a later time, that they would later give the samples?

DR. MANASCO: Certainly, we have had good response from patients in the trials. We have gotten very positive results from almost every, well I think every group that we've talked to.

We've spoken with insurance companies, we've spoken with HMOs, we've spoken with a number of people, what would you do if you could actually predict that a patient is going to respond? And the other question we asked is, if it were only going to work in 10 percent of the patients but you knew which 10 percent or had a high likelihood, again, I think Francis has often talked, we are not going to know yes or no, but had a high likelihood that the drug was going to work, would you have that drug available to those patients? And they said yes. That if we knew ahead of time, then we could use our scarce health care resources the way that they should be used to get the greatest benefit as opposed to using one of these drugs in everybody

when it is only going to work in 10 percent.

So I think the thing that we have seen in all of our focus groups is that the patients are very excited about it, the HMOs think that this is actually a good way for them to be able to use their resources the best way, and even the insurance companies see a value in being able to help them to provide medicines better.

DR. McCABE: Francis, did you want to comment?

DR. COLLINS: Yes. I think this is a very important issue. Clearly, there is an enormous investment right now going into discovering many, many variants in the human genome and to apply them for just this purpose. And this will not be something that has to wait for the next generation of drugs. This could be applied to the current one, and already is in many instances.

I think the white paper that you sent around, which I know Alan Buchanan had a fair amount of consultation involved --

DR. MANASCO: Absolutely.

DR. COLLINS: It is a nice document to try to lay out some of the issues.

I think the tricky part of this basically comes down to circumstances where you are carrying out a test for pharmacogenetic purposes but it also has some potential to make a prediction about exactly what subtype of the disease does that person have and what their prognosis might be whether or not they are treated. Sort of the example of the CETP polymorphism which both predicts your responsiveness to statins but also says if you're not treated what your likelihood is of rapid progression. Those clearly will be tests that have two parameters associated with them.

I actually think though that for the ones that I think you are primarily thinking about, and your diagram sort of implied a separation between the medical tests as opposed to the pharmacogenetic ones, the ones that are related to drug action or drug metabolism where your alleles at that particular locus, if it is a drug action or a drug metabolism situation, may have no effect whatsoever on predicting your future health. They are going to predict your future health if you happen to need that drug, but otherwise it is not going to have a prognostic predictive feature to it. Those probably would fall in most people's view in this sort of low risk category where we as a group I suspect would be less inclined to say, oh, that's one that needs a lot of scrutiny.

But as you move into those categories where you are both making predictions about drug responsiveness and about the likelihood that the illness is going to go badly, a prognostic test of some sort, then I think there will be more serious discussion about, now wait a minute, what is this test telling you. It is telling you something about drug responsiveness, but it is telling you other stuff, too. And as long as we keep clear in our minds sort of the fact that some tests may have both features, I think that will help. And your document points that out.

DR. MANASCO: I think, again, it's a continuum. You can't make every kind of provision but I do think you've got to be aware of all of those kinds of issues.

DR. McCABE: I think one of the classic examples are aminoglycosides in deafness, where not only does

it tell you the risk of a side effect of the drug, but when they've gone into those families they have found that individuals not exposed to that drug also had deafness. So that there also will be cases where identifying the variation will identify potential for disease within that family. But it sounds like you have addressed that certainly in the white paper.

DR. MANASCO: As I said, I think if you look at the great scope of the data that have just been coming out that one out of two Americans has a prescription every year, that if you looked at the vast number of them, that's probably not going to be the case. But there will be subsets and we do need to be aware of those. We believe, again, the issues around privacy and confidentiality are very important issues and they don't change. Because I think, again, patients' medical records need to be kept private. So I think those kinds of issues we agree with the way the committee is going.

DR. McCABE: Wylie, Muin, and then Michele, and then we're going to wrap-up this discussion and move on.

DR. BURKE: We've already talked about the value of case examples, and I think we've heard some things about pharmacogenetics that suggest that a case example, perhaps hypothetical, based on pharmacogenetics might be very useful in following through some of the implications for regulation, in part because a strong case can be made for benefit from this kind of genetic information.

It seems to me as we do so that we need to be particularly wary of the use of genetic testing in apparently benign circumstances. That has not only implications for prognosis in the treated individual, that may not be of that much concern because the person is being treated, but also has inadvertently or of necessity implications for other family members, and the possibility that you sort of get into a pathway, for a very understandable reason, but actually provide information to a family that actually is unavoidable because the genetic status in one person let's say who is a parent leads to at least a very high likelihood of genetic susceptibility information being known about children. So I think it is very good to keep in mind that immediate potential benefits may be balanced by downstream risks particularly for family members.

But the other concern that this kind of technology, this kind of development of genetic testing creates is the possibility that you, by developing efficient research mechanisms, create a pathway to drug development that leads to drugs being available only with prior genetic testing. That is, you create a situation where, in essence, a practice standard is developed that a person can't get access to a certain drug until they've had the genetic test and we know that they are not a person who is going to have adverse outcomes or we know that they are likely to be a responder. A situation that may come close to creating involuntary testing and certainly is likely to make access to tests and costs of tests higher to the users even though the development of the test was much more efficient.

I don't say any of these things to say that pharmacogenetics research isn't likely to produce great benefits, because my expectation is that it will. But I think these kinds of concerns make it a good case example for us.

DR. McCABE: Yes, Muin?

DR. KHOURY: Can you put up your first overhead where you go down two branches. Just a couple of thoughts. I think the field of pharmacogenomics is going to be the paradigm for disease in general and a couple of things that come to mind right away. We're thinking about drugs that we give to patients.

Now we can also think about drugs that you give to asymptomatic people in order to prevent disease or in order to prevent good things or bad things from happening. I'm thinking of, for example, whether women with Factor 5 Leiden should or should not take oral contraceptives. There is a strong interaction between oral contraceptive use and Factor 5 Leiden which is present in 5 percent of the population. And this is sort of testing asymptomatic people. So you can expand pharmacogenomics beyond people with disease to people without disease. You can try to prevent breast cancer with sort of pharmacologic agents depending on whether you have BRCA1 or you don't have BRCA1, or whether you have a polymorphism in something.

The other thing that comes to mind is, as you move to the left-hand side about disease genetics and you talk about common complex diseases with susceptibility genes, this is the whole field of ecogenetics. Essentially, that arm on the right-hand side is the interactions between genes and environment. Environment on that side essentially is the nonpharmacologic environment; things that we come across, like our diet, and infectious agents, and otherwise.

So the paradigm for pharmacogenomics is much bigger than the drug response. It really touches upon all of disease genetics. And I think when it is all said and done, I think I like what you guys have started thinking through this process because it is going to take a few iterations.

But the bottom line in my mind is that the process for going from research to practice will still be the same. You need to collect data on the analytic validity, the clinical validity, the clinical utility and then share those data, and then there will have to be a systematic review to decide whether all women should be screened for Factor 5 Leiden before they take oral contraceptives. And that involves the ethical issues, plus the cost-benefit analyses, and all these other things.

So I don't think pharmacogenomics will be the exception. Right now it looks like it is the exception. I think it is going to be the rule if you expand it to the left-hand side and you think about asymptomatic people as well that might be taking medications to prevent disease in the future or ameliorate, delay certain diseases from happening. So this might be an important paradigm to think about in the next ten years.

DR. McCABE: Thank you.

Our last comment on this topic from Michele.

DR. LLOYD-PURYEAR: I had to leave the room so I don't know if you mentioned this. But when you were doing your focus groups, did you also do focus groups with manufacturers? Because my concern is if a drug that's developed is only good for 10 percent of the population, will the manufacturers engage in that process of development, because it isn't necessarily financially profitable.

MR. HILLBACK: They did.

DR. LLOYD-PURYEAR: They did.

MR. HILLBACK: They are.

DR. MANASCO: I think the important message is that sometimes you don't find that out until Phase III and

you've already done all the work. And so sometimes what you can do is you can actually take a drug that actually is useful to a subset of patients that would not have gone through approval, and if you can identify those patients, it does become available. And, again, I think what we're seeing is there will be a paradigm shift about how we develop medicines depending on whether we can do it efficiently. So then we don't have to spend $500 million in ten years. The idea is to try to treat as many people as we can and get them better.

DR. McCABE: Thank you very much.

We are now going to move on to a session on genetic discrimination. We are very pleased to have an opportunity today to review a very significant step that took place earlier this month to address concerns about the misuse of genetic information in employment. I'll tell you that I felt that this was an extremely important event, so that when invited to attend I immediately cancelled my schedule for the next two days so I could be present and represent the SACGT formally there on what I believe even more now to have been a historical event.

Francis introduced the President at the signing of the Executive Order. Francis has been a pioneer in raising the consciousness of policymakers in Washington about the concerns people have about genetic discrimination and the potential harms that could result without the establishment of stronger laws and policies. He has been deeply involved in formulating possible policy alternatives.

And in recognition of all of your efforts, Francis, I have asked you to introduce and moderate our session. Thank you very much.

DR. COLLINS: Thank you. I really appreciate the chance to introduce this session and introduce to you the two speakers who are going to be giving you a summary of the current status of some of these important efforts. But I thought I would give you a little background before I introduce Paul Miller. I am not using any slides, so if it could get a little lighter over here I wouldn't be hurt or offended or anything.

While genetic discrimination is not the major mandate of the focus of the SACGT, it is clearly a highly related issue. If we are going to see genetics ushered in in the way that we all hope for where the benefits to the public are maximized and the risks are minimized, we need both to have the effective kind of oversight of the testing process that we around this table are taking on in a very serious way, and we need to provide the kind of protections that the public needs and expects to make sure that genetic information is not used in discriminatory ways, particularly in health insurance and in the workplace.

The Human Genome Project from the outset, as you know, has had the ethical, legal, and social implications of genetics, the ELSI program, as a major part of our agenda. Not to say that these are issues that weren't around before the Genome Project came along, they certainly have been there all along, but the advances and the speed with which genetics is moving into the mainstream makes it ever more important that the Genome Project take some responsibility for getting attention to these issues.

So over the course of the last ten years, with the assistance of a wonderful group of scholars and policymakers and legal experts and social scientists, many of whom are in the room, we have had I think a wonderful set of recommendations of policies that ought to be implemented to try to provide those protections. I think particularly of a wonderful partnership that existed with the National Action Plan on Breast Cancer both to wrestle with questions about genetic discrimination in health insurance and also in the workplace, in both instances leading to workshops and then publications in Science magazine with a very

specific set of recommendations about steps that ought to be taken.

We have seen in the states activity occur in many states now to try to provide protections against genetic discrimination in both health insurance and in the workplace. But I think everybody agrees that if we're going to have a really effective safety net of this sort, there needs to be a national one and not a patchwork that varies depending on what state you happen to live in.

And so it is with great gratification that we see real action occurring on those fronts over the course of the last few years. And I will just mention a couple of those events.

With regards to health insurance, I think the fact that genetics is included in the language that is provided by HIPAA, the Health Insurance Portability and Accountability Act, also referred to as Kassebaum-Kennedy or Kennedy-Kassebaum, depending on which party you have allegiance to. That was a remarkably important step forward because that did say that if you are in a group plan, you may not have your genetic information used to deny you coverage or to charge you a higher premium than the rest of the group. Basically setting the standard that genetic information of a predictive sort ought not to be used to discriminate against you.

We still have work to do in health insurance, however, because there are loopholes there and there is insufficient protections against disclosure. Much effort has been going on in that regard and you will be hearing a bit more about that from Cybele Bjorklund when she arrives, and I'm told she will arrive by the time she's supposed to speak, although she's not in the room quite yet. Because there have been a number of legislative initiatives in the United States Congress to try to deal with the remaining difficulties that still I think are sufficient to cause many people to be fearful of finding out genetic information about themselves because of their concerns that that might be used against them in terms of denying them health care.

In the workplace arena, a number of important things have happened, and particularly, as Ed referred to, very recently here just earlier this month, and I think that is a particular reason to talk about it today. But I have to go back a little bit and say I think the first major real step in dealing with genetic discrimination in the workplace was one that came out of the work of the next speaker, Paul Miller, and a crowd of other folks interested in seeing predictive genetic information taken off the table in hiring practices and promotion practices.

And the EEOC, for which Commissioner Miller serves as one of the leaders, did issue guidance a number of years ago saying that the Americans with Disabilities Act could, and should, be interpreted to say that such predictive information ought not to be used in employment decisionmaking, because if an employer were to do so, they would be basically regarding that person as disabled which is against the statute.

That was a very encouraging step. But I think all of us recognize that that is the kind of guidance which might or might not if it was challenged in a court of law actually stand up to the kind of process that occurs in the courts. I think everybody's conclusion after a subsequent workshop, again with the NAPBC, was that we ought to continue to press for federal legislative proscriptions against such discriminatory uses of genetics in the workplace.

And so it was with a great deal of pleasure that I think many of us gathered, as Ed referred to, on February 8th and watched the President of the United States sign an Executive Order that prohibits Federal

Government agencies from obtaining genetic information from employees or job applicants or from using it in hiring and promotion decisions. That then provided 2.8 million Americans with protection against genetic discrimination in their workplace. A very satisfying outcome.

I might say that Executive Order was endorsed by a number of the groups represented on this committee, including the American Medical Association, the American College of Medical Genetics, the National Society of Genetic Counselor, and the Genetic Alliance, as well as Hadassah. I think that reflects the fact that these groups were already very much tuned in to this issue.

It is perhaps noteworthy that that Executive Order was the very first of the new millennium. How appropriate, wouldn't you say, that as we look towards the future of the next thousand years that the first Executive Order of this millennium is one about genetics, trying to provide the kind of protections that everybody recognizes we really need and deserve but which have not entirely been put into place.

I have to say one of the things that has gotten in the way of getting this done sooner and still it seems stands somewhat in the way of getting federal legislation in place to provide those same workplace protections to the rest of the public who are out there not in the employment of the Federal Government is the difficulty in pointing to the sort of hundreds of thousands of injured parties that the legislative process seems to require before action is taken. And we find that rather discouraging.

In fact, there are plenty of injured parties out there, we know of many of them. Almost universally they are uncomfortable coming forward identifying themselves, having their faces on the television cameras because the likelihood that they're going to get discriminated against even further in the future goes up immediately by that kind of self-revelation. But yet we certainly can cite many such examples that we know about without being able to necessarily produce the thousands of people who are willing to walk up to the camera and talk about it.

And, you know, we shouldn't have to. If there is a point to public policy, it seems to me it ought to be anticipatory. If we are about trying to plan a future of genetically-based preventive medicine, maybe we need genetically-based preventive policymaking as well where we try to put the policies in place before we have the crisis, before we have the injured parties. We can see this train coming down the track and we ought to just get ready for it appropriately and take those steps.

It is gratifying that, in general, one sees a lot of enthusiasm for that in both parties, in both houses, and in the Administration. And certainly by the President himself taking such a personal interest in genetics, as was clear to anybody who was there on February the 8th, this was very much something he was speaking from the heart about. And that is gratifying indeed. But we still have a ways to go to get this actually over the finish line in terms of a bill that both parties will agree to and actually pass and bring to the President for signature.

My hope is that 2000, being that first year of the new millennium, is a golden opportunity to see this momentum sustained and that this Executive Order which we all celebrated will not just be a footnote somewhere but actually the beginning of a very exciting year. That is not at all a done deal. There are lots of other agendas and there are lots of other priorities and people, again without being faced by arguments that we're in a crisis situation, sometimes move on to other issues.

So I think it is highly appropriate for this body to consider this. And we're fortunate to have with us a couple

of very significant experts to do just that. I had not planned during this brief presentation that we would talk much about privacy, although that is also a very important topic in my view, and those of you who have had to listen to me talk about this are probably sick of the analogy. But we really need a couple of pillars to this building, and one of them is called let's prevent discrimination, and the other is called let's protect privacy. And if we could build both those pillars, then we would have a real building. The privacy one is much, much more complicated because almost everybody agrees you can't take your medical record and decide which part is genetics and which part is not genetics. For the discrimination part, I believe, and I think most people do, that there is value in taking the genetic issues, particularly the predictive ones about currently healthy people, and providing specific protections against the misuse of that information, especially because the public is so triggered and concerned about this, as many surveys have shown over and over again, as we've learned in taking the public testimony in preparation for being here today.

So I think it is appropriate that we spend a little time hearing about this. And I would be delighted if this committee would get as engaged as possible in trying to push this agenda along. Recognizing that it is not our central mandate, it is certainly a connected one.

So I would like then after that brief introduction to introduce to you Commissioner Paul Miller, who has been Commissioner of the U.S. Equal Employment Opportunity Commission since 1994 when he was nominated by President Clinton and confirmed by the Senate. Since that, he has been reconfirmed twice. So that he is with us until 2004 at least, and we are very happy about that. As a member, he participates with four other commissioners on all matters that come before the EEOC, including development and approval of enforcement policies, litigation authorization, and issuance of charges of discrimination. He also serves on the Executive Committee of the President's Committee on the Employment of People with Disabilities, and on a task force which is developing a coordinated national policy to raise the employment rate of adults who have disabilities.

Paul is a wonderful spokesperson for the disability community, a wonderful person in terms of making the connections between genetics and public policy that we are all delighted to see happening, the author of many scholarly articles, a brand new father, and a good friend.

Paul, you may have the floor. You may speak from there if you would rather. If you would just hit your button there on that machine.

COMMISSIONER MILLER: Wow. Who would have thunk Reagan would be so high tech. That's my last comment about our good friend Mr. Reagan.

Well thank you very much for this wonderful, wonderful opportunity to discuss with you the President's new Executive Order prohibiting genetic discrimination in federal employment. It is really such an honor to be invited to speak to such an august group of professionals.

Genetic discrimination and privacy issues interest me greatly for both personal as well as professional reasons. Obviously, I have achondroplasia, and as far back from my childhood I can remember Victor McKusick as being my personal doctor. Little did I know at that time that he was such a big shot.

In addition, my younger brother, who is now 37, was recently diagnosed, received the diagnosis as having Li-Fraumeni syndrome, which is a genetic cancer condition. Danny has had ten carcinomas since his first cancer was diagnosed at the age of 14. My mother died of cancer at the age of 54. Her brother and her

parents both died of cancer. In fact, after doing a little bit of research, I was unable to find a single person in my mother's side of the family who died of anything but cancer.

In this past year, around the time that we discovered my wife was pregnant with our first child, we began to explore my family's history of cancer. Advances in genetics and genetic testing made it possible to know a lot of stuff about myself and about the fetus my wife was carrying, about my siblings, and my nieces and nephews. However, I think just as we learned in the Garden of Eden, knowledge has its price. At the time I was working on this genetic privacy and this genetic discrimination issues that led to this Executive Order, I could have not imagined the personal impact that these issues would have on me and my family. It has been a wonderful privilege that this President has given me to have the opportunity to work on these issues that are so personal and that have such an impact on my family.

Incidently, as Francis mentioned, about one month ago yesterday my wife Jennie gave birth to a beautiful and healthy little girl, Naomi.

On February 2nd, as has been mentioned, President Clinton signed the first Executive Order of the 21st century, an order which prohibits the Federal Government from using genetic information in hiring, in promotion, in discharge, and in all other employment decisions. Since the prohibition is contained in an Executive Order and not in congressional legislation, it only applies to applicants to work in the Federal Government, to federal employees, and to former federal employees. As the President stated though at the time he signed the order, "By signing this Executive Order, my goal is to set an example and to pose a challenge for every employer in America because I believe that no employer should ever review your genetic records along with your resume."

The Executive Order is built upon a bedrock principle that applicants and employees must be selected based upon their ability to do the job and not based upon myths or fears or stereotypes about that person due to his or her genetic makeup. As it becomes more possible to learn about our genetic predispositions, or as Francis so eloquently says, our genetic misspellings, we as a society I think face the question of whether employers should be able to consider genetic predisposition information in making employment decisions. And if not, how should we protect such workers from this information.

Under the genetic Executive Order, federal departments and agencies may not refuse to hire, or to promote, or to discharge, or to otherwise discriminate against an employee or former employee with respect to the terms of their compensation, the terms and conditions or privileges of employment as a result of any genetic information. Similarly, the Federal Government departments and employees may not limit or segregate or classify an employee or otherwise adversely affect that employee's status because of their genetic information.

The genetic Executive Order defines protected genetic information, which is really at the crux of the order, it defines genetic information as either (1) information about an individual's genetic tests or the genetic tests of family members, or (2) information about the occurrence of disease, or medical condition, or a disorder in family members of the individual, or (3) information that an individual requested or received genetic services such as genetic counseling. So the prohibition is pretty broad.

There is one narrow exception to these prohibitions in the Executive Order which permits a department or federal agency to request or require a family medical history of an applicant who has received a conditional offer of employment as long as three conditions are met. So as Francis alluded to, genetic information, and

the Executive Order recognizes, genetic information does not simply come in terms of results of genetic tests, but in terms also of family history. And that actually was a very, very tricky issue given the historical context with which family medical history is perceived in this country. Very tricky issue to work through.

So the narrow exception in the order permits the government to request or require family medical history if each of these conditions are met.

One, that the request complies with the Rehabilitation Act, which is a federal statute which prohibits disability discrimination, and I'll come to that statute in a moment.

Two, and this is important, the information is used to determine whether further tests are needed in order to assess whether the individual has a current disease, medical condition, or disorder which may prevent him or her from performing the essential functions of the job. So, in other words, not using the information in any predictive way, but trying to narrow the information so that it is used to figure out whether this person can or cannot perform the essential functions of the job.

And thirdly, the information is not disclosed to persons other than the medical personnel involved in or responsible for determining whether further tests are needed.

The genetic order also does a number of other things, which I'll tick off. One, it prohibits federal employers from requiring or requesting genetic tests as a condition of being hired or receiving benefits. So the government can't say we need to do this genetic test on you before we cover you for insurance or what have you. Two, the order also precludes agencies from requesting or requiring employees to undergo such tests. So they can't make you take a test in order to evaluate your ability to do the job. And three, it bars federal employers from using protected genetic information in order to classify employees that denies advancement opportunities.

Now while utilizing health care information to determine whether someone can perform the essential functions of the job may be appropriate, the Executive Order makes clear that it is inappropriate to make employment decisions based upon one's predisposition for disease, medical condition, or disorder which has no bearing on their ability to do the job. So the concern here is really with forward looking development of disease rather than current existence of disease or disorder. For example, federal employers are not allowed to deny employees promotions to overseas posts based solely on their genetic predisposition for certain illnesses. The genetic order also prohibits the disclosure of this information and mandates that such genetic information be kept confidential and separate from their personnel files, as with all other medical information.

On the same day that the President signed this Executive Order, he also endorsed the Genetic Nondiscrimination in Health Insurance and Employment Act, which has been introduced up on the Hill by Senator Daschle in the Senate and Congresswoman Slaughter in the House. This bill basically would extend the protections for genetic information included in the Executive Order to the private sector. And you will be hearing more about this pending legislation and the likelihood of such legislation in a couple of moments.

Under the Executive Order, the EEOC, my agency, is responsible for coordinating the policy of prohibiting discrimination against employees based upon genetic information. We at the EEOC have long been familiar with this area of the law. While there is no enforcement mechanism within the Executive Order, the

EEOC does have today the authority to process charges involving genetic information under both the Americans with Disabilities Act and the Rehabilitation Act.

And I just want to tag along to what Francis said, one of the sort of mystifying, and maybe it's not so mystifying, issues around genetic information is the fact that there is an utter lack of cases out there of people coming forward and claiming that they have been discriminated on this stuff. I think there are a couple of reasons for that.

Generally, people don't know when they've been discriminated on this basis, and so therefore it is very difficult for them to come forward. Secondly, we're really at the cutting-edge of labor law, of employment law and so many employment lawyers out there are really unaware of how this stuff all works together. As I was coming over, I came over with one of our staff attorneys and he was telling me he ran into somebody who was discriminated on the basis of this information, went to a bunch of plaintiff lawyers and they all said, "Well, we really don't know if there is anything there." And so that's a great frustration for us in the agency at the EEOC who were looking for vehicles within which people can secure their rights.

I recently had a conversation with Dr. McCabe, and I hope this is going to work out, I'm going out to Los Angeles on another trip and hopefully will get together with a bunch of geneticists and talk about ways in which the employment discrimination crowd and the genetics crowd can come together to flush out some of these issues, to see what we can do to work together to identify some of these cases so that people don't fall through the cracks, and that we are able to not only enforce people's rights, but develop the law in an appropriate direction and fashion.

Let me spend just a moment talking about how the genetic Executive Order relates to other laws which may prohibit genetic discrimination. Generally, the Americans with Disabilities Act prohibits disability discrimination in private sector employment. Section 501 of the Rehabilitation Act prohibits disability discrimination against federal workers in the same manner that the ADA protects against in the private sector. So we have got these two rubrics of statutes which prohibit disability discrimination.

Now the issue of genetic discrimination is not explicitly addressed in either the ADA or the Rehabilitation Act. Both statutes define disability very broadly, and neither specifically mentioned coverage of individuals with asymptomatic genetic predispositions to a medical condition. Thus, the law is pretty unclear regarding whether an employer, for example, can refuse to hire somebody with a genetic predisposition to cancer even though that person does not have cancer and may never get cancer in their life.

However, we at the EEOC believe that both statutes prohibit such discrimination. And in 1995, acting a little bit ahead of the curve on this, the EEOC adopted the view that the ADA and the Rehabilitation Act prohibits discrimination against workers based upon an identified by asymptomatic genetic condition. While it is important to note that the EEOC's policy guidance can be used to interpret the law, and in fact can be used as persuasive authority in a case, because it is simply a policy guidance, it does not have the force of a statute, of a piece of legislation.

And as I have mentioned, there has been absolutely no cases on this issue in any of the federal courts around the country. Recently, the U.S. Supreme Court has shed a little bit of light on the matter. While I believe that the Supreme Court's decision in a case called Bragdon held that asymptomatic HIV is an ADA-covered disability, so an asymptomatic condition was an ADA-
protected disability, and I think therefore that case can be seen to support the argument applying the ADA

to asymptomatic folks with genetic predispositions, it is important to note that in that same opinion, in a dissent, Chief Justice Rehnquist, joined by Justices Scalia and Thomas, seemed to indicate that genetic discrimination is not covered by the law. So they went off on their own and said, you know what, regardless what the majority says, we think that this decision has great implications for genetic discrimination and we frankly think that covering genetic discrimination under the ADA is nutty. That's what three of the Justices are on record as saying.

I think, though, that the important point here for non-lawyers to understand is the fact that there may need to be additional and specific policy and law, like the genetic Executive Order, like the proposed legislation up on the Hill, to make explicit the prohibition of discrimination based upon genetic predisposition. And if we have time, I would be more than happy to flesh out and to talk a little bit more about some of these legal arguments at greater length, the legal theories. I didn't want to burden very smart scientists with mundane matters of law.

As I mentioned earlier, the EEOC is responsible for coordinating federal policy prohibiting employment discrimination based upon genetic information. And the EEOC has already prepared a Q&A, questions and answers, regarding the Executive Order that are available on our Web site. So if you go to our Web site, we have already got some information about this Executive Order about how it applies. We had our techno whizzes at the EEOC I guess last year figuring out what our Web site address was going to be and we had a big committee, as we do in the government, and they came up with eeoc.gov.

So if you go to eeoc.gov -- trust me, we had our labor unions involved, everybody was involved in this -- eeoc.gov and point and click, you will find our Q&A on the Executive Order.

The EEOC also envisions issuing further technical guidance to federal departments and agencies explaining the Administration's policy, conducting periodic meetings with government departments and agencies across the line. So we intend both more technical outreach to the Federal Government, and one-on-one interaction with the Federal Government to make sure that they understand workers' rights and their responsibilities. Finally, our Federal Operations Office will be carefully monitoring the charges that we receive in this area to ensure that the policy is being implemented as intended and individuals' rights are being protected in this brave new world.

In closing, let me just say that while we can all agree that advances in genetic research and technology portend tremendous benefits for humankind in medicine and science, I think it is absolutely imperative that there needs to be adequate protections in place to ensure that such technology will not be misused or abused. Thank you.

DR. COLLINS: Paul, thank you very much, and I want to say what a personal pleasure it has been for me and my staff to work with you and your very capable staff at the EEOC, and also to mention how many other wonderful heroes there were in getting this effort to come to pass, particularly our colleagues in the Department of Labor who worked very, very hard to make this happen, a number of other folks in the White House who put huge numbers of hours into trying to get something together which, as you and I know, not every federal agency was in favor of.

COMMISSIONER MILLER: But they are all onboard now.

DR. COLLINS: They are onboard now. They are so onboard it is unbelievable.

So we have learned that Cybele Bjorklund was unable to be with us. But we are fortunate that David Bowen, who I think probably got five minutes notice that this was going to happen, has just joined us, probably out of breath from running across town. David is an AAAS Fellow currently assigned I believe to the Kennedy Office, and he can tell us a bit about what is going on in federal legislative initiatives about genetic discrimination this year.

And maybe after you say a few words, I might also ask Judith Benkendorf, who is here with us, who is a AAAS/ASHG Fellow on the House side, to say a word or two from her perspective about what is going on legislatively. But, David, please go ahead.

DR. BOWEN: Well, it's a great, if unexpected pleasure to be here this afternoon. About thirteen and a half minutes ago I was sitting in a Senate briefing on stem cells. So I'm shifting gears scientifically to come talk about legislation and genetic discrimination.

I thought I would give this talk in the exact reverse order that I usually give scientific talks where I start with an introduction, build slowly to a conclusion that describes the most recent work. But I thought what I would do is describe what happened thirteen minutes ago and sort of work backward to give you the framework.

The reason that Cybele is not here, and Cybele has really worked tirelessly on this effort for a number of years, the reason that she is not here is that there are ongoing negotiations with regard to the Patient's Bill of Rights. As I'm sure many of you know, there are two versions of the Patient's Bill of Rights that have currently been passed, one by the House and one by the Senate, and there is a conference negotiation going on to hammer out some degree of hoped for consensus on this issue.

Why does this matter apart from a general interest in access to care? Why does this matter from the standpoint of genetic discrimination? The answer to that is that the Senate bill contains within it provisions regarding genetic discrimination. We feel that these provisions, while they sound very appealing, are, in reality, not adequate and, indeed, may be to some degree counterproductive to the cause of ensuring full protection against discrimination for all Americans. And the reason that we feel that these provisions are flawed stem from two main reasons.

First, the provisions in the current Senate bill deal only with health insurance providers, that they provide protection against discrimination in health insurance but they do not provide protection against discrimination in employment, nor, and this is really quite crucial, nor do they prevent the disclosure of genetic-related information from a health insurer to an employer. The potential impact of this oversight is really quite profound. An employer, if this bill were to pass in the way it is currently constituted, an employer might reach a situation where he realizes that once he or she offers employment to a person, he cannot then decline to give them health insurance, but he or she can decline to give them employment.

So, just from a cost-saving point of view, it might be very simple to say to someone, to request the information from the health provider, which is legal under the bill, to see that they have some genetic trait that may in some way be related to a genetic disorder, and simply say I'm sorry we're not going to hire you. That would be legal, whereas hiring them and then failing to provide them with health insurance would, of course, be prohibited. So we feel that there is a real, an urgent need for a comprehensive look and a comprehensive legislative structure that deals with both health insurance providers and employers.

To this end, there has been a collaborative effort between our office, Senator Kennedy's office, the offices of Senators Daschle, Dodd, and Harkin which really began in the summer of 1998, thanks in no small part to another AAAS Fellow, Ellen Gadbois, and the staff of these various
offices got together and melded together two previously separate bills, one that dealt with health insurance provisions and one that dealt with employer discrimination, they combined these two efforts into a joint sort of omnibus genetic discrimination bill which has been introduced and for which we very, very strongly need the support of the scientific, the patient, and all other affected communities. And I use that term quite broadly because all other affected communities is really a very large universe of people.

Thanks in large part to the work that Dr. Collins has spearheaded and many of you have participated in, as you all know, we're learning more and more about genetic traits. Eventually, perhaps, this problem will be either even more important than it is today, or one might hope even less important as we decide that we all carry genetic traits that are associated to some degree with a disease. But as more knowledge appears, the need for serious protection becomes more glaring.

I just want to touch on one other issue that we feel is a deficiency in the current bill. And I am actually deliberately skipping over the companion House bill because I know that that will be discussed in a few minutes. But another drawback to the current provisions of the Patient's Bill of Rights are the lack of enforcement measures that can be taken. While it does make it illegal to discriminate in health insurance, the enforcement of this is really incredibly weak. The provisions provide for a fine of one hundred dollars a day, which really provides not much of an incentive nor a real recourse for people who have been discriminated against.

I didn't keep track of the time because I was rushing on, so I might leave a second half of the presentation to Judith to talk about the House provisions and then leave some time, Judith, you reappeared, and then open it up for questions.

DR. COLLINS: That sounds great. Thank you very much, David, for a very lucid presentation of a very complicated situation.

Judith, can we hear from you about what is happening on the House side?

MS. BENKENDORF: Sure. Thank you, Francis.

If you had thirteen minutes, I had about thirteen seconds. So, unfortunately, I did not come prepared to talk about the contents of the legislation.

But let me just go back and say that probably nobody in the House of Representatives has really championed genetic discrimination tirelessly to a greater degree than Louise Slaughter. Representative Slaughter, from Rochester, New York, comes with a background in public health and has drafted several bills through more than one session of Congress hoping to get something through. And, indeed, the Executive Orders are patterned on one of the bills that she has submitted.

That bill has gone to the Commerce Committee, on which I sit, and it has indeed gone to the subcommittee on which I sit, and that is the Health and Environment Subcommittee. There is a minor problem. I work for the Democratic staff; we don't set the agenda. Our compatriots across the aisle set the agenda. We can try

to influence the agenda, but only they can decide when we can have a hearing.

So right after the State of the Union, a number of us decided it was time to write them a letter. We wrote them a very strong letter emphasizing certain things, like President Clinton even recognizes that this is an issue, and if you don't know what your genetic makeup is now, you may have a predisposing gene to something sooner or later and perhaps this legislation will help you, too. P.S., we would like a hearing.

The letter went to the full committee chair, Chairman Bliley, and it also went to the subcommittee chair, Representative Bilirakis. I was last told by one of my compatriots on our majority staff, two floors down, that they will not have a hearing on this until medical privacy is worked out. This leads me to believe that there may be some misunderstanding.

And perhaps there are some things that we can do to put a little heat on them. And one is, nobody says that we can't stop educating. And perhaps what we need to keep doing is planting seeds. They do get mail and they do count their mail. And unlike constituent mail that comes into personal offices, very little mail comes into committee offices, so perhaps what we need to do is start filling up the mailbox of the committee office saying that it is time for a hearing. And we can certainly schedule briefings on the Hill which just are education sessions, we can certainly involve consumers from the Alliance of Genetic Support Groups and get genetics professionals involved. And I will do anything I can to stir the pot. The only thing I can't do, unfortunately, is get you a hearing.

DR. BOWEN: Can I just put in one additional point?

MS. BENKENDORF: Sure.

DR. BOWEN: One additional point that I failed to mention, and it is not specifically related to genetic discrimination, but particularly for this audience, I thought you would be interested that we introduced last session, Senator Kennedy introduced last session a bill to provide increased resources for genetic services in public health departments of state and local public health agencies. This bill passed the Senate and a companion bill is once again in the Commerce Committee that Judith is working on.

But, again, this is an issue that is of importance in really making sure that the fruits of these wonderful genetic discoveries reach the people who need them most. And, again, education of members on the need for these sorts of things is always welcome.

DR. COLLINS: So thank you both for summarizing what I'm sure seems to people who aren't used to it is a very bizarre process. But it is our process and it is the way that things get done sometimes. I think it would be appropriate to have some discussion.

Are we okay on the time, Ed?

DR. McCABE: We have about fifteen minutes for discussion.

DR. COLLINS: Okay. So I encourage the members of the committee to raise issues based upon what you have heard from these speakers.

DR. GUTMAN: Well, could we get an address for an e-mail?

DR. McCABE: One of the things that we were just discussing at this end that I want to remind people of especially on the days that we're here, some of you are federal employees all the time, others of us are federal employees certain parts of our lives, and so that we need to be very cautious of our responsibilities during that period of time. In addition, we need to be cautious beyond the days when we're official federal employees because of the role that we play on this committee.

Now that doesn't mean that we can't talk to colleagues. So, certainly, we can pass around the Web site or whatever. Sarah, I may have misstated this somehow. But I do want us to be careful. Though we can certainly participate in the educational process and all of us have friends. Or maybe I shouldn't speak for myself.

MS. BENKENDORF: I'm telling you, I tell people on the Hill I do genetics and they all talk about genetically-modified foods. That is who comes to visit us, the people with a vested interest in genetically-modified foods. The door is open. You can all visit.

DR. McCABE: I had a couple of things. One is, it took me about ten days after I was here for the Executive Order before the lightening finally struck, and I realized that if the President can sign Executive Orders, that probably governors can as well. And so we have actually started within our Government Relations Office in the State of California -- we do have a law there but it is a law that has to do with health insurance and not as extensive as the presidential order -- so we're doing our background, learning the politics of this within the State of California. But I would also encourage others to look at your own states and what the mechanisms might be, and especially those of you who are involved with patient advocacy groups, you will be much more effective than those of us who are perceived as having some sort of bias because of our professional lives.

But there are between thirty and forty states that have some law about genetic discrimination. I don't think many, if any, are as extensive as the Executive Order. I don't know, do you, through

ELSI, do you have a tabulation of those laws, Francis?

DR. COLLINS: Yes. We keep an extensive tabulation. Barbara Fuller keeps track of it. It is on our Web site. If you go to NHGRI and look under ELSI, you can find an up-to-the-minute tabulation of what states have passed laws on health insurance or employment and even some particulars about what they cover.

They are quite variable in their effectiveness. Some of them are statutes that you would be proud of, and some of them are a little odd.

DR. McCABE: Would it be possible for us to get copies of that before we leave, do you think?

DR. COLLINS: It may be easier to just go to the Web site.

DR. McCABE: Okay. I didn't have my laptop with me.

DR. CHARACHE: What is that site?

DR. COLLINS: Nhgri.nih.gov.

Pat?

MS. BARR: Speaking as a nonpartisan member of this body, which is nonpartisan, it seems to me that genetic privacy and the end of genetic discrimination or forestalling such is really very important and it certainly is what we have heard over and over again in public comment and in public meetings. So I think it is very important that this group make a very clear statement in its beginning preface about how that has implications for our ability to move technology effectively into the society. Without that, we will continue to see either people doing it on the sly, which creates all kinds of liability problems for their doctors and incomplete medical records for them, and they need complete medical records to get good care, or we will see just an inability to get services that people need. So I think as a public body trying to address this issue in a full way, we need to be very clear and strong on that.

COMMISSIONER MILLER: If I could just jump in on that comment. I think that to the extent that you are making a report, and I don't want to state the obvious, but from what we hear, and I'm sure what you hear, too, the impact of these discrimination issues have massive impact on the ability of the science to move forward, of people willing to be tested for their own health benefits. There is a great, great fear out there and there are lots and lots of studies which indicate that. And I think that to the extent that you are listening to folks out in the world and putting your finger in the water and getting a sense of what is going on out there, I think it is fair to say that there is a lot of discussion about this and that, as I understand, is having tremendous impact, not just on people's ability to keep and hold jobs, but also on the advancement of the science in general.

DR. COLLINS: Elliott?

MR. HILLBACK: Yes, I guess my question would be, because I come from Genzyme, a biotech company that has a very large testing lab and we have been dealing with these issues forever, with people concerned about having tests done, I can't figure out who is against the anti-discrimination sort of issues. The Executive Order the President signed seems to me to be so logical and I don't know who is the opposition. And even in the case of health insurance, because in employment it seems rather straightforward, I would hope that even the health insurance companies aren't against that. But I'm curious, who is the opposition here? Who is against it? My question is, who is fighting this in the world?

COMMISSIONER MILLER: Well, if I can just make a comment. I think that, as oftentimes is in the case of policy, the opposition doesn't really step up to the plate and say here we are, here's who we are. And I think we have been seeing a little bit of that in the past couple of weeks in the news.

But I think that the discussion around employment discrimination is in some ways a little more subtle. It is very hard to flush people out to say, gee whiz, discrimination on the basis of genetic predisposition is really a good idea. Though there are people out there, and I'll give you an example of that, that will say that. Generally, what the argument is is will we think that that's generally a good principle, but we don't think that Congress intended the ADA or the Rehabilitation Act to be that law. So even though that is the only law that is out there, even though there are all these theories for why it applies, we are arguing around the parameters of the law.

The second piece is, and I hear this oftentimes from employers because I talk about this issue with employers, and it is very interesting because employers will come and tell me or management lawyers will

come and tell me, well Miller that's all very good and interesting, but employers don't want this information because as soon as we know this information we are presumed to have used it for nefarious purposes. And so therefore there are a number of management attorneys that say, hey, we're on your side. We don't want to know the genetic makeup of our folks. Yet, on the other hand, there are a number of studies out there, most notably the American Management Association did a study, that says, in fact, employers are testing employees for this information. They are out there actively testing. Now what they are doing with the information is anybody's guess.

In the context of some policy discussions, I think it is fair that some people were somewhat floored when employers said we need to have this information because we don't want to send somebody someplace if they have got the gene for sickle cell anemia, or that we don't want to send them someplace if they have got the gene for cancer because they may drop dead. And so, therefore, we as an employer want to know this. And so a lot of employers, I think because of health insurance reasons or just bad science, are thinking that this is a predictive panacea, that if you get their little DNA code you will be able to self-select who the healthy ones are and who is going to keel over dead on your watch, and make all these judgements.

So there are a lot of people out there I think, and Francis may back me up, that say, hey, this is a great thing. I want to know who is going to get cancer in my company because I don't want to get rid of them before they get it or before their kids come down with something because I don't want them to be on my payroll and eat up my expenses.

MR. HILLBACK: Can I just follow-up on that, Francis, with one quick question. I would like to do, and I'll make the information available, I would like to find out how many, we have one of the largest DNA labs in the world, and I will try to find out how many tests we do or that have ever been done at the request of a corporation. I don't know that we've done them. But I will try to get that data. It would be interesting.

DR. COLLINS: Ed, and then Pat, and then Wylie.

DR. McCABE: I'd just wanted to follow up on Commissioner Miller's comment about it inhibiting research. Because we found very recently that we were having problems, one of our investigators was having problems enrolling individuals into a CRC-sponsored project. And that had to do with the information. The nature of the rules at UCLA is that they sign a consent and that consent, which describes what is being investigated, goes into the patient chart, and there were other records kept that made this a part of the official medical record.

And we are actually looking, and we have been talking to others around the country and others are looking at this as well because they are seeing the same thing, that as the public's awareness of genetic discrimination increases, the public is becoming fairly sophisticated about these issues and are concerned about participation in research that might stigmatize them.

MS. BARR: I just wanted to speak to Elliott's question in a general way. First of all, there are people in the universe of our political system who really are very uncomfortable with adding any kind of new regulation, whether it is pro something or anti something. And so that is a factor in how you address this kind of issue which has to be an affirmative statement. I think that is what Francis was saying, when you don't have people jumping up saying it's a crisis, it's a problem, then why do anything? If it ain't broke, don't fix it. And I think the other large group of people who are concerned, but quietly concerned, are those who are both employers and insurance providers at the same moment, which is an increasingly large number of

corporations in this country who have special protections because of their status and where the lines are not easily drawn, although they tell us they can be easily drawn, in terms of what medical information they have and how they are going to make corporate decisions.

So that there is some sort of natural groups that would have concerns about legislation that would affect them, particularly those who do both, from two different directions.

DR. COLLINS: Wylie?

DR. BURKE: I really want to pose a question to us as a group. And that is, it seems like there is a consensus that we agree that protections such as were implemented in the Executive Order are valuable and will help genetic technology to go forward. The question is, will the oversight or regulatory mechanisms that we propose be different in the absence of those protections? Do we anticipate that they might change if firm protections occurred? I think that is an important question for us to consider because it I think influences how strong a statement we make in this arena.

DR. COLLINS: That's a very thoughtful point, and I think without trying to completely answer it, but clearly it makes a difference what the risks are, whether discrimination is a real and present danger or whether it has been effectively dealt with by legislative prohibitions. So I think the answer has to be, yes.

DR. BURKE: I think I tend to agree. And I think that is because we've certainly heard tremendous concern about discrimination in our public comment. We have therefore in a linked way heard tremendous concern about the needs for privacy and confidentiality. And I think, and this is I think where we need to be really clear, that most of the concern about discrimination comes around the use of genetic information in insurance and employment.

DR. COLLINS: Yes.

Victor, and then Kate, did you have your hand up?

DR. PENCHASZADEH: A case for employment discrimination on the basis of genotypes was put some time ago in terms of actually protecting people with some genotypes that could be vulnerable in some industry, that sort of thing. I think one of the cases that was put forward was around alpha-1-tytrypsine and some genotypes in some industry that would have a pollution environment. And this brought about the controversy of either you clean up your industry or you select your employment force. How would that fare in this context now?

DR. COLLINS: You want to answer that, Paul?

COMMISSIONER MILLER: We talked about that issue. What I think that we at the EEOC and what the genetic Executive Order really is trying to focus on and really is concerned about is using genetic predisposition where it has absolutely no bearing on one's ability to do the job or perform within the workplace. And that is really the focus that we are looking at.

There are some exceptions within the Executive Order so that, and I know that the scientists around the policy table raised this issue and know it far better than I, but, for example, if you are working in some sort of chemical plant and you can figure out that you have got a genetic predisposition, you're missing a gene

that this particular chemical has a particular impact on, then in a sense the genetic Executive Order says, okay, you can figure out that because that gives us information on your current medical status and your ability to do the job.

The thing that I think has everybody really concerned, and where policy is organizing around protections, is that somebody simply has an asymptomatic genetic predispositions; that is, they may or may not ever get that particular condition, and that the employer is using that information in some sort of predictive fashion to say even though you are healthy and able to do the job today, we are not going to hire you or we are going to fire you because we fear you will get sick, or we fear that your kid will get sick, we fear that your insurance will go up. And that is really the fear, not on somebody's inability to do the job.

DR. COLLINS: Ed is giving me the high sign we need to wind this up.

So, Kate, I think you get the last question, even though many hands are up but I'm sorry.

MS. BEARDSLEY: This is a question about insurance discrimination. Generally, when I hear this I hear this about health insurance discrimination and I don't hear about other kinds of insurance discrimination. I wonder if that is because that is somehow different in kind, or because we just haven't got there yet.

DR. COLLINS: Can I say a word about that? We certainly talked a lot about the differences. I think when you come to life insurance the equation is really rather different because the argument about adverse selection coming to bear is much more convincing. That if you know you're at high risk of dying young, you may have a motivation to go out and load up on life insurance. And if the life insurance company is prevented from knowing what you know, that sets up an equation that many people would judge as sort of leading to an unfair outcome. The evidence that that applies to health insurance is very uncompelling. The evidence that it might apply to life insurance is much more compelling.

Just the same, people would argue, and some have, and maybe eventually we will get there the way say the United Kingdom has, where health insurance is less of an issue because they have universal health care, that there ought to be a floor of life insurance available to anybody without any reference to whether you have predictive genetic information. That might be a case that could be made. But to have a complete open opportunity to load up on life insurance without the insurer knowing what you know, most people would view that as a bit of a unstable situation.

Long-term care and disability, also very important issues and ones that, I think because we justifiably have been so concerned about health insurance as the number one priority, have not been wrestled with as deeply as they need to be and probably should be fairly soon.

DR. BOWEN: Just one brief add-on. Hopefully, there will still be copies of this material available. I've prepared some summaries of the relevant legislation, as well as some admittedly anecdotal evidence of insurance discrimination, as well as, something that struck me quite forcefully, the range of editorial opinions expressed by major newspapers that have come out with strong editorials against genetic discrimination, which range all over the country and all over the spectrum. So hopefully those are still available.
DR. COLLINS: Thank you very much.

COMMISSIONER MILLER: Just in case people have further questions, you can feel free to give me a

holler at the office. Folks have my address or you can e-mail me at paul.miller@eeoc.gov.

PARTICIPANT: What was that address again?

COMMISSIONER MILLER: Paul.miller@eeoc.gov. Again, I'm sure a committee thought that up.

MS. BENKENDORF: I'll bring in information in the morning, if you would like to fill up the mail boxes of the majority and try to get us a hearing, I'll bring in the information that you can send to.

DR. COLLINS: So Paul and David and Judith, thank you very much. I think this clearly caught the attention of this group. And I like Pat's suggestion that we make it a very clear part of what this committee puts forward the importance of addressing this issue and trying to urge some action.

MS. BARR: I just wanted to respond to Wylie's statement, because it seems to me that I, certainly, at our previous meetings have talked about the importance of collecting data. In fact, for us to understand what the predisposition genes mean, we have to collect a tremendous amount of data to understand it. And if there aren't protections in place, we simply can't in good conscientious say there should be a governmental system to collect the data. And, therefore, we simply can't get the information to the public and people cannot make good health care choices.

DR. McCABE: Thank you, and thank you to Commissioner Miller, David Bowen, and Judith Benkendorf especially for your on-the-spot comments, and Francis, thank you very much as well.

We're going to move on now. Michele Puryear will now present a summary of the final recommendations of the Task Force on Newborn Screening. The task force, as I mentioned this morning, was organized by the Health Resources and Services Administration and the American Academy of Pediatrics along with support from the NIH and the CDC, among others. I was honored to co-chair the task force with Tom Tonniges of the AAP.

Newborn screening is the only current public health program involving genetic testing. It has been enormously successful. Genetic developments and discoveries in technology are bringing about new opportunities but also new challenges for the state-based programs. Scientific and technological advancements have also highlighted the fact that state programs vary in the kind and number of disorders that they screen for, from only three in some states to well over ten.

This discrepancy in access to genetic testing was recognized by a reporter at one of the TV networks and they ran a story recently on CBS. It was very interesting because she told me she had fought to get this story on for about six to nine months and she had had a hard time getting it through, but it was the task force that allowed her to move forward. The New York Times has also picked up on this theme and anticipates a story in the very near future.

This problem with access has been a problem since newborn screening began but is becoming even more significant because of the pressure to add new tests, which is increasing tremendously. Given the importance and the scope of this type of genetic testing, SACGT will need to stay abreast of the developments in this area.

So, Michele, thank you for bringing us up-to-date on the task force recommendations.

DR. LLOYD-PURYEAR: You've given a large part of my talk.

So lets see if I can get this right, I'm going to first present a snapshot of newborn screening systems because not everybody is familiar with them, then lay out the national -- I'll do both. Okay. And then lay out the national agenda that Ed referred to that was put forth by the Newborn Screening Task Force, and then summarize some of the findings and recommendations, but actually I'm going to focus on the issues of informed consent and some of the research issues with newborn screening.

The handouts that you have are a little bit different than the slides. Your handouts are actually in a lot more detail than what I'm presenting today.

As Ed mentioned, as with genetic testing in general, the area of newborn screening is not a settled area public health policy, but we think an examination of the newborn screening systems is relevant for the Secretary's Advisory Committee on Genetic Testing because many of the issues that are confronting this committee also confront the newborn screening programs in the states.

Again, as Ed talked about, the task force was convened by the American Academy of Pediatrics at the request of my bureau and agency. However, there were other co-sponsors: the Agency for Health Care Research and Quality, Centers for Disease Control and Prevention, NIH, the Alliance of Genetic Support Groups, some state public health organizations, the Association of State and Territorial Health Officials, the Association of Maternal and Child Health Programs, and the Association of Public Health Laboratories.

Ed co-chaired the task force, along with Tom Tonniges of the American Academy of Pediatrics, and we also solicited from other organizations some expertise in the area of genetic science, genetic medicine, public health policy, ethics, and law.

This is what we call a system map of newborn screening. In your handouts, we break it down into sections, but this is just to show how complicated the system is with newborn screening, and actually for tests that are relatively well-accepted and done on a regular basis, the complex relationships that are necessary to arrange between families, between the health care providers, birthing facilities, and public health.

The newborn screening programs, as Ed mentioned or as many of you probably know, are in every state and are located within the public health agencies. States vary in the public health infrastructure around the newborn screening programs.

They vary in how policy is established for newborn screening programs. They vary in laboratory capacity, the techniques used for screening for the same conditions, they vary in the health care delivery systems that they have that are available both for diagnosis and treatment, and they also vary in the scope of services mandated.

Interestingly enough, they also vary in the conditions that are screened for. All state programs do screen for phenylketonuria and congenital hypothyroidism. More than 41 programs screen for sickle cell anemia and almost all screen for galactosemia. Some newborn screening programs include congenital adrenal hyperplasia, homocystenuria, maple syrup urine disease, biotinidase deficiency, and tyrosinemia.

A few states also include cystic fibrosis and additional other metabolic conditions, and some other conditions, such as congenital infections and hearing loss or hearing deficits, are new to the newborn screening programs.

However, with variations in state and political and economic environments, and also public health capacity, state newborn screening programs have not embraced a national model for periodic assessment and nor have they offered it in equal access for all newborns in this country to be screened for a common set of conditions.

So the task force to that end thought that a greater comparability in national standards could address all the inequities, and this is the national agenda that they laid out.

They defined responsibilities for federal and state agencies. They asked for model regulations to help guide states, and the establishment of minimum standards for the state programs.

They also called for model guidelines and protocols for health care professionals and to have designs for systems of care that went from infancy to adult that would fit the national framework for children with special health care needs.

They called for effective tools and strategies to engage the public and families and also demonstration projects to evaluate technology, quality assurance and health outcomes. Most of the recommendations targeted states and state policies.

For the Federal Government, they called for federal agency collaboration of process to advance the task force recommendations. This is one of the processes that was put forth. They called for the presentation of recommendations to the Secretary's Advisory Committee on Genetic Testing.

They called for federal resources to sustain a newborn screening quality assurance program for all the state programs, and they called for my bureau to have demonstration projects to fund improved coordination of infant health programs and also called for funds to help design systems for coordination and integration of program activities, including information services.

I should mention that part of the impetus for the task force report was the states coming to the federal agencies, specifically the CDC and HRSA. However, another impetus came from Congress itself. For my agency, our appropriations language said that we should investigate the use of newborn screening programs to screen for cystic fibrosis and fragile X syndrome. They mentioned those conditions in particular, and that those screening programs be designed or be set upon good public health practice, which was our impetus to engage in this task force process.

For states, they maintained that state public health agencies had a role to play in oversight, assuring access to services and quality services, and here are some of the recommendations they laid out.

And then for professional and public involvement, they wanted to ensure that the state programs both engaged the professional groups, health care professional groups, and also the public, noting again that newborn screening programs were probably one of the many -- well, one of the few programs that actually engaged public health agencies and called for close collaboration with professional groups outside those

agencies and also families, that having that kind of oversight coming from the public was very important.

So although most newborn screening programs have an advisory body, not all of them, probably only half, include the public, the general public, on those advisory bodies in the form of oversight of the newborn screening system.

The committee here has also recognized the importance of access and financing, and the task force also looked at the issue of financing and also suggested several ways to finance that newborn screening system.

Then, finally, the task force indicated a need for adequate public health policy development and infrastructure for surveillance and research activities, recognizing some of the issues that Pat Barr just laid out.

They pointed to the need for an evaluation of new technologies, and similar to the Secretary's Advisory Committee and the Task Force on Genetic Testing, they pointed to a need for the evaluation of screening tests to determine the analytical and clinical ability and utility of tests before they are used in newborn screening programs. To this end, they also pointed to the need for the development and involvement of information systems for the data collection and need for that evaluation and policy development.

Then I thought these next two issues that I'm going to bring up would probably be of particular interest to the Secretary's Advisory Committee. This was the issue of informed consent, and the debate centered around whether or not you needed what some people termed "informal informed consent" for all newborn screening tests versus could you just have a system where the right of refusal was recognized?

Formal informed consent probably would be better characterized as a document of informed consent. Everybody agreed that the conversation between parents needed to occur, whether or not it was documented informed consent or not was not necessary, but the conversation and the education needed to occur to achieve some form or some level of shared decision-making between the health care practitioner and the parent.

Some of the questions that were asked are listed here. Currently, 49 states have specific legislation that requires informed consent -- I mean, requires newborn screening. However, only three states have a process of informed consent. Maryland has a voluntary newborn screening program, Wyoming uses an informed consent model, and Massachusetts recently began using
the informed consent process in a pilot program.

So the consensus was reached that probably most conditions that are tested for within the newborn screening program do not require documented informal informed consent process, but the education needs to take place between the parent and the health care practitioner.

They recommended that this really should begin during the prenatal period and then also be reinforced following the birth. Looking at Maryland as a model, they recognized that informed consent occurring at the time of birth really wasn't adequate and really wasn't occurring, and that those conversations were probably really not taking place.

But they also recognized, just given that, that the right of refusal needs to be adequately enforced and recognized as part of the educational process, and when a parent refused, at that point written

documentation needed to be established. They thought that any conditions or tests that were investigational or developmental, that a documented consent was necessary. At the same time they said that, given this, a state should protect privacy and confidentiality of the results of the newborn screening conditions.

The next debate where consensus was hard to achieve focused around residual samples. In the newborn screening process, for those who aren't familiar with it, heelstick blood sample is taken and placed in most states on a filtered paper. All states store those samples. The time of storage varies from one week to 20 years. So there's quite a bit of variability in that.

Policies either don't exist or vary greatly between states in terms of what you can use them for, how they're stored. I think Alan Guttmacher told me in Vermont they were on his shelf, but it's the same in most states actually. I mean, very few states have written procedures governing either the use or the storage.

Positions that were debated varied from a narrow position calling for a short storage period -- two years -- and informed consent and permission for use of these samples for any reason was required.

Another debate centered around making distinctions between what they called unlinked or anonymous with linked coded identifiers and identifiable, and then criteria laid out for the use of specimens and suggested criteria where, beyond the process of screening, residual blood spots should only be used to benefit the child in particular or help the children, and that in that case, only when they are the optimal source and other samples arenot available.

For the use of unlinked samples or samples with no identifiers, parents should be informed that unlinked samples may be used in the educational materials that were supplied. They could be used for routine quality assurance, and no IRB review would be required. They could also be used for epidemiologic studies, and again no IRB review would be required.

However, with identifiable samples, parental permission and written informed consent for the use of identifiable samples in research would require IRB approval, which is no different than anywhere else. In fact, a lot of these are no different than anywhere else.

There's one more thing. The other point that they made is that states should develop policies, written policies, and involve the public in those written policies, so that, for instance, states -- quite a few states don't have them -- to engage in that process with the public to say what you can use the blood spots for, how long should they be stored, so that there was consensus reached within the state for that, that things wouldn't be so haphazard.

And then last, a task force report is in the process of being reviewed now for publication in Pediatrics. It's being reviewed by the American Board of Pediatrics for acceptance, the stamp of approval by that board, and although not formally endorsed by the co-sponsoring organizations, all co-sponsoring organizations have had a chance for comment.

Our original intent was when this was presented last June in your first meeting, that we would allow and ask for the Secretary's Advisory Committee to also comment formally on the task force recommendations. However, the agenda was too busy in October, and at this point, the task force report is embargoed until publication.

If any of you have questions?

DR. McCABE: Thank you, Michele.

Yes, Ann?

MS. BOLDT: Just a few questions. One is if someone does have the right to refusal, is it all or none? I mean, if they refuse, they refuse all of them or can they pick certain conditions that they would want to be screened for? Like just PKU or just CF.

And also, my other question would be do you take into account existing family history? So if there is no family history of CF, because that could significantly alter the adjusted CF risk.

DR. LLOYD-PURYEAR: Well, I think there are only three states screening for CF, and I think those programs vary, but in some it is -- in Wisconsin -- I don't think they are all universal, actually.

But in general, only three states have informed consent, and it isn't specific to a test at all. You're buying into the whole package, but the right of refusal would depend on the state, and I haven't read all the laws, but it seems logical that you could refuse one.

DR. McCABE: In practice, though -- I'm part of a team that goes out to do site visits on newborn screening programs. We've done about 20, and the right of refusal is blanket. Most states, the statute reads that the refusal will be based on religious conviction, but in fact, functionally, that's not followed. Refusal's permitted for any reason, which is a problem in terms of liability, and it's one of the issues regarding uniform regulations.

Regarding family history and CF, I'm not aware. These are handled -- I mean, basically four million samples come through these various laboratories every year. In Texas, 600,000. The large states, California, Texas, New York, it's huge numbers.

So just keeping the identifying information straight is a major effort, and they have various ways of doing that, but they really don't look at additional family history or anything like these. These are screening tests, so they definitely have false-positive and false-negative rates.

Yes, Pat?

DR. CHARACHE: Just going back to our earlier discussion, I wonder what thoughts have been for the uninsured families. You indicate the infants are checked for insurance coverage.

DR. LLOYD-PURYEAR: That also varies by state, but most state programs the -- well, actually right now, with the new Child Health Insurance Programs, that shouldn't be a problem for that group of uninsured kids. But the fees, the newborn screening fees, are covered by third-party payers, be they Medicaid or insurance programs, or since they're mandated programs, they're covered by the state itself.

Is that what you're asking? I don't think anyone goes away without being screened because they

don't have the ability to pay.

DR. CHARACHE: I guess I'm also thinking of the follow-up care.

DR. LLOYD-PURYEAR: The services? That also varies. I mean, the services vary with or without insurance in terms of what they offer, what they mandate. So that would be dependent upon that system that's been set up by the newborn screening program in the state, and the inequities are there in terms of what state you live in for the kinds of services that are offered for follow-up.

DR. McCABE: Muin?

DR. KHOURY: I just want to make a few comments.

DR. McCABE: Can you turn on your mike, please?

DR. KHOURY: First, the Task Force on Newborn Screening was, I think, based on an event that happened last year, which underscores the need for a lot of input in this field.

I mean, newborn screening is the primary example of public health genetics programs where four million people are tested and, you know, that happens silently every year, and people are not aware of it.

I'm glad to see the recommendations coming to fruition, and this is an area of tremendous partnership between HRSA and CDC in helping the states move together on this. The Division of Birth Defects at CDC has a strong interest in the newborn screening area and so are the labs on all the newborn screening quality assurance programs.

To tie this issue with what this committee is doing really, I think it's very important to use newborn screening as a paradigm or as an example for the kind of oversight or discussions. Although it's a little bit different, it's, for the most part, a mass program, but the processes should not be that different.

We need to apply scientific foundation and scientific basis for what do we test for. Again, the same issues of analytic validity, clinical validity, and clinical utility should be collected before you add newborn screening to the panel, rather than after, and sometimes that area is so blurred.

There is quite a bit of discussion around tandem mass spec right now, whether you can test for 20, 30, 50 conditions. Most of them, there is really no clinical validity. Or clinical utility, for that matter.

So I think having a rigorous process is very important. You need the continuous collection of data that would even collect additional information after tests are in practice and also to evaluate whether these programs are making a difference.

Three years ago, we supported three states to look at the outcomes of newborn screening for sickle cell disease -- California, New York, and Illinois -- and after a couple of years following up the cohort of almost

1,000 children with sickle cell disease in these three states, it became painfully obvious that if you don't do the follow-up on a continuous basis, first you lose the families. You're unable to catch them to find out whether they have good outcomes or bad outcomes.

So it's not only enough to define clinical utility in a controlled clinical trial environment like they found for penicillin reducing the risk of sepsis, but in the real world, sort of clinical effectiveness in the real world.

So coming back to this, the charge to this committee, newborn screening is a paradigm for mass testing, essentially, and as you think about the next wave of the hundreds and hundreds of tests that could be used on a mass basis, perhaps hemochromatosis coming down, maybe not in the newborn period but later on in life, I would think that you have a lot to chew on to think about the kind of processes that you need to move a test from the research phase to the application phase, and the kind of data that you need to use throughout the process.

DR. LLOYD-PURYEAR: And really, actually, this is what the task force really recognized. I mean, most of the people who are in the newborn screening programs really look at newborn screening as not just a test, but have really embraced the idea that it's a whole system.

But the need for integrated systems and information system development, they recognized it was really of utmost importance to get at the kind of data that's needed to really be able to do the kinds of evaluations that are needed or will be needed in the future as you begin to add more tests to those panels.

DR. McCABE: Wylie, I'll let you have the last comment.

DR. BURKE: I just want to say that I think this meeting is very important and informative for us with two important points, the one being the linkage of a delivery system to ongoing research. That is the recognition that there needs to be tight linkage there, and I think what's also important is the sort of working through of different options that resulted in different levels of consent, both for accepting tests and also for what kind of informed consent or IRB review would be required in subsequent research with the newborn spots, depending upon the identification of information. I think those kinds of precedents are extremely important if we're going to achieve the kind of post-market research that we want to see.

DR. McCABE: Thank you, and thank you very much, Michele.

I think that you recognize that the time frame slipped a little further ahead than we had wanted on this. The fact that the conclusion that we reached, as much consensus as we were able to reach, I think, is a tribute to Michele's diplomacy in dealing with the many different factions, and it all comes out looking very nice and clean, but there's been a lot of discussion with people having thought they had agreed on things, and once they saw it in print, realizing that they hadn't really, so that Michele should be congratulated on that as well.

Thank you very much.

DR. LLOYD-PURYEAR: Can I make one family announcement? Besides my husband being here, to make sure that when you wander around outside, not in the front of the building, but sort of in the middle of the building is a sculpture by Martin Puryear.

DR. McCABE: Okay. We are going to take a 15-minute break. We will reconvene at 3:50, 10 of 4:00.

(Recess.)

DR. McCABE: Why don't we go ahead and others will join in, but we need to keep on the schedule.

We're now going to review the public comments on Issue 3, and Issue 3 is what process should be used to collect, evaluate, and disseminate data on single tests or groups of tests in each category?

Who's leading off? Susanne?

DR. HAGA: The general response to the main issue question was that professional committees would be preferred to collect, evaluate, and disseminate data, single tests or groups of tests, and they would be established with the composition of all stakeholders involved in the genetic testing process.

When they answered Subissue 3.1, given that collection of data is an ongoing process, what type of system should be established to collect, evaluate, and disseminate data about analytical validity, clinical validity, and clinical utility of tests, three answers arose.

One, they arose from the discussion that we gave them. They thought it was a multiple choice of four, either status quo, laboratory, government, or consortium, and the consortium was the slight favorite. The other one that was a new one was to establish a centralized database, a registry, clearinghouse, repository. We lumped them all into one, thinking that they meant the same thing. The third choice that was very close in numbers was government agencies. Either the CDC or the FDA should be responsible for data collection, evaluation, and dissemination.

Professional organizations were most in favor of the consortium approach, though, as I said, there was no really clear consensus, and it was just a close call for the first three answers listed here.

The other two responses were existing mechanisms or the peer review system or collection at local levels, meaning institutions or just local community groups, state level.

For Subissue 3.2, how can the system or process for data collection, evaluation, and dissemination be structured in such a way as to protect the privacy and confidentiality of the data that is collected, this was a much more straightforward question and response. Data should be anonymous. It should be stripped. It should be coded. That was the overwhelming response.

We also would like to interject here the answers or responses to the issues of 6.1 and 6.2, which we felt were research oriented, that we won't get to otherwise.

6.1 was a question about is the public willing to share, for research purposes, and make test results and individually identifiable information from their medical records in order to increase the understanding of genetic tests? It also asked does the public feel that this could cause confidentiality problems, and is special informed consent necessary?

The responses to that question were that informed consent should be necessary for individuals participating in genetic research, supplying genetic information, or tissue samples. Confidentiality and privacy were

major concerns for these individuals.

6.2 asked whether genetic test protocols should be reviewed by IRBs. Overwhelming response was that IRBs should review all experimental genetic tests, but there were a number of concerns of whether IRBs could adequately handle the load of genetic test protocols.

There were comments that raised the IG report on IRBs. They raised whether the IRBs had sufficient expertise and whether they had sufficient funds to adequately monitor a genetic test protocol, not just pass review at the very first stage. So there were a number of concerns raised, even though it was very strong response that IRBs should be involved in reviewing genetic test protocols.

That was all I had for Issue 3. Alan?

(No response.)

DR. McCABE: Okay. So we've heard Issue 3 in terms of processes. Why don't we open it up? Well, first, Muin, you've been leading the Department's efforts at data collection and trying to develop a system there, so maybe you can lead off the discussion for us.

DR. KHOURY: I'd be happy to. Thank you, Ed.

Actually, this subject is fairly complex, but let me distill it down to a few sound bites here.

I'm glad to see that the public reaffirmed the idea of data that we've been talking about here. As you know, last year, in collaboration with several HHS agencies, we started a process to explore the feasibility around working groups or consortia that would begin to collect, analyze, and disseminate data around specific conditions, and those consortia, we had two meetings last year, one on cystic fibrosis and one on hemochromatosis, and they had a fairly wide representation from consumers to the epidemiologists and the clinicians and laboratorians, et cetera, and as a result of these two meetings, we are in the midst of these pilot data collection efforts that are going to lead to something by the end of December this year.

I would say the success or failure of these -- I think we've already succeeded in one sense, that people understand the importance of data. They don't understand what it means yet, but they understand that in order to make data usable for policy or health care utilization, it has to be put in a certain framework, that you can compare Study A with Study B, and has to be systematically reviewed and rigorously analyzed. So at least we are there.

The first few steps are going to be around analyzing to see what exists out there, and that's going to be both a fairly elaborate literature review as well as inviting a larger sphere of consortia, members who actually have data in their possession, who may or may not have published the data in the same format that we want it in, but they have existing information, to invite them to be part of that group and see whether or not they'll be willing to share that data, and all the indications have been positive so far.

The interesting thing about hemochromatosis that Francis mentioned this morning is there are really two steps in the data gathering process. First is the original research that is supported by groups, mostly NIH

because that's where most of the research dollars are, and the hemochromatosis is an example of that. Currently, those studies are being done.

There are actually other population-based research of the kind that CDC does support, which we call prevention research, and that's also possible, but then you have to put all of these things together. So there is another layer of research which would be second data analysis, if you will, evaluating what already exists and putting it in some framework.

So that process is ongoing, and I'm really looking forward to see how this may or may not fit in. It's not going to be easy because it's costly to do these things.

On the other hand, I've been thinking about the various layers of data collection from the simple to the most complicated. At the simplest level, you can talk about a passive data collection mechanism in which, through some oversight, be it regulatory or otherwise, test developers are asked or required to submit certain kinds of data, and those can be pulled and put together in some format and analyzed and displayed on our Web site, so that people can make some decisions.

On the other hand, you have a more active data gathering component in which groups, working groups, that know the subject matter can, for selected tests, and it couldn't be too many of those per year because it would be costly, would review more in-depth and analyze existing data, and then at the end of the spectrum, the data is only the first piece because the final piece would be to make the technology assessment and evaluate whether this data is good enough to make some kind of pronouncement. This is sort of the step around the U.S. Preventive Services Task Force in order to move it from here to there and make some recommendations whether a test is appropriate to, you know, reduce morbidity and mortality from Disease X and Y.

So there is this continuum, and the objective, if it can be achieved, would be to know where we are at any given point in time with respect to the morass of genetic tests, know what we know and point out to the gaps in our knowledge base, so that appropriate policies can be made as well as opportunities for further research can be implemented, so that we can move forward.

So I don't have the final deliberations of those two working groups, but work is being done. We're slow to get started because of the holidays, but more will be to come in the next few months.

DR. McCABE: Thank you, Muin.

I'll open it up for discussion now. Elliott?

MR. HILLBACK: Yes. I was lucky enough to be part of the CF group, and I think the concept is great. I think the practice is a good idea. I hope that it works well.

I think one of the fundamental challenges that we really are going to face because we all keep talking about trying to improve the quality of information that we can make available, the fundamental problem is that the lab performing the test, whether it's a home brew or a kit-derived test, doesn't have the capability to follow patients, and so one of the fundamental issues that we are going to have to get to -- and we can argue all we want about how much labs have to do in the early stages to get a test to the point that we feel comfortable

provides enough good information to put out in clinical practice, it's not totally clinically valid, and then we say fine, now we're going to do a Phase IV.

The kind of Phase IV we're talking about is 10,000 patients, 5,000 patients, 100,000 patients. A million patients was a number someone floated around earlier today, and it just isn't going to happen if the onus on doing that is the lab.

So unless we can find a way to do what Muin is talking about or something else similar, the step that we all think is really crucial, which is to get this data and analyze it, isn't really doable, and I think that's one of the things we need to talk about as a group as we think about what we're going to recommend.

DR. McCABE: Pat Barr, then Pat Charache.

MS. BARR: I think the other problem is I was struck by the answer that data should be anonymous, strip identifiers, coded data. That in itself is inconsistent, and if what we want is long-term data collection, then we're going to have to have a coded system, and we have to understand there's some risks of information being shared. And then you have this whole -- you know, what are the consent requirements over time long-term, which really brings us back to our last discussion, that if we want a good data collection system, which would allow less oversight, in a way, we need non-discrimination and legal protections for people, so we can put that system in place in a way that we can feel good about, that we're not putting people at risk.

DR. McCABE: Yes. I think that's a very important point, and you had mentioned before that we needed to get this into the very beginning of the document, and I think the logic puts it there because without that, it is going to be hard to go forward.

Recognizing the political reality, we may have to try and figure out how to begin to do it if we aren't successful in seeing a discrimination bill move forward, and I don't know if any of you saw Trent Lott's response that evening on CNN after the presidential order. They interviewed him, and he was unenthusiastic about this in terms of concept. So I think that it is going to be caught in a difficult political year, so that we need to put it in, we need to make it a very strong
point, but we also need to perhaps begin to do it in the absence of that.

Pat Charache, Judy, and then Michele.

DR. CHARACHE: I had three points. One is the one Pat's already covered, the anonymity issue that this collection of data, which is essential, can only go forward if there's confidentiality.
Second, the issue of who provides the data. I'm going to agree with Elliott. In a way, it's sort of like the reportable diseases, however. The physicians who take care of the patient are required to report an infectious disease, communicable disease.

In truth, it's the laboratories that provide 80 percent of the data because the clinicians don't get around to it, and so I think that in fact the laboratory could provide the information that there was such a case in the name of the clinician without having to even say anything about the patient for follow-up. So you could keep the confidentiality there, but the person who's going to follow the patient and who knows the story would then provide the raw data.

Finally, I think there are really two levels in which we need information, and they may need to be done by

different people. This major data collection, which is going to look at what happens to patients who have this genetic variant, is really in Phase IV. It's the post-market collection of data from many sites. Before that, to know that you can introduce the test, it would probably be much more simple, and it would be the group that wants to market the test that would be
responsible for it. So I'm wondering if we can think of it in these two levels.

DR. KHOURY: May I make just a quick response?

DR. McCABE: Yes. There are a number of people. We'll remember where we were when we get back to you.

MR. HILLBACK: I'm not sure I will.

DR. McCABE: Write it down. Tell your neighbor.

Judy?

DR. LEWIS: If part of what we're going to be doing is sort of looking at patients longitudinally to see how this information affects -- you know, not only are they looking at the tests, I believe we're looking at the outcomes in terms of the patients, and we may also need to look at people who get the information and then choose not to be tested because I think that's an important group of people.

We've been spending a lot of time focusing on what are the sequelae of having tests, and the other question is what is the sequelae of choosing not to be tested? So I think that if we're doing
data collection, that's a group of people we need to pay attention to as well.

DR. McCABE: Michele?

DR. LLOYD-PURYEAR: I'm just thinking that in order to carry this out, we really have to engage the public and actually health care providers far more effectively than we are in terms of getting other than the people here at the table to understand the importance of engaging in the data collection process, and it's similar, I think, in terms of some issues of confidentiality.

My experience is with the immunization registries. In those communities where they sat down with the public early and up front and engaged them in the question of immunization registries, the establishment of them, issues of privacy and confidentiality, while they didn't go away, they could address together at the table, instead of being surprised by the public's reaction to them. So that's my recommendation.

DR. McCABE: Elliott?

MR. HILLBACK: It's quick enough I don't think I forgot. I think just to respond to Pat, the problem issues are not the single gene disorders, where it's pretty straightforward. The issues are going to be the bulk of the tests in the future which are the presymptomatic, predispositional, where you're talking about trying to follow outcomes that might be 10 or 20 years later, and there's no way that a lab has any means of doing that.

I mean, basically, we send off a sample answer to a physician, and that's the end of our involvement, and what happens to that patient when they move, they travel, we have no mechanism, no need, and in fact we

don't want to try and track that patient.

So I don't think that any lab is going to have the wherewithal, and that's why we've debated other approaches, including the CDC with the massive Cray computers that has everybody in them approach.

It's funny, it's laughable, I agree, but I don't know what the alternatives are, and I think that's a fundamental problem we're going to have, and I know Muin's thought about it a lot.

DR. McCABE: Muin?

DR. KHOURY: Thank you.

There are different phases of data and different types of data. If you think at the simplest level of analytic validity, clinical validity, and clinical utility, we're not talking about in fact ELSI issues and costs and other things, but sort of the basic parameters.

Analytical validity usually is within the lab. It's easy, more or less, and there is all the quality assurance proficiency testing around it, and whether people are doing the right thing or not.

Now, when you talk about clinical validity before you market a test, you need to know what's the relationship between this genotype and this disease to be done in a diagnostic setting -- people come in with the disease, like breast cancer -- or it could be done for predictive purposes on healthy people.

Now, a lot of the initial data will come in from research protocols, such as the ones that NIH is funding. So there is this research component that would lead to data.

Now, those types of data can be collected even individually or in aggregate form, you know, keeping the anonymity and the confidentiality. Once we know what the empty table shells should look like for specific diseases and genetic tests, then we go to the producers of these data and say can you fill this group of tables for us?

So it should be as complicated as individual identifiers with all of the variables in it or you're involving what happens to a person after he or she gets tested and what kind of treatment or interventions he receives. So there could be controlled clinical trials, things that aren't pharmacogenomics, other nutritional interventions, whatever.
So there are also ways to collate those data, and we're still talking research here. I mean, we haven't even made an initial cut whether a test is worthy of making it past the threshold.

Now, you get types of data, active data, and then somebody somewhere needs to make a technology assessment to evaluate whether we need to cross a certain threshold, and it doesn't have to be for every single use, but at least for some use, and then there are the post-market trades where a test is used, perhaps appropriately or inappropriately, and then you refine your parameters that you've already defined -- analytic validity, clinical validity, and clinical utility -- in the real world, and then you begin to evaluate these other outcomes and impacts on society and cost, et cetera.

So there is a pre- and post-component, and I think the task of this group, which is not easy, is to oversee how this movement is going to move, because right now the transition is haphazard. It's quick. It's driven by

commercialization, and it's not driven by the scientific foundation of the step by step that needs to happen.

I think newborn screening is a good example of that. It's a mass program, and you would think that there is a scientific process that moves it through the process, but it happens to varying degrees, and when you're talking outside the realm of public health and individual genetic testing, the picture is even more bleak.

So we need that transition of process, and when we talk about data, focus on what kind of data we need at what point in time because it will vary from that point to another.

DR. McCABE: Victor?

DR. PENCHASZADEH: Well, thank you, Muin, because I really was trying to get to that type of sequence, which was kind of anticipated by Pat Charache, also, because it seems to me then that the responsibility of gathering those initial data will be put on essentially the developers of a particular test.

DR. KHOURY: For research.

DR. PENCHASZADEH: Yes, as part of our research. I mean, it has to be a research program. There's no other way.

The difficulty is that if we are talking about predictive testing, it will by definition take much longer time than the tests for confirmatory diagnoses of Mendelian conditions and so forth, but it's very difficult to speed up things when the development of a condition takes years to develop.

Now, what you can do, of course, is to try to -- you know, I think we have to come up with minimum standards of information, first of all, before you even put something beyond the research category.

Now, while it is in the research category, I think it has to follow all the guidelines, IRB research protocols, and so on and so forth that should address, essentially, analytical validity, and certainly have information about clinical validity and utility. What we will have priority to define is what is the minimum set needed for some agency to say okay, this is ready to be marketed for this particular purpose.

But up to that point, who else but the developer of a test or the developers -- I don't know if there are more than one. I mean, if this is coming from wherever it's coming, I think that the onus is on the developer of a test to provide that information. I can't see any other way.

I don't know how your example about CF and hemochromatosis, which is more on a long-term thing, based on a consortium -- this essentially is to look at what happens long-term, but many tests will probably be available on the market if they comply with minimum data required to analyze and to define, albeit in a preliminary way, something about analytic validity, clinical validity, and something about clinical utility.

I don't know, what do you have to say about that, Elliott? I'm sorry to ask you, but you say labs cannot provide that information, but what you meant is the labs that are performing a test that is already marketed, but we're talking about premarketing.

MR. HILLBACK: Let me go back, if I can, Ed, if it's all right. The way I think of this, and I

try to think in my stupid non-scientific terms, so, let me go back, I think that is clearly the lab's responsibility, and this is what Genzyme does today, and I believe it's what every other lab that does home brew, it's their responsibility to develop the test to the point that they believe and their lab director believes that they have information that's useful to patients or to physicians and patients, and back to my favorite phrase, we can tell people what we know, we can tell them what we don't know, but we believe that what we know is enough to help make a decision.

So to get to that point, it's totally the lab's responsibility. That means conducting some sort of a trial, working with a group of physicians, a group of patients, whatever it takes.

At that point, when we believe in the current environment that we have a test that is informative in some way and therefore is worth making available, we start that process. We put the product out. We put the test out, but the problem we've talked about many times here is that at that point in time, we may only have a test that has limited total clinical validity in the true sense of, you know, can we say a hundred percent where it's going to go, and in clinical utility, it may only be something that changes the individual patient's risk by 20 percent, but that 20 percent is useful.

We want to get to the point eventually that we're getting to in some parts of the cystic fibrosis arena but still a long way away there even, where we can be much more specific than that.
But the problem in doing that is you need lots of time and lots of patience, and it's that second phase that we have no capability on our own to follow those patients and to do that.

So we need what Muin is talking about. We need some way to relate to the CF Foundation's treatment centers who are following the patients and are comparing patient outcomes, genotype to phenotype, so that we all will be able to improve the medical care between what the lab can do and what the physician can do with that information if we share our notes, and there's been sort of an artificial gap.

This was sort of an odd conversation at Muin's meeting because here we have the CF Foundation with all their treatment centers, keeps track of the outcomes of all these patients, and Genzyme, who I believe has done by far more genetic tests on cystic fibrosis than anyone else, with all this testing data, and we've never put the two things together in a consolidated way and said, wait, where are all the correlations?

That's what Muin's trying to orchestrate with his exercise, and it's not just us, it's now three states that are doing neonatal screening, et cetera.

So there are different levels and there are different steps, but the problem is this knowledge gap that Muin used in his description, his presentation a couple of meetings ago.

DR. PENCHASZADEH: Can you do a follow-up question? Because there is something that is not clear from what you're saying, because at some point, you say, well, we develop a test. We think it's useful, and we start a process. What do you mean start a process? You spent --

MR. HILLBACK: We offer the test.

DR. PENCHASZADEH: You offer a test?

MR. HILLBACK: Yes.

DR. PENCHASZADEH: You don't start a process. You offer a test without any agency or anyone --

MR. HILLBACK: Under the home brew rules, we have to satisfy CLIA, all the CLIA requirements.

DR. PENCHASZADEH: I know.

MR. HILLBACK: Which means that CLIA can come in to our lab in part of their regular inspection and ask to see all the work we did to justify to ourselves the test and to document the information we're giving out.

DR. PENCHASZADEH: Yes.

MR. HILLBACK: So it's not totally --

DR. PENCHASZADEH: Analytical validity.

MR. HILLBACK: Right.

DR. PENCHASZADEH: Essentially.

MR. HILLBACK: No. It's beyond analytical validity. If our counselors in giving advice says this changes the risk factor for this patient, then we have to be able to say this is how we document it. A lot of it is going to come out of peer-reviewed literature and, you know, comparison. In Huntington's disease, we actually put a lab collaboration together. Barbara Handlon, who was our lab director at the time, got six other labs, and they met for a weekend and started to compare, once the gene was discovered, how we're going to do this.

DR. PENCHASZADEH: I think that one of the tasks that we have in front of us is to see whether if that is sufficient --

MR. HILLBACK: Absolutely.
DR. PENCHASZADEH: -- and then, you know, my take on this approach is not sufficient to offer a test just simply because a lab developed something, and think that, you know, they have some information, and CLIA Council says, well, yes. So that's the point.

MR. HILLBACK: Right. I happen to disagree with you, but that's okay.

DR. PENCHASZADEH: Yes, I suppose.

MR. HILLBACK: Right.

DR. PENCHASZADEH: So you know, we will definitely have to tackle this issue today and tomorrow, I suppose.

MR. HILLBACK: And that's the fundamental principle of home brew.

DR. PENCHASZADEH: Yes, yes.

MR. HILLBACK: And there are lots of tests like that, not just genetic tests, that are done that way.

DR. PENCHASZADEH: Right. Of course, yes.

MR. HILLBACK: Okay. But there is the second stage which is much different, which is closing the gap in the longer term, because it's much broader.

DR. PENCHASZADEH: That's right, yes.

DR. McCABE: Wylie's been waiting for quite some time.

DR. BURKE: But what I want to say, I think, relates to the conversation that's been going on. I think the difficulty we know we all deal with with genetic testing, really you're alluding to it, Elliott, is that we can't have knowledge of everything we would like to know about the clinical validity and clinical utility of tests at the time that they appear to be useful, and so that post-marketing research is crucial, and I think part of the oversight mechanism that we put in place is one that links the ability to bring a test to market with a commitment to participate in the ongoing data collection.

MR. HILLBACK: I don't disagree with anything you've said.

DR. BURKE: Yes, and obviously, your point, I think, is let's not be overly facile about what we can accomplish. So it's not just to say we're going to do the data collection. Let's recognize the barriers, and I think what that really leads to is that collecting the kind of data that we might most like to collect, which would be prospective data on outcome. Therefore identifiable data is collecting data that -- it is the kind of data collection that involves some risks and some costs,
and we need to recognize that, but I think we're also saying it is essential.

What we're saying when we say that is that the risks and costs to society of not collecting that data is substantial and justifies taking -- actually, what we really need to do is in an ad hoc way with each test, figure out exactly what is justified in terms of the risks and cost of data collection, taking into account the loss to society if we didn't collect that data, and I think we just need to be very, you know, very honest with ourselves and with the public about that, which includes, I think, being perhaps more explicit or making an effort to be more explicit than we sometimes have been about how little we know, the limitations of what we know at the time the tests first come to market.

MR. HILLBACK: What we know and what we don't know today is the fundamental phrase.

DR. BURKE: And our plan for closing the gap.

MR. HILLBACK: Yes. I mean, some of us were talking at lunch that the fundamental issue
we have to say is we, at all times, over a hundred-year life of a test, we want to be able to tell people this is what we know today, and this is what we don't know today, and that's a moving target, and fundamentally, our mission on this committee is to figure out, you know, how do we live up to that and make sure everybody lives up to that?

DR. McCABE: Pat?

MS. BARR: Well, all morning and this afternoon, I've been drawing little boxes that probably have some meaning to me and not to anybody else, but it seems to me that let's start with a minimum standard being reached, whether that's Elliott's service model or it's some other review, and let's assume that that review really encompasses not much more than what Elliott's model encompasses, but it might be done by an independent group, and the test is out, and it's got its label or its, you know, description of what it's for and what it can do at that moment.

Then, let's say that this lab really would like to use this test more than that or add to this test in a meaningful way. Is it unreasonable for there to be a laid-out plan, and then I think this is where you get a government and private partnership in funding the necessary research, and that you have this consortium group on the top or there's some sort of review panel that includes the right epi people and the various other groups and says this test is important enough because it's a large enough population, and its meanings to the society over long term is very important, and so this is a test we're going to invest in in that way, and there are going to be other tests of less importance that we will not invest in in that way.

But they get to sell their tests. They get to put their tests out, and everybody is working together to gather the data that's needed, and it might at that point move into CDC's area of responsibility.

I mean, I think the question I'd like to ask, and I'm glad Steve is back now, is, what can the FDA do to make it easy, expedited, and somewhat uniform if we wanted to have an independent review rather than just the lab making the review?

DR. McCABE: Steve, do you want to respond to that?

DR. GUTMAN: Well, I have been at work, just on the telephone. I've obviously missed what probably has been a very rich discussion. As I was actually telling you at lunch, the FDA actually has a variety of tools that it's put into place over the last year or two that allow it to do things in different ways than probably at the time that the original task force was in place, and it certainly has the capability of doing individual reviews.

Those individual reviews have historically been labor-intense, and I have to be honest. I'm an honest man, I believe in truth in labeling, and even with a lighter touch, there are likely to be heavier reviews and probably are on the table now, certainly, heavier reviews than Elliott would like, but that are more data-intensive, and from our resource perspective would need to be confined to a small group of tests, however you might define them as deserving of that attention.

The ASR rule that we put in place that codifies home brews is an example of our ability in fact to establish labeling for classes of tests, and our classification system has in it room to put controls, voluntary controls, mandatory controls, guidelines, to put things into place.

So we have mechanisms for direct review. We have mechanisms for labeling. We have mechanisms for incorporating data requirements, and we have a more malleable system than we're probably generally given credit for that might be used to apply to a variety of end points.

So I think one thing you as a group ought to do is decide what the end points are, decide, you know, what

you want in terms of tests, recognize that we have limited resources, and then challenge not us but us along with CDC and HCFA to see if we can find models that meet the appropriate scrutiny that you think are right for different categories, and we might surprise you and come close.

DR. McCABE: Kate?

MS. BEARDSLEY: No, sir.

DR. McCABE: Okay. Joann?

DR. BOUGHMAN: In this conversation, I actually was seeking, and Victor provided, I think, part of this, a restatement of the charge from the Surgeon General or the Secretary via the Surgeon General with regard to this topic.

I hoped that we got what Wylie said on tape because it was stated extremely well and then clarified, I think, and put into who is already doing what and how could it be done better approach by Pat.

I want to make sure that we are meeting our charge, but I also, as a lowly university vice president, am absolutely overwhelmed by the concept that it would be this group sitting around the table that would have to in fact go beyond where Wylie and Pat took us in their statements about recommendations at this point.

Maybe we do need to define end points as Steve put it, but beyond that, I'm not sure in rereading our questions under Number 3, I think we may have overshot on this about asking what processes and what kind of data and so on with the caveat that we aren't going to go anywhere until the public feels comfortable in allowing us to go forward.

DR. McCABE: Reed?

DR. TUCKSON: Does anybody know on the Cystic Fibrosis Foundation's aggregate capacity to collect that data? What was their reaction? Were they willing to actually do that, and what were the constraints that they put on it?

DR. KHOURY: Yes. Actually, we are actively working with the CF Foundation. We have the data in-house, stripped of identifiers. We're looking to evaluate the impact of early detection in the neonatal period on long-term pulmonary function. Actually, one of the fellows was writing a paper, and it should be coming out soon, and they have data on thousands of kids.

They've begun linking the genetic testing data to it only recently. I mean, it started in the '70s, and they have like 5 or 6,000 kids on that. So they're agreeable to collaboration, and I think they are willing to be an active partner.

DR. TUCKSON: Were they ever asked or do you have any sense of what their reaction would be if you asked them under current legislative conditions to give you something coded or something beyond the anonymous?

DR. KHOURY: Probably they would not like it, but let me just sidestep a little bit further, because, I mean, I haven't asked them, but obviously they might not look at this favorably.

But I want to come back to a fundamental issue here, which I think is relevant to all of this discussion, and let me quote Elliott. We should tell people what we know and what we don't know at any given point in time. If that's an end point that we are shooting for, I think that's doable. You don't need to invest into, you know, millions of dollars to collect the data.

As a matter of fact, and I want to take Genzyme to task on this -- forgive me, Elliott.

MR. HILLBACK: That's okay.

DR. KHOURY: When we did the CF meeting, I had a fellow who actually created the empty table shells of analytic validity, clinical validity, clinical utility, and she laboriously went through the literature and through the Genzyme brochures to try to fill in the tables, and she couldn't.

So Genzyme today is not telling people what we can do and what we know and what we don't know, at least to the extent that my criteria or the criteria of that group that met that day decided it was appropriate. We ended up with empty table shells, and we could only fit parts of the numbers.

So an important end point in this, and I'm not singling out Genzyme, but basically the whole world, including the research community, because if we create the empty table shells, and we give them to people, and they come up with numbers in them, that's what we know and what we don't know at any given point in time.

If the table comes back empty, that's fine. It means that we don't know this information, and that empty table shell can be displayed at this given point in time, saying to the world, we don't know this data. I mean, a group has met and decided this is the important data, and we tried to find it from what we know from the literature, both published and unpublished, and we couldn't find it, and that's part of the truth-telling mission that any test development process has to go through.

So conceptually today, what we know and what we don't know, so that we can try to fill in the gaps as we move forward, and that's an easy exercise to do, believe it or not. It's not that difficult.

DR. McCABE: One thing I'd just like to comment, Reed, and I know you want to follow up, but I think the concept of an end point, I don't think there is, I don't expect in my lifetime, for any genetic disease, for there to be an end point.

I think that it's going to be a series of intermediate points as we continue to gather data, and I think we have to recognize there is. Even for things that we thought we knew the end points on, it's turning out we didn't know them. We don't know them.

Reed?

DR. TUCKSON: Yes. Muin, maybe you can help me, because I don't understand also. Is the CF Foundation unique in that that ability to have that aggregated large-scale data, so we don't have other -- that we can't use that as a model, as it were, and reproduce that?

DR. KHOURY: No. The CF Foundation is a relatively wealthy organization. They sponsor tremendous research and 120 or so CF clinics around the country, and they require that each year, each person with

cystic fibrosis -- there is a data collection instrument that comes back to the foundation. It gets analyzed, and there is a yearly report that comes out in aggregate numbers.

Now, it won't be easy for other things, definitely. I mean, CF is a unique situation. When we tried to do the same with hemochromatosis, we fell flat because there is no such group that takes care of hemochromatosis as a model.

DR. McCABE: But I think that while we can say that CF is a unique model, it's a model that we're going to have to see more often or we're not going to be able to get where we need to be.

The beauty of the CF Foundation is that they sponsor clinics, and they have criteria for those clinics, too. The clinics need to meet standards, so that if you know that you're being seen in a CF Foundation-approved clinic, there are certain amenities and a certain knowledge base of the professionals involved there.

So I think in that sense, while it's relatively unique, it's a very important model that we have to recognize, and I think we're going to need to see it duplicated elsewhere or we're not going to really get the data we need.

We'll come back. I have a long list here. Pat Charache?

DR. CHARACHE: I'm going to comment swiftly on two things. One is the test introduction, and the other is the issue of how to get it out safely with this first step.

When somebody looks at any test, but particularly genetic tests, they will almost always start with somebody who has the disease. So they're going to be sure that that disease is associated with the change that they're looking at.

I think to then look at the kindreds and say that this same change is predictive of disease is where we get to the off-label use and where we particularly need this data collection capacity.

So I think we can know that as things come out, it's going to be worst case and most likely to be true, and then as you extend it to other family members and try to say whether these people will develop disease, you're in a very different world. So I just wanted to get that thought out.

In terms of the test introduction, I think that many here will agree with Victor that the current program is not adequate, that the people who are making these decisions don't necessarily know what to look for and don't have a specific strategy of how to look.

Personally, I think that my own view is that it requires a different upgrading of CLIA and CLIAC, sharp upgrading, different mindset which we're now seeing very positively on the part of the FDA where actually two things can be done.

The framework of the kind of information that needs to be available before you introduce a test is a type of strategy which the FDA has been quite good at drawing up for other types of tests, and that type of thinking and framework could be designed by the FDA for others to critique and to modify as appropriate for a given test, and then, in addition, high-intensity tests, high-risk tests, perhaps should be reviewed according to whatever criteria that will permit the FDA to do it without forming constriction sites because of volumes

that would prevent anything from getting through.

Finally, I think that the consortium concept and certainly the private groups can be critical in doing things like designing the shells and so that those who are developing a test know ahead of time what shells have to be filled in, and elaboration of the FDA test production to meet the data collection needs, and these would be very practical things to do and give a tremendous upgrading of the requirements for introducing a test.

DR. McCABE: Muin, did you have any more comments?

DR. KHOURY: No, I didn't.

DR. McCABE: Michele?

DR. LLOYD-PURYEAR: Actually, I have a question back to Steve, but it sort of adds on to what Pat said, because I know my experience with FDA is only again with immunizations and drugs, but you do have databases for -- it's different. It's for adverse events, and so you do have the mechanism, while a drug or a vaccine is in development and actually also within use, to collect both. You collect clinical data actually and demographic data on those individuals, and you're tied in to the physicians in some way.

So could that also be a model that, during the different stages of development, with a genetic test that you could enforce or not enforce necessarily but ask cooperation with?

DR. GUTMAN: Yes. We actually have two post-market systems that are in place. Neither of them are perfect. I have to be honest with you. There is a system of reporting of adverse events. There was actually a legal change in the early '90s which made it actually mandatory for health care providers to report to the agency, and we have a user-friendly reporting system called MedWatch, which you can fax, you can e-mail, you can phone, you can write.

We can get a ton of data, and sorting through the data is not always easy, and actually the post-marketing reporting system is the subject of one of the reengineering efforts, and if we were to have a role in looking at genetic tests in a way that we haven't before, probably it needs to be considered in the context of reengineering because it's a powerful signal when things are just dreadful, but it misses the subtle changes, I believe, and we also have the ability, certainly with our Class III devices and to a certain extent with Class II devices, to ask for post-market studies and post-market data collection.

That system again, I'm an honest man and believe passionately in truth in labeling, is an imperfect system, that the controls we have to bring about timely closure and reporting and to negotiate the appropriate protocols is frankly less than perfect. Again, that's not a subject of reengineering, but in the context of what we're doing, as long as it was on a limited scale, we could attempt to supplement other activities.

We certainly couldn't solve your problem through either of those two mechanisms. They both are tools that we could put into the game, but those are not comprehensive panaceas. They're tools we could work with.

DR. McCABE: Did you have a follow-up, Michele?

DR. LLOYD-PURYEAR: Well, I realize this is sort of lobbying, but, I mean, if this group could come up

with sort of a concrete mechanism, it certainly would require some resources that probably no federal agency has.

So with the advent of this Kennedy-Slaughter legislation, which only addresses genetic --

DR. McCABE: It's Daschle-Slaughter.

DR. LLOYD-PURYEAR: No. It's Kennedy. I don't mean discrimination.

DR. McCABE: Oh, I'm sorry.

DR. LLOYD-PURYEAR: The genetic services legislation that really is largely going to the states. In order to really deliver genetic services, it needs a knowledge base and a public health infrastructure that we don't have, and it could actually be part of that legislation, if we could be concrete enough at this table.

DR. McCABE: I would remind you that I think Pat mentioned this morning, the tumor registries, and they're very interesting. I wasn't aware until I got involved in some of the IRB issues that that's basically a clinical data collection mechanism that is done blindly to the patients but very powerful in terms of collecting some of these data.

So there are models out there, but we'd have to be very cautious as we got into genetics about the use of those models.

I have Kate, Victor, and then Elliott.

MS. BEARDSLEY: I guess, Elliott and Pat, I wanted to go back to sort of where we began here when Elliott said that the labs couldn't be responsible for post-market data collection, and I can understand that the labs can't, you know, run 10,000-person studies, and they can't run registries, and there are lots of things that they can't do.

On the other hand, it's not clear to me that it's appropriate -- I don't know why it's appropriate for the lab to say, well, it's out of our hands all together. I mean, the lab in theory is making the money off the test, and it seems somewhat reasonable to ask the lab then to contribute back in some way, whether it's doing a study itself or whether it's contributing to, you know, a consortium or something, and maybe I just misunderstood you.

DR. CHARACHE: No. I did say that I thought the laboratory should report that they have a patient who tested positive for whatever it is they were tested positive for, and it can be an encoded form, and they can then provide the name of the clinician who knows the patient and the patient's family, and that would parallel what is done for communicable diseases.

So then they get back in touch with the clinician who knows the clinical status of the patient and follows it, but this is a marvelous way of capturing those families, and it's far more reliable than just expecting the clinician to tell you about it. So I think it is a merger there, but they don't have the clinical data.

DR. McCABE: Elliott, go ahead.

MR. HILLBACK: Thank you.

I mean, I think this is totally unrealistic. Let's be serious. We're talking about virtually every adult onset disease having a genetic component. We're most concerned about presymptomatic and predispositional diseases, and so we're now talking about laboratories at some point doing tests that say there's a mutation in this gene, that various people who are treating patients, not us in the lab because we don't treat patients, various people who are treating patients, various research that's been done looking at this gene, indicate there's a relationship between this gene and this disease, and right now what we take primarily is the information that's available in peer-reviewed papers that says here's the connection, and we try to use that the best way we can.

There's absolutely no way that the laboratory is going to start telling somebody somewhere every patient that tested positive for some mutation of some gene that might be related to adult onset diabetes or adult onset cardiovascular disease and going to start calling all those physicians and saying follow this patient for the next 10 or 15 or 20 years and make sure you tell us. It's just an unreasonable approach, Pat, that you lay out. I'm sorry, but it isn't going to work.

I'm also disappointed that you'd make the comment that the people developing tests don't understand what they're doing, but we'll talk about that some other time.

So I really think that we have to be very careful what we're trying to do here, that we are in a process where it's the entire health care system that's generating this information, and all the laboratory is doing is taking a look at some DNA and saying we've looked at this DNA, here's these changes. Based on what we can see, what we know, this isn't our original research in most cases. This is taking data that other people have helped put together and saying we've tried to collate everything that's there.

That's another problem we have, is that if you take five different labs that are all developing a BRCA1 test, they're all using different data sources for their different papers, different data sources at any point in time to provide the information that we have. So we don't have the follow-up data. We don't have a clinical trial going on in BRCA1.

So you have to understand where the lab sits in all this, and it's really the whole health care system that has to respond, not just the labs, and we're happy to do our part. That's why I've been here for three or four years now on these issues, because we want to be here.

But it's not something the labs could do on their own, if they wanted to, and, you know, I go back to Muin's point. We have not gone to the CF Foundation and said here's all our data, let's compare, but we were very happy to join up, to join this consortium, and I think we committed to pull that data together and to compare it with what the CF Foundation has and to put it in your table, but it's not something the labs could do, and if you put it back on the labs, the whole thing will collapse.

DR. McCABE: Victor, and then Mary, and then Wylie.

DR. PENCHASZADEH: The only thing I wanted to stress is that I don't know who will have to do it, but you cannot put a test in the market if you don't have the proper information to know the validity and utility and you study it in everyone. This pile of papers say the same thing.

So it seems that, however, that some tests have been put in the market without the proper information, and so what we have to see is that we develop a system that prevents that from occurring and that enables, you know, or develops the way in which information, the minimum criteria or the minimum standards for information, before a test is approved to be put on the market.

I mean, you say that we should always say what we know and what we don't know, but there should be someone or some kind of entity based on scientific criteria that states, you know, what is a ratio. I mean, what is a minimum ratio of knowing and not knowing?

MR. HILLBACK: What is the minimum ratio?

DR. PENCHASZADEH: Well, I don't know, but there should be some ratio to make it, you know, to make it either appealable to the public or at least if we are in the business of protecting the public, we should protect the public from things without future or protect, you know, the economy of the country from things --

MR. HILLBACK: We're not in the business of protecting the public.

DR. PENCHASZADEH: Oh, no, no.

MR. HILLBACK: We're developing their health care.

DR. PENCHASZADEH: Well, protecting, yes, the health care of the public, yes. A wrong test or a test that gives you wrong information, you know, is not particularly positive for your health.

MR. HILLBACK: Which tests are you talking about, Victor, when you say there are tests out there that are wrong?
DR. PENCHASZADEH: Well, the tests, the APOe test, when it was launched in the market for prediction of Alzheimer's disease, was wrong.

MR. HILLBACK: Yes. It shouldn't have been used for that purpose.

DR. PENCHASZADEH: That's right.

MR. HILLBACK: That's right. And it stopped.

DR. PENCHASZADEH: Yes. Well, it stopped, you know, after a number of people looked at the data and then decided -- what I'm saying is this should probably have been protected before.

MR. HILLBACK: Yes.

DR. McCABE: Mary, you're next.

MS. DAVIDSON: Speaking of the public, actually I wanted to go back, Reed, to your comment and Muin's, and also pick up on Michele's, because the CF model I think really is an important example to capture here, and while at this point it's really the CF Foundation alone that I know of that has this level of data collection, what we are seeing in some of the support group organizations in terms of research is collection of tissue

samples and tissue registries in order to address the issue of confidentiality and to protect their members and also to control the research that's coming out of this.

Now, again, this doesn't typify all of our organizations, but it is a beginning tool of organizations that are really looking at that capacity, not only to direct their research and protect their members, but also to create and to be a kind of natural community so that as data collection needs progress, and as these groups, you know, their research progresses, that they can continue then to be this natural community that groups like this could approach and really work with them, so that we have the information that we need to be able to understand all these conditions.

So I just wanted to bring that up because I'm not sure to what extent that's really aware outside of the support group community.

DR. McCABE: Wylie?

DR. BURKE: I actually want to respectfully disagree with some of the comments that Elliott made a little while ago, and Mary's comments, I think, are also a good segue into this.

I think we have said here that lab tests are often made available with less information than we would ultimately like to have. In fact, Muin's example about what's known about CF testing makes that point very well, and I think it's a little too facile to say that labs cannot do follow-up data.

I think it's unrealistic for labs to do follow-up data alone. I think it clearly has to be a joint effort, but I think it's very reasonable to take Pat's suggestion and use labs as a very efficient point of contact.

If we say that one of the things that we would like to understand is what happens over time to a group of test-positive individuals, the lab's the best place to identify them. The lab might be the best place to identify a companion sample who had the test and tested negative, and I think that cancer registries do provide a very important model.

What you would be beginning to develop would be a cooperative process in which labs are the point of identification. Labs are probably also an important source of funding because labs, after all, are making money on these tests, and I think it's reasonable to include that in the equation, and then, after that, there is a consortium that undoubtedly has federal and professional and organizational support and undoubtedly has community support, and that consortium develops the mechanism to create the CF database-type entity and to address to what extent some of those may be like cancer registries without formal identification or whether none of them should be because it's genetics.

In other words, whether there is a consent process. But I think the most efficient way to do that is to start with the lab, and I think the lab should be an enthusiastic supporter of this because the lab needs that follow-up data.

MR. HILLBACK: Let me say it a different way. The lab has absolutely no capability to reach out and follow the patient. There's no question that we know whose samples we've tested. If a consortium was set up that said, you know, we will get informed consent from the patient that says we can put their name into this system because I don't think we can make that decision on our own, that we will put their name into the system. I don't think most patients would send us samples anymore if we made that decision on our own.

So our informed consent document, which we do require informed consent for every DNA test we do, if we get that form, and the patient says sure, you can put my name into this system, so that over the next 20 years, my physician will be asked to give feedback to see what happens to me, you know, I don't have a problem with that. That's why we went to meet with Muin on CF, because we thought that was a great idea.

We would clearly be part of that, no question. The problem is that people talk about the lab as if we can do the full follow-up down through the medical system, and we don't have the patient. We don't ever see the patient.

MS. BARR: We don't want you to.

MR. HILLBACK: Okay. But that's the way -- trust me. That's the point that's been made for a long time, is that somehow we should do that.

So I don't have any problem, and I think that there are lots of labs that would be very interested in being part of the system in that way, as long as we have the proper agreement from the patient, one way or another, that that's the way we're going to work.

The consortium -- I mean, what Muin's trying to do is very appealing to us because it gives us better information. We've gone on CF testing from one mutation, now we're, I think, 86 mutations, and we're constantly upgrading the test and upgrading the information we provide, and that is part of our job, to make the tests better this week than it was last week, and that's the lab's job, and we get that information, a lot of it, back from the clinicians who are treating the patients as they write papers or as we work with them directly.
But we can't do it on our own at all. We really don't have the resources.

DR. McCABE: The list I have right now are Kate, Judy Lewis, Pat Charache, Barbara and Reed, and we're going to need to then begin to wrap it up, and if you have other thoughts, we have some time tomorrow to discuss it. So I'd ask you to make notes to yourself because we do want to have time, if there's public comment, at the end.

So Kate?

MS. BEARDSLEY: I just want to make one quick, probably unrelated point to this discussion, and that is that I guess it didn't show up in this set of public comment, but in the hearing, one of the things that we heard, and Judy alluded to it earlier, was that if there's going to be a consortium, the consortium needs to have consumer representation, and I just want to say that in connection with this particular issue, so that it gets down on some list of things we think about.

DR. McCABE: Yes. What I've heard of the consortium is that it would be federal agencies, professional organizations, the public advocacy groups, whatever, and then the private sector in terms of industry, so that I think there are a number of different components to that.

Judy?

DR. LEWIS: I've been sitting listening to this discussion and feeling very troubled as I've been listening to

it because it seems like -- I mean, my sense is that everybody's got their own piece, and that we're getting a hard time of putting it all together, and when I was listening to Elliott talk about the fact that labs develop the tests, and when they think it's ready to be offered, they offer it, and it's a home brew. So therefore, it's subject to some external controls, but not as many, and what I'm looking for is where is the independent piece of analysis that talks about -- and that's the piece that I've been sitting here struggling with, you know, but yet -- I know what people can do, what people can't do, but it's sort of that peer-reviewed standard that's the blind peer-reviewed piece that isn't --

MR. HILLBACK: We have to send out samples.

DR. McCABE: Please turn on your mike, Elliott.

DR. LEWIS: Well, can I--

MR. HILLBACK: Our normal protocol would be, for example, to send out blind samples to somebody else, unless we're the first one doing it, and then we have to do things on our own that way. We get samples from researchers of both positive and negative controls.

So we try to do all the things that one would do, and then we are subject to CLIA coming and saying, yes, you guys did everything you needed to do to launch this test or you didn't.

DR. McCABE: But I think that Judy's point would be that that's not really blind.

DR. LEWIS: But the piece that's missing from this to me is the external person coming in who doesn't have any motive in terms of having a test that's ready to be sold or having patients ready to be served. That independent peer review that happens in science before it says that science is ready to be used, and that's the piece that I've been sitting here struggling with, the fact that at some level -- and I'm not saying it sounds like a turf war, but it certainly sounds like an interest issue, and that's the piece that to me has been missing as the person who really doesn't deal with this on a daily basis because I'm a generalist. I've been missing the piece that tells me, the generalist, that sort of independent peer review, and that's the piece that I think is important in terms of collection and evaluation, is that it needs to be somebody who's not involved with the production, the selling, the marketing --

MR. HILLBACK: But can I come back one second? I mean, remember that I don't think there's any lab that is the leader in a disease research. In other words, the research in Huntington's disease wasn't done in our laboratory. We put a test together based on published genetic correlations that were made, and then us testing against those samples, you know, against that.

DR. LEWIS: But what I'm –

MR. HILLBACK: So it's not as if, you know, we've come up with some new gene. We've discovered it, and we've done everything on our own, and there's no researcher anywhere. We're not out on our own. We're working always with practitioners who are treating patients who made those correlations.

DR. LEWIS: And I'm not disagreeing with you, but these actual responses are sort of illustrating the point I'm trying to make.

MR. HILLBACK: Right.

DR. LEWIS: Which is, you know, you've talked about the fact that you are a leader, and you do more CF testing than anybody in the world. So you know, I'm not saying you've got a corner on the market or not, but if you're developing a new test, if you're a new lab developing a new test, somebody other than that lab needs to be the one who's doing the analysis and is doing it independent with none of any of the motives that we all have.

MR. HILLBACK: And understand that the whole home brew system, whether it's genetic tests or non-genetic tests, doesn't make that assumption, except that all of our records are open to inspection under the CLIA, normal inspections, and that is ex post facto. That's true.

DR. LEWIS: No, I'm understanding that.

MR. HILLBACK: But that is the way the system works.

DR. McCABE: Let's move on. We need to move on.

Pat Charache?

DR. CHARACHE: I'm not going to talk about this right now, other than to say that I do think that it needs upgrading along the lines that we discussed before, not because any one lab is bad, but because there are tests out there that are bad, even from good labs, and there are some bad labs.

But I want to comment on two things. The first is two more thoughts about the cancer model, committee model, that I think are very valuable here. One is that right now, reporting to the cancer committee, the national committee, is a requirement of Joint Committee on Accreditation of Hospitals, JCAHO, hospital organizations, and I think that that's part of its strength, and it has specific components that have to be reported on every patient.

It does have a pathology component. You have to have a tissue diagnosis that goes in with it, and the laboratory diagnosis is the clinical pathology equivalent. So there really is a good model.

And the second thing I'd point out is that these are sent in anonymously. There's coding done, and the code is kept by the institution that sends it, and that is one of the reasons they haven't told the patients.

The institution that sends it is responsible for knowing that code, knowing the patient's name, and knowing when the patient comes back for a clinic visit or whatever the follow-up is.

So I think there's strength there in the structure that they have developed.

The other comment I would have has to do with the orphan diagnosis and the little lab. Not everyone doing lab tests makes money. We don't, and we'd love some of yours, but I think the key problem is with the small labs, in which they may do a single test, they may do two. They know more about that disease than anyone else in the world.

I understand that it may be up to 200 of these models, and in many cases, the investigator who does the tests

loses money on every test they run. They have to interrupt their research because they're no longer interested in patient care. They do it as a service.

So I think that as we come up with a model, this group absolutely demands accuracy because there's no one else to check to see if they've done it right. So they need to have someone looking over their shoulder and giving them a hand, if they haven't done it right, and there are ways of doing this within the institutions in which they work.

But I do think we have to remember that model as we come up with our own.

DR. McCABE: I'm going to ask the next speakers to be brief because we have two of our liaison individuals who wanted to make comments.

So Barbara, Reed, David, and Judy Yost, and if you can keep it real brief, please.

DR. KOENIG: I'll keep it very brief. The first is just a general comment on the topic, and we've heard the issue a key thing is to tell people -- I wrote it down -- what we know and what we don't know at any time, and I agree with that, but I just want to make the point very strongly that that's necessary, but it's not sufficient, and the medical marketplace is a slightly different marketplace than in other kinds of issues in terms of disclosure and choice.

But I want to turn it back and maybe we can talk about this tomorrow, I'll just raise it. I had hoped for more guidance, and maybe I didn't read the public comments as carefully. I was sort of hoping that maybe Susanne and Alan could -- did we really get any concrete guidance from the public on this issue on 3.2, which is really what are the way the public is thinking about the issue of trade-offs between and protection of confidentiality and privacy?

It seemed the way this is written, it sounds like, as someone pointed out, that they're fairly confused. Do they really want all data to be anonymous? Well, that, of course, is completely opposite the whole idea of what we need is perspective data on outcomes, and you can't do that with totally anonymous data.

So it wasn't clear to me, you know. So maybe we can talk about that tomorrow, unless someone has a quick comment about what really is the public saying about this? What do they want?

DR. STOCKDALE: There was one person on the Web site that said that there was a necessity to link the data back to the clinical stuff, but most of the people who were commenting through the Web site didn't really understand that necessity.

DR. McCABE: Reed?

DR. TUCKSON: We can talk about it more tomorrow. I don't want to add any more burdens to the challenge here, but I just do want to make sure that we also are aware, Pat, as you said, the JCAHO is the stick that makes the tumor registry go.

In this system, we would be having managed care health plans and individual physicians having to be the people to send this data forward.

I spent the last two years of my life intensely involved in trying to make outcome measurement systems work. I'll tell you right now, the NCQA is the biggest burden on the part of the managed care organizations, and they are beating them back, you know, with a hatchet to diminish the amount of stuff they've got to report. To think that these folks are going to accept another reporting element -- it will just be trench warfare and revolution in the streets.

Meanwhile, for the individual docs, who are already burdened as well, to think that they're going to have any ability to take -- you know, hardly any of these people have computerized records, have any ability to collect this stuff -- to think that they're going to do it, despite their interest in doing it, is going to be just tough.

So I just wanted to just sort of remind -- just however we respond to the -- I'm not trying to say that, oh, my God, it's all doom and gloom, but I think whether we call for a consortium or whatever we do, our report, I think for it to be credible will have to speak to the notion that we understand the whole health system burden now.

I went a little longer than I wanted, but I just want to get that on the table.

DR. McCABE: Thank you.

David?

DR. LANIER: This follows up with what you were saying, Reed. There's an assumption here that the clinical data must come from clinicians, is that right? Because why couldn't you just go directly to the patients and follow them over time? Surveys are sent out. Why do you have to burden the system?
DR. TUCKSON: By the way, I wanted to say that one of the things that I think we really do need to do is to lay out what is that data, and I've tried to make sure that we're real clear about -- I mean, I think that Muin ought to help us tomorrow with, you know, what were those data shells, and I think maybe that is the answer. I never in my sense assumed that the patients could give you that level of specificity.

DR. LANIER: Well, I think we should look at that because, you know, that would allow them to give you permission each time to get the information when you do it.

MR. HILLBACK: Would you fill it out?

DR. LANIER: Well, if I were going to be tested and agreed to give this information on a yearly basis afterwards, I might send the survey in.

MR. HILLBACK: To the big computer in the sky?

MS. BARR: I just want to answer Elliott for a minute. I think there's a tremendous amount of beneficence in the groups that think they can benefit from this process, and I do believe that it might be a problem in the selectivity of those who answer in the sample, but that in fact there are people who would answer those questions every year.

DR. McCABE: Judy?

MS. YOST: Just two things. Just a reminder from our own document that talks about what CLIA does, that it has not at least heretofore emphasized anything but an intralaboratory review, looking at analytical validity, and so it's important to know that that middle piece is still missing, and it's really important to know, and somebody's got to do it. Somewhere, it's got to be done. This group or somebody has to decide what the threshold is as to when that test can go to market because obviously that utility information is going to come later on.

So you've covered that piece, and we have the finance sort of covered, but we have that interim space, and not every laboratory may have the scruples that maybe Elliott's lab has that says --

MR. HILLBACK: Well, they're all geneticists signing them out.

MS. YOST: -- this is our information. But, boy, we know some folks that would, you know, here's a gene today, and tomorrow, here's a test for it, and so we've got to be able to look at some kind of a mechanism or group or identify how we want to accomplish getting that middle piece done so that test can go to market, and somebody could have some confidence in that information that's provided by that lab.

DR. McCABE: And I don't think that it's only the private laboratories. I live in a university, and we go from the gene to the test very quickly. Most laboratories report where they get positive results.

As people are beginning to report more, we looked at this population, and in this percent, we found a positive result for a mutation. So that people are selective in their reporting in universities and that skews the data set.

So I think it's a general problem, not just a problem with the industry, and we need to recognize that.

DR. KHOURY: Can I say a couple of words?

DR. McCABE: Sure. Just a couple, though, Muin.

DR. KHOURY: I'm done. I am done.

There is a certain mystique about data, and I think, you know, data is not the same thing, and I think Reed challenged me here with an issue that's very important.

I do not think that every single test done on every single individual needs to be reported. I mean, you can do that under the rubric of a research protocol, where, you know, you go into a geographic location or a community or a state or a county and do this in the context of a consortium.

So I mean, this is not like infectious disease reporting. We're not trying to prevent an outbreak of influenza or measles or something. This can be done in a controlled environment, but let me come back to the piece that's easily doable. I mean, relatively easy doable.

The piece that says we can tell people what we know and what we don't know at any given point in time. I believe we can do that today, using rigorous consortium approach with all the representation, scientific methods, creating the empty table shells and go to both published and unpublished literature and see what we know, and if we come back empty, we display that data, and we say it's empty.

I mean, I agree it's not sufficient, but it's necessary, and I think it has to belong to a concerted number of steps that precedes that and follows that. But the data piece does not -- I mean, I don't think people should leave this room with the idea that every single test needs to be reported and linked with all the clinical outcomes. It could be done in only geographic locations.

DR. HUDSON: That's right. It's called sampling.

DR. McCABE: Well, thank you very much for this discussion. We always allow time for public comment, and I just wanted to check to see if there's anyone here who would like to make a public comment.

(No response.)

DR. McCABE: If not, then we will be recessing for the evening. We have a dinner scheduled at 7:00 at Les Halles, which is at 1201 Pennsylvania Avenue. You'd go out the Pennsylvania Avenue exit from the J.W. Marriott, turn left, I'm told, and go one block.

MR. HILLBACK: And we start tomorrow at 8 o'clock?

DR. McCABE: And we start tomorrow at 8 o'clock, yes.

(Whereupon, at 5:20 p.m., the meeting was recessed, to reconvene at 8:00 a.m. on Friday, February 25, 2000.)