# SECRETARY'S ADVISORY COMMITTEE
# ON
# GENETIC TESTING

**FIFTH MEETING**

Monday, June 5, 2000
The Governor's House Hotel
1615 Rhode Island Avenue, N.W.
Washington, DC

IN ATTENDANCE:

Chair

EDWARD R.B. McCABE, M.D., Ph.D.
Professor and Executive Chair
Department of Pediatrics
University of California, Los Angeles
Physician-in-Chief
Mattel Children's Hospital
10833 Le Conte Avenue, 22-412 MDCC
Los Angeles, CA 90095

Members

PATRICIA A. BARR
Partner
Barr, Sternberg, Moss, Lawrence & Silver, P.C.
507 Main Street
North Bennington, VT 05257

KATE C. BEARDSLEY, J.D.
Partner
Buc & Beardsley
919 18th Street, N.W.
Washington, D.C. 20006

ANN HAPP BOLDT, M.S.
Certified Genetic Counselor
Maternal Fetal Medicine and Genetics Center
St. Vincent Hospital Family Life Center
2001 West 86th Street
Indianapolis, IN 46240

JOANN BOUGHMAN, Ph.D.
Vice President for Academic Affairs
Dean of the Graduate School
University of Maryland, Baltimore
520 West Lombard Street
Baltimore, MD 21201

Members (continued)

WYLIE BURKE, M.D., Ph.D.
Associate Professor of Medicine
Department of Medicine Box 357720
Division of Medical Genetics
1959 N.E. Pacific
Seattle, WA 98195

PATRICIA CHARACHE, M.D.
Program Director
Quality Assurance and Outcomes Assessment
Department of Pathology
Johns Hopkins University Hospital
600 North Wolfe Street
Baltimore, MD 21205

MARY E. DAVIDSON, M.S.W.
Executive Director
Alliance of Genetic Support Groups
4301 Connecticut Avenue, N.W., Suite 404
Washington, D.C. 20008

ELLIOTT D. HILLBACK, JR.
Senior Vice President
Corporate Affairs
Genzyme Corporation
One Kendall Square
Cambridge, MA 02139

BARBARA A. KOENIG, Ph.D.
Executive Director
Stanford Center for Biomedical Ethics
Stanford University
701A Welch Road, Suite 1105
Palo Alto, CA 94304

Members (continued)

JUDITH A. LEWIS, Ph.D., R.N.
Associate Professor
Maternal Child Nursing
Director of Information Technology
School of Nursing
Virginia Commonwealth University
1220 East Broad Street
Richmond, VA 23298

VICTOR B. PENCHASZADEH, M.D., M.S.PH.
Professor of Pediatrics
Albert Einstein College of Medicine
Chief, Division of Medical Genetics
Department of Pediatrics
Beth Israel Medical Center
First Avenue at 16th Street
New York, NY 10003

REED V. TUCKSON, M.D.
Senior Vice President
Professional Standards
American Medical Association
515 North State Street
Chicago, IL 60610

Ex Officio Members

Agency for Healthcare Research and Quality

DAVID LANIER, M.D.
(Alternate for JOHN M. EISENBERG, M.D.)
Acting Director
Center for Primary Care Research

Centers for Disease Control and Prevention

MUIN KHOURY, M.D., Ph.D.
(Alternate for JEFFREY P. KOPLAN, M.D., M.P.H.)
Director
Office of Genetics and Disease Prevention

Ex Officios (continued)

Food and Drug Administration

DAVID W. FEIGAL, JR., M.D., M.P.H.
(Alternate for JANE E. HENNEY, M.D.)
Director
Center for Devices and Radiological Health

STEVEN GUTMAN, M.D.

Health Care Financing Administration

JUDITH YOST, M.A., M.T. (ASCP)
(Alternate for NANCY-ANN MIN DePARLE, J.D., M.P.H.)
Office of Clinical Standards and Quality

Health Resources and Services Administration

MICHELE LLOYD-PURYEAR, M.D., Ph.D.
(Alternate for CLAUDE EARL FOX, M.D., M.P.H.)
Chief, Genetic Services Branch
Maternal and Child Health Bureau

National Institutes of Health

FRANCIS COLLINS, M.D., Ph.D.
(Alternate for RUTH KIRSCHSTEIN, M.D.)
Director
National Human Genome Research Institute

KATHY HUDSON, Ph.D.
Assistant to FRANCIS COLLINS, M.D., Ph.D.

Executive Secretary

SARAH CARR
Office of Recombinant DNA Activities
Office of Science Policy
National Institutes of Health
6000 Executive Boulevard, Suite 302
Bethesda, MD 20892

# P R O C E E D I N G S

DR. McCABE: Welcome to the Fifth Meeting of the Secretary's Advisory Committee on Genetic Testing. The public was notified about this meeting through an announcement in the Federal Register on April 19th and a posting on the SACGT's web site. We very much appreciate the public's interest in our work.

We have a very full agenda over the course of the next three days. I am going to take a little time to summarize the major topics and goals. We will be discussing four major issues: one, the adequacy of oversight of genetic tests; two, the education of health care professionals in genetics; three, informed consent for gathering family history information; and four, patents and licensing of genetic tests.

Our first goal will be to complete the work we began last June on assessing the adequacy of oversight for genetic tests. During our meeting of February 24th to 25th, we reached agreement on five major issues, around which our oversight charge was framed, and we outlined preliminary conclusions and recommendations regarding options for oversight of genetic tests. We also decided at that meeting that it would be important to seek further public input on our preliminary conclusions and recommendations.

Following our meeting, we submitted a preliminary report to Dr. Satcher on March 15th of this year, and we notified him of our plans to gather additional public commentary. He accepted the preliminary report, shared it with relevant agencies within DHHS, and agreed that providing an opportunity for further public input on our specific recommendations would be helpful.

On April 19th, we issued a request in the Federal Register for public comments on the preliminary report of our conclusions and recommendations. In keeping with our previous approach, we also posted the report on our web site and sent requests for comment to approximately 400 individuals and organizations who submitted comments during our initial consultation in December and January.

We have received about 60 very thoughtful comments. We will spend time this morning and part of the rest of the day considering the issues raised by the public. We will also review the issues that some of you identified during the drafting of the preliminary report.

In addition to four hours of scheduled discussion time, the agenda today includes a public comment period and presentations from the FDA and CDC.

Dr. Feigal's presentation, which grows out of a question that surfaced as we were putting final touches on the preliminary report, will describe how the FDA considers clinical utility or effectiveness data in its review processes.

Drs. Khoury and Martin will provide updates on public-private partnerships in data collection on genetic tests and genetic testing processes.

We will close the day with brief updates from Drs. Boughman and Charache, liaisons respectively to FDA's Medical Devices Advisory Committee and CDC's Clinical Laboratory Improvement Advisory Committee, on activities within those committees.

We will turn to the oversight issue tomorrow afternoon around 3:30 p.m. In addition to reaching agreement on final conclusions and recommendations, we will also make a concerted effort to prioritize the recommendations we are making. Given that a number of them have significant resource implications, our view of what should be tackled first will clearly be helpful in providing additional advice to Dr. Satcher and Secretary Shalala.

Tomorrow, before returning to the oversight issue, we will have an extensive presentation of some of the issues surrounding the education of health care professionals and a discussion of informed consent of family members when family information is gathered during the development and use of genetic tests. We have also allotted time for public input on each of the issues we will cover tomorrow and Wednesday.

Well-trained professionals play a critical role in the safe and effective use of genetic tests, and the SACGT has identified genetics education of health care providers and the public as a high-priority issue. The education session, which was planned with much input from Dr. Michele Puryear, is intended to provide SACGT with an introduction to some current governmental public-private collaborative and private-sector efforts to enhance genetics education and training of health care providers.

We will have eight presentations, and then during a roundtable discussion, we will have an opportunity to discuss the issues, identify additional information that may need to be gathered, and consider whether or how SACGT might best contribute to addressing the education issue further.

At our meeting in February, we heard briefly about a case involving a genetic epidemiology survey of twins at Virginia Commonwealth University (VCU) which had been cited by the Office for Protection from Research Risks (OPRR) for failing to comply with human subjects regulations. According to OPRR, the investigator and the VCU IRB failed to consider that family members of the twins to be surveyed were also identifiable human subjects whose informed consent needed to be obtained or waived by the IRB. Although the issues raised by the VCU case are broader than genetics and genetic testing, we want to learn more about the implications of the decision for research involving the development and use of genetic tests.

We have invited OPRR, several patient advocacy representatives, and a representative of the genetics research community to help us understand and discuss the issues. They will make presentations, and then we will have a roundtable discussion with the presenters and also an opportunity for public comment. The goal of this session will be to enhance understanding of the decision and its implications for genetic testing.

On Wednesday, we will devote most of the day to an exploration of current issues in gene patents and licensing. The Human Genome Project and rapid developments in diagnostic technologies provide many important new tools for enhancing patient care. As with any rapid technological

change, however, these developments also raise new questions. We have heard concerns from members of the public that gene patenting and licensing practices are having an adverse impact on the cost, accessibility, and quality of genetic tests. We need to learn more about these concerns.

We also need to understand the role that patents play in the commercialization process and how they lead to the development of many beneficial products. Our session on Wednesday pulls together a balanced range of perspectives on the issues. Our presenters will help us learn about how patents and licenses work, how they enhance the public good, and along with understanding the benefits they provide, we will also hear more about the concerns they are raising. We want to come away with an understanding of the issues and a clearer idea of whether further study of the issues is warranted.

After the patent session, we will have another opportunity for public comments. Our last session of the meeting is scheduled for discussion of next steps and/or other issues. SACGT will need to determine the issues it wishes to take up next and sketch out agenda topics for the next meeting.

Now, before we get started on the oversight issue, Sarah Carr, as she customarily does, will review conflicts of interest rules with us.

MS. CARR: Thank you.

There are three rules I actually want to touch on, as I usually do. One is, you cannot lobby while you are here on behalf of the committee. Number two, you have to keep confidential information confidential. Number three, you have to be cognizant of your interests and any conflicts they may bring up.

We reviewed your financial disclosure statements. Most of you have waivers, and you have waivers for general matters, but if there is a specific issue that comes up that could raise a question about whether you have an interest in it and you might not be impartial, you will have to excuse yourself from the deliberation or participating in the discussion and leave the room.

Brenda Farmer, Becky Lawson, and I will be here, and can answer any questions you may have about that.

DR. McCABE: Thank you, Sarah.

Before we start to review the public comments on our preliminary conclusions and recommendations on oversight, I want to take another minute to recap where we are on this issue and how we got here.

As you all know, at our first meeting last June, along with a general charge, Dr. Satcher gave us a specific assignment to assess in consultation with the public the adequacy of oversight of genetic tests. Dr. Satcher further asked that if, based on what we learn from the public and after considering all the issues, we found that further oversight measures were warranted, we were to recommend options for such oversight. He also provided a framework of five central questions

around which we were to organize our analysis.

Dr. Satcher asked us to submit our oversight report to him by March 15, 2000. We worked throughout last summer and fall to develop a proposal for public consultation and a framework for gathering public perspectives. We developed a document called "A Public Consultation on Oversight of Genetic Tests," which provided background information about genetic tests, the provisions for oversight now in place, and the five main issues we were asked to address.

At our second meeting in October, we discussed those plans, reviewed the framework document, and agreed to a multifaceted effort to gather broad public perspectives. This effort included a web site consultation and a public meeting, along with standard outreach approaches.

We carried out the initial consultation during December and January, and by the time we met in February to complete our report, we had the benefit of broad-based input from our public meeting and almost 400 written comments received by a letter, fax, e-mail, and web site consultation.

During our February meeting, we reviewed the public comments, systematically considered the five questions, sketched out answers to these questions, and reached agreement on preliminary conclusions and recommendations. Because we were breaking very new ground with our recommendations, we also decided that we would submit a preliminary report to Dr. Satcher by the March deadline, take more time to flesh out the reasoning behind our recommendations, and solicit public input on them.

We released the preliminary report for public comment in April. In addition to a Federal Register notice, we posted a solicitation on the web site and requested comments from everyone who had commented on the first consultation document.

We have, again, been rewarded for these efforts and have received about 60 very thoughtful comments. You each received copies of these comments along with a summary prepared by Dr. Susanne Haga of the SACGT staff. The comments have been made part of the public record, and copies are on display for the public at the registration desk. Copies of the summary have been made available to the public.

I have asked Dr. Haga to take a few minutes this morning to highlight some of the major issues that have emerged from the public commentary. I believe we will want to focus our discussions on these issues. We will also want to consider the issues that a number of you raised during the final drafting of the preliminary report. These were issues that we felt could not be addressed without further deliberation.

The issues you identified are outlined in a document in your briefing book at Tab 2 of the Topic 1 Oversight tab. As we go along, members are, of course, free to raise other issues.

At this point, let's turn to Dr. Haga for highlights of the issues raised by the public.

DR. HAGA: Thanks.

Just to sum up, there were 58 comments that were received by the office: 15 from the general public, five from patient advocacy groups, eight from academic individuals, seven from genetic counselors, two from health care providers, 10 from professional organizations, nine from industry, one from a state health department, and one from a religious organization.

Of the 15 that were received from the general public, seven were identical. It was a form letter imploring that tandem mass. spect. be used for newborn screening that all states should use, as we saw the same form letter in the comments received from January.

You have a copy of the overview of issues and a copy of the summary of public comments. These are the two documents I am going to be referring to and flipping back and forth as I go through the overview.

First off, there were a number of comments regarding the definition of "genetic test," as stated in the report. Many commenters felt that the definition was too broad and inclusive, that the definition needed more subdivision between various types of genetic tests. The definition does not distinguish between genetic and non-genetic test, and it also does not distinguish between somatic and germline testing.
Some commenters also stated that the definition is not defined in what context the genetic test is being performed in, whether it is in the clinical setting or whether it is in the research setting.

One commenter stated that there was a lack of distinction between presymptomatic and predictive tests, and particularly, the predictive test leads to two recommendations, the FDA review of predictive tests and the informed consent recommendation. So there was a need for a clarification of what exactly predictive test was, is newborn screening included in predictive testing.

One commenter asked is a cholesterol test defined as a genetic test, is it defined as a predictive test, and if so, do the recommendations for FDA review and written informed consent apply to a test such as a cholesterol test.

Moving on to the overarching principles that are in the beginning of the report, most commenters generally agreed with all of the overarching principles. The one exception that did appear was regarding the recommendation of federal legislation prohibiting genetic discrimination. No one was against the recommendation, but many commenters did not distinguish between genetic information and other types of health and medical information, and that all medical information should be protected and that they would not isolate or pull out genetic information for special protections or treatment. Likewise, as carried over to testing, that genetic tests should not be separated from other types of medical laboratory tests and, thus, do not require any additional or special oversight or regulations.

Moving on to Issue 1, which were recommendations regarding the criteria for risk/benefit assessment, most commenters generally agree with the criteria as stated in the report of analytical validity, clinical validity, clinical utility, and social issues. There were some concerns, though, raised about how social issues would be used to evaluate the risk and benefits of genetic tests, that this is a subjective criteria, who would be doing the analysis, this is outside of the FDA's

scope of review.

One commenter stated that the focus for social issues is on the delivery of the service. That includes the test, but it is not the test itself. More focus needs to be on counseling, education, and service delivery to avoid social risk.

Regarding the recommendations in Issue 2 which are on test categorization, there was some confusion about the discussion in the report in Issue 2, that there was no specific recommendation laid out.

Some commenters stated that the discussion in Issue 2 and the criteria listed in the issue, it is not clear how the criteria would be used to differentiate tests into certain categories.

Some suggested adding additional criteria than the ones that we have listed, such as detection rate, false positive rates, rates dependent on what population is being tested, variable expressivity, et cetera. And there was some concern that the dimensions listed in Issue 2 may be oversimplified as stated, that tests cannot be pigeonholed into certain categories which would then be used to determine what level of oversight would be necessary. That tests would have to be evaluated on a test-by-test basis, looking at all of the unique features that are part of that test and then making a determination of what oversight would be necessary for that test.

I wanted to point out in particular the National Society of Genetic Counselors designed an algorithm for determining tests and determining which category they would fall in, whether it would be high risk or low risk, and that is on page 153 of the public comments. They came up with 10 criteria, and they weighted the criteria anywhere from zero to six. They gave some examples of how you could rate a test based on these criteria and come up with a total value. They said that these numbers were arbitrary, but a total value that if it was above a certain number, and 17 was the number they picked, it would be high scrutiny and, thus, would require high oversight. If it was below 17, it would fall into the category of low oversight.

The criteria that they used were type of test, whether it was predictive, presymptomatic, diagnostic, et cetera; prevalence, availability of treatment, locus heterogeneity, detection rate, genotype/phenotype correlations, penetrance, variable expressivity, anticipation, and cost.

Moving on to Issue 3, these were the recommendations regarding data collection. There was general support for these recommendations. There were some suggestions that one agency or a clearinghouse should be established to handle the data collection efforts. Some comments encouraged public accessibility to the data, that the data should be nonproprietary, that it should be available to all, perhaps on an internet site that people could access it. But there were some concerns expressed about the delays and burdens that would be created by requiring data collection efforts such as these on the availability of tests and on academic laboratories.

There were also concerns expressed about the impact of these recommendations on testing for rare diseases; that there were no special considerations allotted for tests for rare diseases and the special circumstances that are associated with them.

Issues 4 and 5, I combined into the category of oversight. First off, this is not a recommendation, but several commenters questioned the rationale of the proposed increased oversight and the consideration of the implications of these recommendations. There were several concerns about the proposed recommendations on the development, availability, and access to tests, and the lack of discussion of these implications in the report.

There were a number of criticisms regarding the justification of singling out genetic tests for additional oversight; that there was no meaningful discussion about the additional regulation of genetic tests; that there was insufficient time for deliberations and public participation; and that consideration of only a subset of public comments were considered in the draft of this report.

Regarding the specific recommendation of FDA review of all new genetic tests, the people that commented on this specific recommendation were divided, but there was a majority that favored FDA as the lead federal agency for reviewing, approving, and labeling of all new genetic tests.

There were concerns raised about the resources and personnel of FDA that would need to be made available to the agency in order for these recommendations to be carried out in a timely and efficient manner.

There are some commenters who stated they felt that existing CLIA and FDA regulations were adequate and were appropriate and sufficient to address the issues regarding genetic tests and that no further regulations were needed.

Regarding the recommendation for expansion of CLIA regulations, there was almost total support for this recommendation with the exception of two groups, CAP and AMP, who are against the recommendation for expanding CLIA regulations.

Regarding the recommendation of IRB review of genetic testing research protocols, there was general support for this recommendation for protocols of genetic tests using individually identifiable subjects or samples, though there were a number of concerns that were raised regarding the ability to implement the recommendation, the ability of IRBs to assess genetic testing protocols, and there was a comment regarding the definition of "identifiable," that that has not been defined in the report and that they would like to see information or subjects that are linked or encrypted to not be included in the definition of "identifiable."

Regarding the specific recommendation of FDA review of predictive tests, there were only a few comments that specifically commented on this, but they generally supported the recommendation.

There were some comments that wished to see pharmacogenetic testing excluded from the recommendations of FDA review. This can go back to narrowing the definition of "genetic tests" in general, that pharmacogenetic testing is different from genetic tests, that not enough consideration or thought has been given to including pharmacogenetic testing in these recommendations, that it would be premature at this stage to include this type of testing for FDA review and additional oversight along with other types of more traditional genetic tests.

Regarding the review of tests currently on the market, there were several concerns raised about this recommendation. There was a suggestion that tests that are on the market that are approved by FDA or have reached a standard-of-care status or level should be exempt from further review and evaluation beyond CLIA requirements.

There were comments that this recommendation is not in the public's interest and adequate discussion of regulatory schemes and oversight mechanisms has not occurred, and there were several suggestions that laboratory representatives from industry should be involved in the review of tests already on the market.

In looking at all of the comments that specifically addressed oversight, which was about half of the 60 comments, subtracting the seven that were identical on the newborn screening, there was a majority of comments that stated that additional oversight was unjustified or unnecessary, were against FDA oversight, supported existing regulations, or supported expanding CLIA regulations, rather than recommending that FDA be lead federal agency for review, approval, and labeling of all new genetic tests.

There were only two additional recommendations in the report. One is on genetic counseling and education, and there was one on written informed consent for predictive tests.

Regrading counseling and education, there was overall support for this recommendation, though some have suggested stronger wording in the recommendation. Right now, it reads "should." Some people would like to see "must."

There were comments regarding the training and competency of those providing genetic counseling and education services, how one would determine the appropriate level of counseling dependent on the type of test. Reimbursement issues have not been addressed. There is no CPT code for genetic counseling services, and counselors stated that they are feeling the effects of downsizing and layoffs. There was also a suggestion to provide discussion of work force requirements and cost issues inherent in the implementation of this recommendation.

Regarding the written informed consent recommendation for predictive testing, there was general support for the recommendation as stated, but several concerns were expressed regarding the extent of the recommendation, and they concur with the committee's recommendation. That they stated that further discussion would be needed, and they wished to participate in these future discussions.

There was also the same suggestion that stronger wording should be used. Right now, it says "should." People would like to see "must," but as I said, most were happy and satisfied with the recommendation as is.

There are a number of miscellaneous issues that did not fall under any of the specific recommendations in the report. One was the role of SACGT. Commenters did not wish to see duplicative efforts. They suggested that SACGT could serve as a coordinating body, not be involved in test-by-test review, but be a special oversight body.

There were some comments regarding regular review of genetic tests in light of the constantly changing nature of information as it affects test performance and test parameters and interpretation of genetic test results.

As I mentioned earlier, many would like to see special considerations for testing for rare diseases. Some commenters were concerned that postmarket data collection efforts would compromise confidentiality and privacy of genetic information. There were some concerns regarding off-label uses of genetic tests, and that the report should be more explicit in discussing this.

One commenter stated that there appears to be an emphasis on clinical utility in the report, which indicates that the committee regards a genetic test as a component of a genetic service, and that a laboratory and evaluation and a clinical trial would be needed.

There were some commenters that would like to see the committee establish what constitutes standard genetic testing for specific conditions, and there were some commenters that stated that access to genetic testing is a general issue and other issues that should be addressed include the cost of testing and follow-up of individuals who test positive.

I can answer any questions. That concludes my part of this.

DR. McCABE: Thank you. Are there questions?

Some of the things that I picked up, one of the big ones, and a lot of people who stopped me in the hallways at various meetings picked up on, the issue of the definition. That was clearly one that we got a lot of comments on.

So I would like to start off with a discussion of the definition.

DR. TUCKSON: Before we launch into that, I am just wondering in terms of the agenda and what we are trying to accomplish by when. Is it your sense that by the 2 o'clock hour that our goal is to resolve all of these issues that are before us, such that they can be incorporated into a final report on this activity, or is there another crack at this? I just do not quite understand the sequence.

DR. McCABE: The goal is to have the bulk of the discussion today, but then as Sarah and I talked about the meeting, I think it is good sometimes to rest and reflect. So we have another 2 hours tomorrow, at the end of tomorrow from 3:30 to 5:30, but by the end of tomorrow's meeting, I am hoping that we have reached the conclusions and can then develop the final document from this point. So that, by the end of this meeting, but according to the schedule, by the end of tomorrow afternoon, we should be in a position to have the document finalized.

DR. TUCKSON: One other thing is that I could not help but notice in some comments, and I do not know whether it was in one set of comments or more than one, but critics are -- I do not mean "critics" in the negative way at all. Let me make sure I extract any pejoratives out of my comment here because I do not mean it. That is why it is important. There were people who were pulling the transcripts to note whether or not there is consensus around the table on various points. That certainly got my attention in the sense that when we make a conclusion on sensitive matters, to

the degree that we can have a consensus noted or reached or achieved, I think it is extremely important. So I just think great care on the part of all of us around the table for the nature of our deliberation and the way in which we come to conclusions is going to be very important for the future.

DR. McCABE: I think that is an important comment, and we do know that people are pulling the transcripts. I think it is very important that we are making the transcripts public, but we may find ourselves quoted, as some of us have, out of those transcripts.

And I would caution also, though, not to be so concerned about that, that it inhibits our discussion. We need to have open discussion recognizing that, if you speak for three days, there may be a word here or there that, if you had a chance to review the transcript, you would have placed elsewhere. But I would caution all of us not to be so concerned about being quoted that we do not have open discussion.

DR. TUCKSON: That is important. What I was more getting to is the nature of the final decision-making on controversial points. Ultimately, in terms of the end point of discussion, which could go on forever, are you trying to drive us to a consensus, or are we going to wind up to a vote? I am looking more at that kind of issue.

DR. McCABE: The way we did it last time was we went to a vote. We will try to achieve consensus where possible, but if it is not possible, we will go to a vote. That is what we have done in the past, and certainly, it is open to discussion in terms of whether or not that is the process individuals wish to continue.

Okay, other general comments like Reed's?

[No response.]

DR. McCABE: Okay. Could we tackle this issue of definition? We have been fairly vague with the definition, and I think that has been identified as an issue before us.

I would point out there are a couple of responses that I saw that got fairly specific in terms of the definition. One was the AAMC response, and the other was the ASHG response. The ASHG is on page 132 under Tab 4, and the AAMC is on page 157 under Tab 4. So, if people could take a look, the ASHG is Item 2. I can just read them if that would be helpful.

The ASHG says, "From our perspective, there are problems with the definition of what exactly constitutes a genetic test that should require additional oversight. We suggest restricting the definition of 'genetic tests' that would require additional oversight to those that tests were a particular nucleotide sequence directly or indirectly. This would include all DNA and RNA testing. Protein truncation and similar tests of expression that are based on DNA or RNA sequence and FISH or equivalent kinds of molecular cytogenetic testing. While many genetic diseases can be diagnosed equally well by looking at a gene product, it appears that tests involving nucleotide sequence are the ones that generate particular concern among non-geneticist health professionals in the public, and it is this concern that justifies additional oversight." That was the

ASHG.

The AAMC suggests that a genetic test could be defined in the following manner: "A genetic test is a test that is performed on presymptomatic individuals to determine the presence of a particular inheritable gene or DNA of established prognostic significance for purposes of genetic counseling or medical management or prospectively on population samples for epidemiological purposes."

There were a couple of comments that suggested that we either needed to broaden or restrict to include metabolites, and we need to consider that as well.

The real issue is have we been thoughtfully vague and do we wish to remain vague as a matter of choice or were we vague by a sin of omission and, therefore, we should consider tightening up that definition. So I would like to hear some discussion.

DR. TUCKSON: First of all, I think it was a sin of omission. I think we should tighten it up. I think it is frustrating to a number of observers, as we've heard.

I thought that the AAMC definition, particularly its distinction between clinical utility and fundamental research purposes, was, I thought, at least an important one for us to discuss, and I thought it was a good dividing line, to be quite frank.

DR. McCABE: I notice just the way the table is set up, those of you especially along this arm of the table will have to basically beat on me for me to see you.

DR. CHARACHE: This was an issue that was discussed very extensively at the CLIAC genetic working group, and there were two key areas of concern. One was whether we should think only of heritable diseases or heritable and acquired that use the same types of technologies and could have significant implications.

The SACGT definition included both heritable and acquired, as did the CLIAC. There was not a difference in emphasis, however, in the second issue, and this had to do with whether we were concerned only with molecular technology, as we have just heard an interest a moment ago, or whether we should consider both molecular and biochemical or non-molecular technologies.

On discussion, we came down strongly on the concept that we should consider non-molecular as well as molecular because of the overwhelming move towards monitoring gene products, largely the assays. So we felt the issues were the same.

We did, however, make a very clear distinction that got rid of the cholesterol testing and this type of thing which was in the objection, and I will just read you what we have down under the biochemical which is in the Notice of Intent which is now out for review. We separated the genetic testing into two definitions, the molecular genetic test, which parallels the SACGT one, and biochemical genetic test, which used mostly the same terminology, but as it reads, it is, "Biochemical genetic tests -- The analysis of human proteins and certain metabolites which is predominantly used to detect inborn errors of metabolism, heritable genotypes, or mutations for clinical purposes. Such purposes would include predicting risk of disease, identifying carriers and

establishing prenatal or clinical diagnoses, or prognoses in individuals, families, or populations," and then we added in brackets, "{Tests that are used primarily for other purposes, but which may contribute to the diagnosing of a genetic disease (e.g., blood smears, certain serum chemistries), would not be covered by this definition.}" So the operative word was it is used "primarily" to detect or diagnose heritable or similar disorders.

DR. McCABE: Thanks, Pat.

I have sort of arbitrarily set a deadline for this discussion of about 10:10 so that we can then try to come to some conclusion. We could probably spend three days on this issue with definitions.

DR. BURKE: I will just say I think Pat's comments are very helpful in resolving what I think was the remaining question with the ASHG definition, and I would support that.

I think it is worth noting that the AAMC request to limit to predictive testing seems to me too restrictive in terms of what we are trying to accomplish.

DR. COLLINS: I would like to also echo what Wylie just said. I think the AAMC's definition is really of a particular subtype of genetic testing, and surely, when you are doing testing for diagnostic purposes in an individual who is already symptomatic using genetic methodology, that is still a genetic test. It sort of would be difficult, I think, for the definition they propose to convey the meaning that you would like for those words.

I liked what Pat had to offer.

I do think we ought to wrestle a little bit with this issue about testing for DNA or RNA or protein changes that are purely somatic in their origin and whether we are intending to apply the same standards to those.

The difficulty, of course, is that many times you do not know when you go looking what you are going to find, and if you are looking for a p53 mutation in a tumor, well, you might uncover somebody who has a germline mutation, who has Li-Fraumeni syndrome, if you are looking for a BRCA1 mutation, et cetera.

But there are some examples, say looking for micro-satellite instability in a colon cancer, for instance, where what you are assessing is extremely unlikely to be a germline phenomenon, and I think the argument could be made that many of the concerns that have caused us to gather around this table all these many months are perhaps less prominent in circumstances where you are extremely unlikely to uncover something that is in the germline.

While I am not sure I would alter the definition of a "test" in that regard, we might consider whether it has implications for the oversight.

DR. McCABE: Thank you.

I would also point out that I identified, just to get the discussion going, a couple of the

commentators, but if you go to Susanne's summary of public comments by specific issue on page 1, there are a number of other organizations and groups that have also commented on this, again, dealing with whether we wish to include germline or not, whether we wish to include metabolites or not.

I think that Francis' comment probably gets to the heart of some of these, and that is that we get to some issue about the difference between the definition of a "genetic test" and the degree of oversight required for that genetic test.

Pat, could you read your definition again for us?

DR. CHARACHE: Yes.

DR. McCABE: This is the CLIAC definition.

DR. CHARACHE: Yes.

MS. CARR: Can I also point out that it is in your blue folder, the Notice of Intent. Right, Pat? That is where it is coming from.

DR. CHARACHE: Yes. I just had an earlier copy. It is the same. Let's find the page.

MS. CARR: In the blue folder, look for the CLIA Notice of Intent of Federal Register Notice. It came to you in a blue folder. You had directions as to where to put everything, but, anyway, we can pass it around. How about that?

DR. McCABE: All right.

DR. CHARACHE: The Notice of Intent, first, has a lot of material that you will know to tell people where it is coming from. This is Section B, which is CLIAC recommendations. The first was that CLIAC suggested the following definitions for the specialty of genetic testing to be adopted.

I did not read you the molecular. I can. It really parallels what this committee has done in slightly different wording. Molecular genetic and also cytogenetic were linked here. That is another issue. Some people would like those separated. "Molecular genetic and cytogenetic test -- An analysis performed on human DNA, RNA, and chromosomes to detect heritable or acquired disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes. Such purposes would include predicting risk of disease, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations."
Then, in biochemical genetic test, "The analysis of human proteins and certain metabolites, which is predominantly used to detect inborn errors of metabolism, heritable genotypes, or mutations for clinical purposes. Such purposes would include predicting risk of disease, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations. Tests that are used primarily for other purposes, but may contribute to diagnosing a genetic disease (e.g., blood smears, certain serum chemistries), would not be covered by this definition."

DR. PURYEAR: When we go to prepare this, can we also have a copy of the definition of a "genetic test" that was put out by the Task Force on Genetic Testing, just to make sure? That was an accepted definition, also. This looks like it is just an expansion of that, but I want to make sure that things were not left out.

DR. CHARACHE: There is one definition, as I recall, that did not include "acquired."

DR. McCABE: Yes. Let me read the task force definition for you. "The analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes. Such purposes include predicting risk of disease, identifying carriers, and establishing prenatal and clinical diagnosis or prognosis. Prenatal, newborn, and carrier screening, as well as testing in high-risk families, are included. Tests for metabolites are covered only when they are undertaken with high probability that an excess or deficiency of the metabolites indicates the presence of heritable mutations in single genes. Tests conducted purely for research are excluded from that definition, as are tests for somatic (as opposed to heritable) mutations, and testing for forensic purposes." So the definition there is somewhat similar, but it is very specific for heritable mutations.

I can pass around what Pat read from the CLIAC recommendations.

DR. TUCKSON: Let me ask Pat. Inherent in the definition that you read, when we come later to Issue 4 regarding oversight, organizations like AAMC and others were concerned, again, about whether or not the definition we would promulgate would carry over to just pure research, research activities.

It seemed as I heard the definition that you read that pure research would not be covered under this definition, but it has to be applied in certain sorts of clinical ways. Am I correct in understanding that?

DR. CHARACHE: This was a CLIAC group. So it is concerned with anything that is used for patient care. So you hit this definition if the results are given to a patient or a patient's family or a health care provider. At that point, it is defined as a patient care test.

DR. BURKE: I had another question for Pat. The ways in which the definition you read diverge from the Task Force definition, were there any deliberate changes? In other words, does your definition reflect any reaction to the Task Force definition, or simply a parallel effort to come to a similar definition?

DR. CHARACHE: It was an effort to be concise and to make very clear the distinction between monitoring somebody's cholesterol and measuring a genetic test.

DR. BURKE: I do think the Task Force is a little bit vague on this assessing both genotype and phenotype.

DR. McCABE: What we are going to do is we are going to have typed up both the CLIAC and the

Task Force definitions and then look at those. So what I would suggest that we do is move on for now and then come back and see if we wish to consider the specifics of either one of these. It sounds like, though we have not had nearly a consensus discussion on this, that there is a bit of a favoring of the CLIAC. Why don't we see and let's get it up before us and really see if it is what we want to include in the final document.

What are some of the other issues that people identified coming out of that discussion?

DR. BURKE: I am not sure if we are ready for this, but certainly an issue that came out as a very sharp point in some commentary was a distinction between pharmacogenetic and other genetic tests. I just wanted to comment that I thought the point was well taken that there has not been the kind of study of implications of genetic testing for pharmacogenetics as there has been for other genetic tests, but I think that is because we really do not have enough examples in front of us yet.

A point that was made in our discussion in February was that a genetic test that is used for the purpose of directing specific drug therapy, that is, to avoid complications, a classic example of what we think of when we say pharmacogenetics, is on the face of it very straightforward, but that the particular tests that might be used for that purpose might, like many genetic tests, provide information additional to the information that is being sought.

My comment here would be that I think the point is well taken that we do not know a lot about what pharmacogenetic tests are going to be like; that we should not a priori exclude them from regulation, but rather recognize that there may be a reason downstream to exclude them when we have more information. In other words, I would recommend that we remain inclusive until we know more.

DR. McCABE: Yes. At this point, I think the definitions that we are considering which talk about DNA and RNA changes and their role in prognosis would include pharmacogenetics.

I think the trap with these, as you also said, that there may be unexpected, unanticipated information and relationships that come out of these, but I think they would be included if we use a definition similar to what we are considering.

DR. CHARACHE: Using the broad definition, the CLIAC group thought was probably a good idea because then you can narrow its oversight implications subsequently in any way that is appropriate. So we wanted to keep a big umbrella and then handle the fact that not everything needs the same type of approach as a later decision.

DR. McCABE: I think an implication here, and an implication in our document, is that there would be ongoing review of our recommendations or any subsequent material that came out of these recommendations.

That really, as I looked back on it and reflected on it, I think it is an implication. We state that there ought to be involvement of the public as well as other individuals and organizations in ongoing review, but we are fairly vague in that and it is more to include the public.
One of the commentators recommended and they were fairly specific about this, that there be a

reconsideration of these recommendations every five years. I think that might be something we would want to put in more specifically rather than by implication. Because remember, this group may not be in existence. We are on a two-year re-up schedule. I think it might be important to include a very specific recommendation that there be review of our recommendations on a periodic basis. Do others agree that that should be put in here?

What is the time frame that individuals would consider? I would think that given the change in knowledge in this field, three to five years is roughly the right time range, but certainly no more than five years.

Muin is holding up four.

DR. CHARACHE: I would think the first one should be in three years because we will not get everything right, and then perhaps five years after that.

DR. McCABE: Yes. I would think a reconsideration in three years might be the way to go because I agree that as careful as we are and as desirous as we are to get everything right, we probably will not.

So would it be appropriate, then, for us to assert a recommendation under the general considerations that there be a reexamination and reevaluation of these recommendations three years from the time of submission.

DR. COLLINS: I am not clear what the implications of that are as far as who does that reconsideration. Is that part of the recommendation?

DR. McCABE: This is a recommendation to the Secretary. Certainly, if this group continued, I think it would be appropriate to have this group. On the other hand, if we were not in existence at that three-year mark, then it would be the party or parties within the federal government that had responsibility at that time.

DR. COLLINS: You would prefer to keep that somewhat vague at the moment, vague in terms of not telling the Secretary what to do.

DR. McCABE: That is a matter of discussion. How specific should we be in this? I think it is the Secretary's decisions as to whether this group continues or not. So I would not wish to bury in our report a recommendation that we automatically be continued beyond one cycle. That is what I was trying to avoid. I think that it ought to be in the report that there be a specific recommendation for review.

DR. TUCKSON: Were there not several recommendations from commentators about a consortium being formed, academic centers? There were other mechanisms that were suggested that will come up later in the discussion which may turn out to be the appropriate place for this three-year review.

One of the things that I am not sure about anymore is the relationship between those other

consortium-type activities and in our group.

DR. McCABE: At the last meeting, we decided and voted, as I recall, on a decision that there had been a discussion of a private-public consortium for consideration of some of the more detailed aspects, and as I recall, we voted that we would be that consortium, that there would not be a separate consortium. Am I recalling correctly?

DR. PENCHASZADEH: In supporting the need for reconsideration after some period of time, in addressing Francis' question, I would not be specific enough in saying which body, but at least the type of composition that that body should have in terms of representatives of government agencies, from academic establishments, from professional organizations, from the industry and so on and so forth.

The other issue is not only the development of technology, but also we are recommending a number of steps that have to include government agencies with a number of provisos we are giving them in terms of increasing resources. This is something that will also have to be monitored, how good our recommendation will be carried out by the government agency that we are advising an action on this. All of that will be required to revisit.

DR. McCABE: So the recommendation, then, would be the group that we are suggesting to reevaluate and reexamine would include representatives of federal agencies, the public, academic health centers, and the private sectors. It sounds like we have described ourselves, though what we are saying is that it should be a broad-based look at this. I think that is important, too. Thank you, Victor.

Okay, there are other considerations that we need to bring up. Another big one that I want to point out –. I am not taking these in any specific order other than my recollection -- was discrimination.

By and large, people supported the concept of our position on genetic discrimination with the exception, and there were a large number of these exceptions, arguing that there is no difference in issues of privacy and confidentiality for general medical information as well as for genetic information.

And a concern that, by our emphasis and the need for legislation regarding genetic discrimination that we were contributing to the stigmatization of genetic discrimination.

I would also remind you that I have written a letter to the Secretary. We felt that this was an important enough issue that we did not want this to drag on, and given the nature of the legislative calendar, we, meaning with me signing the letter, have sent a letter, a strong letter, in support of legislation against genetic discrimination. I think there were enough comments about this issue that we need to have the discussion.

DR. BURKE: It seems to me that it comes at three levels in the comments that we have had. There was, for example, the comment that we should not suggest additional oversight for genetic tests because we are implying that genetic tests are intrinsically different from other kinds of tests, and that is not so; that we should not suggest better or more privacy protections for genetic

information than other medical information because all requires strict protection. Then the third issue was the one specifically about legislation vis-a-vis discrimination.

It seems to me it is very important for us to say that in our oversight recommendations we are responding to our charge, that is, our charge is oversight of genetic tests, and, therefore, we are responding in our view, providing advice about oversight of genetic tests, and not by doing that making any implication about what kind of oversight should occur for other kinds of tests. We are simply responding to our charge.

In terms of the privacy issue, I would certainly support the notion that all medical information is potentially sensitive and requires strict privacy and confidentiality protection. Genetic information is not different in that respect. Our standard should simply be as high as it possibly could be.

On the third issue and, again, I think they are three separate issues, I think we as a group have had discussion that is in common with a lot of discussion going on in the country and clearly around state legislatures around the country, and that is a lot of concern about the potential that genetic information might be used in a discriminatory fashion. And again, that does not imply less concern about other forms of discrimination, but does identify one that is of great public concern.

DR. McCABE: I think that is an important comment, and we probably need to state it explicitly that we are responding to our charge, but not intending to elevate genetic information or distinguish it from other privacy and confidentiality issues.

In fact, from our public comments, we have learned that genetic discrimination is a real occurrence, contrary to some of the reports in the literature. I think that with the information that will be coming out of Mary Davidson's group that that will help inform all of us about this better than we are informed at this time.

DR. COLLINS: I would just like to also make the point that we should be careful not to conflate issues of privacy and confidentiality with issues of discrimination. They are obviously connected with each other, but in terms of the principles that need to be adhered to and the legislative solutions, they can be disaggregated and have been. So, clearly, when it comes to privacy and confidentiality of medical information, the practical ability to separate out the genetic part of that information from the non-genetic part is an extremely difficult problem, and virtually everybody has agreed that at a policy level, if you are going to deal with privacy and confidentiality, you sort of have to deal with the whole thing.

Discrimination, on the other hand, virtually most folks who have looked at this issue conclude that there is a special risk here in terms of genetic information. It is predictive. It relates to families and so on. And therefore, specific legislative initiatives at both the state and federal level are appropriate and are underway. So the best evidence of that thinking is the legislative pathway that is being followed, and I think your letter was highly appropriate in that regard in terms of pushing the notion of doing something about the discrimination risk, recognizing that privacy and confidentiality may be more difficult.

MR. HILLBACK: I would like to pretty much second exactly what Francis just said. Don't

everyone faint. We agree on lots of things.

DR. COLLINS: I retract everything.

MR. HILLBACK: We are going to start that way? It is only Monday morning.

We have worked in a number of states from the trade association, and what we have found is that it is very difficult to try to separate when you get to privacy and protection of the information to do the definitional lines that we are struggling with ourselves, what is a genetic test, and the family history is still one of the best genetic tests we have and you are not going to block the family history.
So to try and do it there is a horrible situation, and that is why both Bio and Genzyme and all the companies I know are very much in favor of the anti-discrimination legislation and going forward there.

I wanted to respond to one thing that actually came up at the last meeting. Paul Miller was here and raised the issue of companies requesting genetic tests in order to analyze whether an individual was appropriate or not or companies calling labs and saying we want to do a genetic test on individuals. I told him at the time that I would go back and do a survey. I have talked to several people, including Ann Merrifield who is president of Genzyme Genetics who is here today, but also several of our lab directors and our medical directors. None of us over a 10-year period can remember a single instance of a request for a genetic test coming from a company or coming from a physician who identified himself as working for a company.

It may happen that occasionally one may slip through where a physician makes a request for a test and does not identify themselves, but none of us can remember a single situation, and I talked to five or six of the senior people, Dr. Puck who is our medical director and the lab director of our DNA tests, and we cannot find a single instance at Genzyme in our genetics business. So it may happen, but we have never seen it.

I did have a chance to relay that back to Paul at a conference we were at together a few weeks ago.

DR. TUCKSON: I really like Wylie's three distinctions. I just want to make sure that I completely understood your second one, which I think is the key for me.

I think what I hear you saying in the first assertion is, in responding to our charge, we feel these things must occur. Number two, we say that genetic information is a subset of the larger medical information, all of which requires a certain level, and this, therefore, is a part of that and must reach that high standard. Third, therefore, let's deal now with the special issues as Francis has given the addition on discrimination legislation in this area because that, again, is our charge. If that is the point you are making, I like that distinction a great deal.

DR. BURKE: That is correct. That is exactly what I was saying.

DR. CHARACHE: I am not sure how to word this. I have two things. First of all, I think the issues

are not the same for the genetic tests as for other tests in one very key regard in that, although we need confidentiality for all tests, genetic tests involve entire families. And I think this is of concern.

I do not know whether perhaps Elliott has not seen them because they are using cheaper labs.

DR. CHARACHE: But I hope that comment will not be in the minutes.

The second point I would like to make is I think there are really two very key outside groups that came out strongly against any change in oversight, and the discrimination was one of the three points that was raised there. I will not name them, but I can tell you, they are very close in length. They almost sent in only a single letter, and they are on pages 28 and 29 of the table.

I have had the opportunity to speak with some of those who helped write the letter, and I believe that it is truly a matter that the particular people involved in writing a letter needed more information about both the pressures, the issues we have been dealing with, and the understanding of some of the problems out there which do not involve many of their own members. So I am hopeful that we will also see some changes perhaps reflected in the responses to the Notice of Intent from those two groups.

DR. McCABE: Mary and Kate. Then we are going to go back to the definition.

MS. DAVIDSON: I just want to add my concurrence to Wylie, Francis, and Elliott. I was really heart-warmed by the public comments because I thought industry in particular really came out supporting the need for legislation.

I wanted also to throw something to you, Elliott, that has always been thrown at the Alliance in terms of looking at studies. It is so important that we get a real clear handle on all of this. It would be really interesting to do a study of laboratories to really trace to what extent this is happening or whether this is just a case vignette.

The other thing is just to bring everyone up to date. The Genetic Alliance has just posted a questionnaire on our web site, and we are sending it out by hard copy. This is an attempt to really document and identify cases of discrimination. It is not only a lengthy questionnaire, but it is going to be followed by a half-an-hour interview by a genetic counselor. We are hoping that through this effort that will be over the next six months that we can begin to get really a better profile on the condition so that we can never again sit at a meeting and have somebody kind of just say, "Oh, it is just a story."

I like the letter we sent out. I think this is really the direction we need to go.

DR. McCABE: Thank you.

I would ask you again to please turn off your mikes when you are not using them because we are getting some problems with feedback.

MS. BEARDSLEY: I just wanted to add to what Francis and Elliott were saying about the distinction between confidentiality and discrimination. It seems to me that it is right to say that discrimination might be a more fruitful area to pursue, but I, for one, would not want to put all our eggs in that basket because I think that the problems in proving a discrimination lawsuit, and we have seen it in so many different areas, are so great that we need to maintain some sort of balance between the two.

DR. McCABE: I would also point out, in one of the pieces that we received from the press, you might have noted that a suit is being brought by Paul Miller and the EEOC -- or by the EEOC -- I assume Paul is involved -- on a genetic discrimination that occurred with an individual with alpha one, and that is in these materials. I saw it both when you came over. You got it by e-mail, and then it also was included in these materials. So that, that is progressing under the existing statutes.

I think we have a clear direction, then, in a way of outlining that in the document. What I would like to do is go back to the definition now that has been typed in for us, and we can select the specific wording that we want to include in the final document. It is my indication by the body language around the table that people feel we should become more specific in our definition.

Is there anyone who feels we should remain intentionally vague?
DR. BOUGHMAN: I wonder if we might be directed in our document what paragraph we are talking about in our own words.

DR. McCABE: Joann is always good with the details.

DR. BOUGHMAN: I think this may be part of our problem in why the public comments or the organizational comments challenged us on our definition. In fact, I was having a difficult time finding exactly where we obligated ourselves to definition at least in bold.

DR. McCABE: If you will go to page 1 of the Adequacy of Oversight of Genetic Tests, not the executive summary, but page 1 of the body of the document, and go to the bottom of page 1. It looks like most of the people in the audience have that as well, but I will read it, just so that we know what we were talking about.

"Genetic testing involves the analysis of chromosomes, DNA, RNA, genes and/or gene products to determine whether an alteration is present that is causing or is likely to cause a specific disease or condition. Genetic tests can be performed for a number of purposes. Moreover, a test can be used in more than one way. For example, a genetic test" -- and then we go into a series of examples of genetic tests.

I would also point out that Elliott has raised concerns about this before, as were some of the same concerns that were raised by a number of the respondents, and that is that this was vague and perhaps too overly inclusive. So we have had this discussion, but I think that the input from the commentators have focused attention on this more so than we perhaps had considered in the past.

So that, what we would be doing is, then, substituting for the first three sentences here, starting with "Genetic testing involves" and ending with "one way," as the definition that we will decide upon. I think that it is good to have examples, and we were being specific by the examples. So we will leave the examples in, but we will change those first several sentences of that paragraph.

Again, I am seeing people shaking their heads in agreement.

So I think we have been able to accomplish getting most of it all on one screen. The CLIAC definition is very specific about: "Analysis performed on human DNA, RNA, and chromosomes," and it includes heritable or acquired -- again, there is some discussion by the commentators on this point -- "disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes." This would involve predicting the "risk of disease, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations."

So, in terms of the molecular genetic and cytogenetic tests, are there any disagreements with that? In fact, our examples really were playing to this definition. Any disagreement with the first paragraph? Do we agree that we should include "inherited and acquired"?

DR. KOENIG: I very much believe that both "inherited" and "acquired" need to be included, and I was not convinced by the arguments of those who tried to limit it in a very narrow way to inherited conditions. It seems to me that that is sort of freezing the field 15 years ago and not looking to the future. So that seemed to me to be a problem.
I still have concerns, and I may be the only one, and if that is the case, we do not have to continue, but I believe Pat Barr also shared this concern about the limitation to clinical purposes in this way. That is slightly different than in the task force wording, but I think it is not going to be very long before we are going to have many tests on the market that might not fit within the definition of "clinical use." I guess we have been there and had this discussion already, but I just want to raise it again.

DR. McCABE: Yes. Thank you, Barbara.

Before we leave the "acquired," I just want to finish that discussion and then move on to the point on the "clinical." I think that Francis' distinction where we include them both, but we recognize that there are differences in levels of concern and need for oversight, is that okay that we proceed from there?

Pat, were you going to talk about the issue of the "clinical"?

DR. CHARACHE: Yes. I think that this group can remember that this was targeted towards the issues that are the responsibility of CLIA, but I think if you just remove that phrase for clinical purposes, it would apply more broadly, including insurance monitoring and things that CLIA does not cover.

DR. McCABE: Barbara, would you be better satisfied with this, then, if we stop that sentence after "karyotypes"?

DR. KOENIG: I guess I would be more comfortable if we did not.

DR. BOUGHMAN: What if we took the other side of the equation, if you will, and inserted "non-research"?

DR. McCABE: Again, that was one of the issues that was raised also, that we might be limiting research, but we need to clarify this.

DR. BURKE: I actually think that the best solution in the definition would be to remove "for clinical purposes," that phrase. There is obviously a good reason why it is there in CLIA, but for our purposes, we are just trying to define a genetic test.

I would strongly support and endorse comments that we had that oversight is different when things are being done for research purposes than non-research purposes, and I think our discussion already tells us that oversight is primarily through IRBs for research purposes. But I think that should be separate from the definition.

DR. McCABE: Victor had his hand up.

DR. PENCHASZADEH: I would like to go back to the definition in our document. Instead of saying "for clinical purposes," we could go back to what we say here, "to determine whether an alteration is present that is causing or is likely to cause a specific disease or condition." So that we are not getting into issues as to whether it is research or clinical, we can address that as a separate issue, but we are still considering all of those types of tests that are linked to the probability or certainty that there is a specific disease or condition, either present or future.

DR. PURYEAR: If we look at the task force report, don't they list a whole series of vignettes of where it would not? I mean, you would not be looking at oversight with forensic testing. I cannot remember. If we go down on the task force definition --

DR. McCABE: No. On this one, it is there.

DR. PURYEAR: The last sentence.

DR. McCABE: If we also inserted that last sentence as an exclusion. That gets into the issues of –, the last sentence excluded "somatic" here, which we specifically included.

DR. CHARACHE: I think if we simply remove "for clinical purposes," we have a definition, and what we have to do is separate the definition from the use of that definition.

And I would strongly urge that when we talk about research purposes, we have to define what "patient care" is. Because our IRB stumbles a lot over people who think they are doing research, but are reporting results.

DR. BURKE: I would support those comments and, again, say that I think we should be careful to provide a definition and then deal separately with different categories of genetic tests that might

have strikingly different oversight needs.

I think we do not want to exclude "genetic tests used for research purposes" because we have in fact made an oversight recommendation concerning IRB oversight for all research involving identifiable human subjects.

So I think if we remove the "for clinical purposes," we have a good definition and should deal in other places in our report with different categories of genetic tests that lead to strikingly different oversight requirements.

DR. McCABE: Victor, you were in favor of inserting a different phrase. Would you be comfortable with just the removal of "for clinical purposes"?

DR. PENCHASZADEH: If nobody thinks that we should really keep adhering to “alterations that cause or are likely to cause a specific disease or condition”, I have no problem in just leaving it that way.

For my own clarification, what those two definitions are doing basically, compared to our original definition, is we are separating two types of genetic tests, molecular and biochemical. In our original definition, we were talking about gene products as well analysis of DNA, RNA, and chromosomes. So we have to use both definitions, then.

DR. McCABE: We were going to get to the next one after we are finished with this one.

DR. PENCHASZADEH: In that one, we are leaving out gene products. We will take them up again under biochemical genetic tests.

DR. McCABE: Right. In fact, in looking at that second sentence there, we will have to modify it. It will have to say "the purposes of these genetic tests would include" rather than "such purposes," if we delete "purposes," and then I think that includes pretty much what you were going to include as another clause to the first sentence. It is really still there in the second sentence.

DR. TUCKSON: On this research question, since we are reaching a consensus, I do not want to mess that up. What I would urge, then, would be that our writer would in the introduction to this section indicate that here is a definition that we are using, but that the implications of that will be dealt with in greater specificity in other parts of the report, thereby keeping those who are concerned about this from tearing their hair out right from the very beginning. So I think we can say what we are doing, lay it out, and then I think we will be okay.

DR. McCABE: So that is an important point. So we will include something in the preamble to make sure that people do not only look at this paragraph and become concerned about the research issues.

DR. PENCHASZADEH: I have a question.

DR. McCABE: If we could, I would like to make the changes here that we have made, and that is,

at the end of the first sentence, strike "for clinical purposes." Then it would read, "The purposes of these genetic tests would include." New sentence. So are we satisfied with that?

DR. PENCHASZADEH: Are we getting rid of the list of purposes that we had?

DR. McCABE: No. We will have those at the end. We will leave those at the end, but we will have the definition up front.

DR. PENCHASZADEH: Yes, but I have a formal comment. Shouldn't we say "and/or chromosomes," "Analysis performed on human DNA, RNA, and/or chromosomes"?

DR. McCABE: Yes.

DR. PENCHASZADEH: Thank you.

DR. KOENIG: I am just wondering if we should add "pharmacogenetics" as one of our examples to make this totally clear, or is it actually in the text? Is that included? There is a paragraph later, I know.

DR. PENCHASZADEH: I thought of that, but perhaps we could add that to our list of purposes.

DR. BURKE: We could add a more general one, directing management. "The purposes of these genetic tests would include predicting risk of disease, directing clinical management, identifying carriers." In other words, if we do that, we are covering it.

DR. McCABE: So we will insert after "predicting risk of disease," comma, and what was your wording, Wylie?

DR. BURKE: "Directing clinical management."

DR. McCABE: "Directing clinical management."
DR. COLLINS: Just as a placeholder, as we are clarifying, and I think this is good, a broad umbrella for the definition of "genetic tests," this is going to have some consequences for some of the recommendations that we made later in the report.

For instance, where we say the FDA should have responsibility for the oversight of all new genetic tests, if we are now including genetic tests that are being solely used in research, we may want to come back to that and try to clarify that circumstance.

DR. McCABE: Except that what I heard people saying was that genetic tests used in research still were under the purview of the IRB.

DR. COLLINS: I agree that is the right thing to say, but it is not quite what we said.

DR. McCABE: Okay. Well, thank you.

DR. COLLINS: If we go to Issue 4 and look at the bullets that we put forward, I think maybe in our minds, in Issue 4, the definition of "genetic tests" was a bit narrower than what we are now agreeing to. We just need to make those modifications.

DR. McCABE: Let's use that as a placeholder, and as soon as we are done with this, we will go to Issue 4 so we do not forget about it.

Since we are using the CLIAC definitions, we arbitrarily have here the separation of molecular genetic and cytogenetic tests from biochemical genetic tests. Let's now look at the biochemical genetic test, and then we can see whether we are going to leave these as separate paragraphs or meld them together, but for purposes of discussion, let's leave the separate at this time.

So we are talking about metabolites, primarily proteins and certain metabolites, "predominantly used to detect inborn errors of metabolism, heritable genotypes of mutations for clinical purposes. Such purposes would include predicting risk of disease, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses for individuals, families, or populations."

DR. TUCKSON: Can I just ask Pat. In your comment, Pat, you implied in 2 milliseconds, these two distinctions will merge, anyway. Can you explain that just a little bit more?

DR. CHARACHE: It is a lot cheaper and more efficient to monitor the gene product than to detect the gene, and you can also then screen when it is multiple genes that result in an abnormal gene product. So that is the drift of a great deal of work.

A key reason that these were separated was because there was a lot of confusion about this second group of tests. People were talking about well what about monitoring glucose and what do you see if you see a target cell on a smear. So it was decided to separate them for clarity purposes of those who were reading it.

There obviously is a great deal of overlapping words here, but we were concerned that if we tried to include that by just adding a couple of words, such as "metabolites" and "gene products," that we would not get out from under this issue of a lot of tests that are used predominantly for other purposes and would clutter up the work.

DR. PURYEAR: Can we add "newborn screening" to the purpose list?

DR. McCABE: It is actually listed as one of the examples.

DR. PURYEAR: Where? We do.

DR. McCABE: We do.

DR. PURYEAR: Yes.

DR. McCABE: But it is not in the definition.

DR. PURYEAR: I would like it as part of the definition.

DR. McCABE: Okay. So you would say "used to detect inborn errors of metabolism" --

DR. BURKE: "Such purposes would include predicting risk of disease, screening of newborns" --

DR. McCABE: Okay, okay. So insert after "predicting risk of disease, screening of newborns."

DR. PENCHASZADEH: That should be also then in the purposes of molecular genetic tests because eventually they could be used for newborn screening as well.

DR. PURYEAR: Yes. Actually, we do with cystic fibrosis and some hemoglobinopathies.

DR. McCABE: We could even say "screening of populations" up there. Again, these are "includes" rather than "excludes."

Why don't we include up in the first paragraph, after "directing clinical management," "screening of populations." Is it already there? Okay, never mind. Take it out again.

I think we are scheduled for a break, and people are beginning to take breaks. So why don't we take a formal break, and we will resume in 15 minutes.

[Recess.]

DR. McCABE: During the break, Sarah and I did some word-smithing because there was quite a bit of redundancy between those two definitions. I think for our purposes to keep them separate, it would not be an advantage. So let me read what we have written for you, and then we will decide on whether we have any exclusions.

It now reads, instead of the CLIAC definition, the SACGT definition of a genetic test. "The SACGT definition of a genetic test is an analysis performed on human DNA, RNA and/or chromosomes to detect heritable or acquired disease-related genotypes, mutations, phenotypes, or karyotypes. A genetic test is also the analysis of human proteins and certain metabolites, which are predominantly used to detect inborn errors of metabolism, heritable genotypes of mutations" -- it does not read very smoothly, but we will have to work on that -- "heritable genotypes or mutations for clinical purposes."

DR. BURKE: Why would you put "clinical purposes" there?

DR. McCABE: Well, we will get rid of it, or mutations," and then strike "for clinical purposes" at the end of that one since we struck it before.

"The purposes of these genetic tests would include predicting risks of disease, screening of newborns, directing clinical management, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations." We basically put together what we had included before, and I do not think there was anything left in the second definition.

MS. BEARDSLEY: Could I just ask a question? When we say the "purposes of these tests," do we mean those to be the only purposes, or do we mean them to be illustrative purposes?

DR. McCABE: "Would include," so they are illustrative. Then we have a list that goes into a little bit more detail.

DR. BURKE: I think we have created an inconsistency that I do not think we need by defining in the first sentence these tests as tests to "detect heritable or acquired disease-related genotypes, mutations, phenotypes, or karyotypes," and then using a very different phrase in the next sentence. I think the next sentence could read, "A genetic test also is the analysis of human proteins and certain metabolites which are predominantly used to detect," and then use the phrase from above, "heritable or acquired disease-related genotypes, mutations, or phenotypes." In other words, I think if you just omit "karyotypes," you can use the same phrase, and it has a certain greater consistency that way.

DR. McCABE: Okay. So if we could make that change.

Now the exclusions. Do we want to put in the exclusions? Remember, we are taking this from another document. So we are not obligated to put the exclusions in, but do people feel that these are worthwhile?

The exclusions were edited to take out the "acquired" that was there before. It says, "Exclusions. Tests that are used primarily for other purposes, but may contribute to diagnosing a genetic disease (e.g., blood smear, certain serum chemistries), would not be covered by this definition. Tests concluded purely for research are excluded from the definition and testing."

I would say let's strike the exclusions. They are there as part of the CLIAC, and that we really do not need them.

DR. BURKE: I do think the first sentence of the exclusion is useful because it helps to clarify the use of the word "predominantly" in the biochemical test, the second sentence above. That is, I think, pointing out that there are tests that are used primarily for other purposes, but may sometimes contribute to diagnosing genetic disease -- is very useful for clarifying the definition in the foregoing paragraph.

DR. KOENIG: We did take out "clinical." However, in our previous document, the reason that we had said, as Victor pointed out, "disease or condition" was because we were so concerned about the issue of limiting this exclusively to things that are currently understood as diseases. If we take the CLIAC definition which says "disease-related genotypes, mutations," then we are sort of back. We have the same problem again.

DR. McCABE: I'm sorry. Could you point that out?

DR. KOENIG: The very first sentence, "to detect" -- and I cannot read from here. I'm sorry.

DR. McCABE: "Heritable or acquired."

DR. KOENIG: "Disease-related genotypes." Couldn't we just strike?

DR. McCABE: "Disease-related."

DR. KOENIG: I do not think we can say "disease-" or "condition-related." Why do we need to specify "disease"?

DR. PENCHASZADEH: I think we are talking about disease-related genotypes. I mean, it is the same thing that we were saying in our own definition, "alteration that may cause or likely to cause a specific disease or condition." So we are limiting that to disease-associated genotypes.

DR. KOENIG: But then, a test for obesity, for example, or a predisposition to obesity, could it be argued that that is not a disease and, therefore, oversight would not apply?

DR. McCABE: I think this has been Pat Barr's concern also that if one leaves that as an opening that then it gets to the definition of whether a disease is a disease or a condition unrelated to a clinical problem, and then that is going to become more of an issue.

So, other discussion on whether we should just strike "disease-related"?

DR. CHARACHE: Can we just make that "disease-" or "condition-related"?

DR. McCABE: I think that was the question. That did not quite roll of the tongue.

DR. CHARACHE: It does not roll off the tongue. I think if we leave off "disease-related," it just is us. It is very, very global. I mean, everything is a genotype.

DR. McCABE: But isn't everything a disease or a condition? I guess that would be the argument.

DR. PENCHASZADEH: Why can't we go back to our original wording? One could say "acquired genotypes, mutations, phenotypes, or karyotypes that are causing or are likely to cause a specific disease or condition."

DR. McCABE: Okay.

DR. PENCHASZADEH: So we are clarifying what you mean by "disease-related."
DR. McCABE: So we get rid of "disease-related," and then you would insert that after "karyotypes."

DR. PURYEAR: Are we going to be worried about genetic tests that test for blue eyes?

DR. McCABE: Certainly, the public expressed some concerns about these, and I think then you get into a gray area, also. Certainly, the public has expressed a concern about genetic testing for

cosmetic purposes or non-disease-related purposes. So that, I think that is one of the issues that certainly has been discussed with us.

So, are people satisfied? I think it reads a little better than "disease-" or "condition-related" and still gets to that point. It captures the same purpose.

And Joann is saying that we need to do the same in the second sentence. So get rid of "disease-related." Here, if we say, "acquired mutation," I do not know that we need to insert that phrase again because it refers back. Plus, also you have phenotypes there, which is broad.

Thank you for clarifying that so that we did not have an internal problem.

Let's now look at exclusions. The discussion had been that people liked the first sentence of the exclusions.

DR. BURKE: I would take the second sentence out, leave the first as is.

DR. COLLINS: I agree that the second sentence comment on research ought to go, but what about forensic tests? Do we really intend in this whole set of recommendations to cover that area which is rather distinct in many ways from everything else we have been talking about? I would be comfortable having a second sentence that does say, "Tests conducted for forensic purposes are excluded from the definition," but I would like to hear what everybody else says.

DR. McCABE: Does anybody wish to include "forensic purposes"?

DR. CHARACHE: I do not want to include "forensic," but let me specify that tests that are designed for forensic purposes are currently being used for clinical purposes. This is particularly true for looking for identity in pathology samples, for example, where you could have a piece of tissue on a slide from a different patient, and in order to be sure it came from the real patient that you want to look at, specific forensic tests are being employed. So it is being used in pathology. I think that is far enough out that I would remove it.

DR. BURKE: But does that mean we have to be sure to put the words "Tests conducted exclusively for forensic purposes are excluded"?

DR. CHARACHE: Yes, that would do it.

DR. TUCKSON: I think I agree leaving it out.

Sarah, I guess this is to you. I do not know how we deal with that troubling bizarreness at the beginning of our meeting, that first day, with the Department of Justice's presentation. I guess what I am just simply wondering then, because that was introduced into the record for us and if we make the point that Francis makes, does that purge us from having to have dealt with that? I do not want to have to struggle with it, but I also do not want to leave it as if we say that is okay and it would be inferred that we somehow tacitly agreed with that.

MS. CARR: You could possibly make a statement, an overt statement of disagreement. Maybe you want to exactly say what it was that troubled you so much.

DR. McCABE: Yes. Reed, could you?

DR. TUCKSON: Remember, this is the one where they somehow in their public testimony to us suggested that they would use these tests as a way of determining criminality, predisposition to criminal behavior. And I just do not know how to handle it. I do not want anybody to come back and say that was presented and then when we got to this issue of forensics --

DR. McCABE: I would argue that just because material is presented before us does not imply tacit agreement with any of that information. The fact that you have now stated specifically that we are not agreeing with that, I would feel comfortable with that.

Barbara, I know you had some comments, but is it a follow-up to what Reed had?

DR. KOENIG: Just very briefly on the forensic thing, I share Reed's concerns about this as an area, and even beyond actual law enforcement agencies, if we say that forensics are okay by a legitimate authority, such as the courts who might want to use DNA testing or whatever, does that then mean that other groups, private investigators, others could use these tests and they would not be considered in any way under our oversight? I just want to make sure we are careful about how we set out this language because I think it is an important issue.

MS. YOST: My comment is separate from this. I will wait until you are finished with this discussion.

DR. BOUGHMAN: In response to Reed's concern about the Justice Department being here, I think in part their comments were meant to acknowledge that the Justice Department and the courts are now understanding that genetic testing of all sorts has entered into the court's arena. Forensic testing, DNA identity in criminal cases is only a sliver of the kinds of genetic testing that is being presented in a wide range of courts, including in family courts, adoption courts, and a wide variety of health-related issues as well. So that, I think that the one point that you made about the criminality was in fact one of the questions we get most often, and that has to do with these conditions versus disease-related phenotypes. And once again, I think it was an acknowledgement that the Justice Department realizes that somewhere down the road, there may be the ability to do predispositional testing for certain kinds of measurable personality inventories that covers a wide variety of issues, but that does not necessarily mean that we are condoning any of it.

DR. McCABE: That would then get to conditions rather than forensic purposes.

DR. BOUGHMAN: That is right.

DR. McCABE: What I am saying is if that were to occur, it is not for forensic purposes. It is for conditions among an incarcerated or high-risk population which I think is different. I do not think we are excluding consideration of this by the exclusion of forensic purposes.

DR. COLLINS: I appreciate Reed bringing this to attention because I think the definition does need to be carefully thought about in terms of what do we mean by forensic purposes.

Maybe there is an easier solution which is to replace that sentence which basically says, "Forensic identity testing is not included," so that it is very limited to circumstances where you are trying to figure out did this DNA sample and that DNA sample come from the same person. That would then not say anything about an exclusion of the kind of testing for a predisposition, which I agree we ought to be quite concerned about.

Does that help, Reed?

DR. TUCKSON: I think it does.

I'm just, obviously like you all, I'm just real worried that –. Joann's comments were very important to me. What she is saying is that in this world, the distinctions between medical and other uses is going to get very blurred, and just as we have the same ethical issue regarding the role of physicians in termination of life or prisoners, what is the appropriate role in that. You get these very close distinctions in public policy.

I do not want to take us too far out on these sort of issues. At the same time, this is a historically important moment. Being precise about these kinds of things, about drawing a line, and to conclude, I am sorry to be long-winded, if we say we refuse to deal with those issues, they need to be dealt with in another forum, that is one statement. If we say, on the other hand, we are concerned about these and will continue to look at them with care and concern, then that is another kind of statement. I am not sure which is the right answer.

DR. McCABE: I think that Francis has specified the exclusion more precisely than we had before. And so one could argue that "forensic" might include these conditions, but if we say "now for forensic identity testing" or "forensic identify purposes," then anything beyond the identity testing per se would not be excluded and would come under our definition of "conditions."

MS. YOST: Just on a similar but related topic for later on when we get to the CLIA discussion, but it also does affect the definition currently, CLIA currently defines a laboratory test as "testing done on a specimen derived from the human body." So, that when you talk about pre- and post-implantation embryos, you are crossing over into a new arena, just as a word of warning.

DR. McCABE: Again, that is a CLIA issue. I do not think we have excluded those in our definition, but thank you for pointing that out.

In terms of our recommendations, and it is an important point to make, our recommendations may go beyond what is prescribed by the current statutes.

I would strike "exclusions," and we can decide later whether we make this the same paragraph or a different paragraph.
What I would like to do is move on because there are a lot of other issues that we need to discuss.

What I would like to recommend is to try and do this in a little more systematic fashion, that we now look at the issues that were raised. If we go to the overview that Susanne prepared for us, we have two.

One is that we have the issues raised by the members. We might want to go through those first and then try and complete those in the next 30 minutes, if at all possible. If someone is organized enough, we can try and do it together with the others, but at least let's get through ours.

We have dealt with the definition, and I think this was an important point because we know how important definitions are and how they will be used. We have dealt with all three of our bullets under general issues. We have also dealt with that under the definition of the "genetic tests," the public concerns.

The public was also concerned about overarching principles, but generally agreed. One exception had to do with the issue about genetic discrimination versus other information. I think we have already dealt with that in our discussion this morning.

If we now look at the public concerns, Issue 1, because none of us on the committee had concerns about Issue 1, there was general agreement with the risk/benefit criteria, concern about how the criteria of social issues would be used to evaluate genetic tests.

I think that one of the points that I would make now, but as to lay it out on the table so that we can discuss it, is that we may not specify every situation. We are making recommendations to the Secretary. I think we and the community, the public, have been very concerned about these social issues and the social implications of genetic testing, but let's talk about that for a little bit.

DR. KOENIG: After reading those comments, I went back through the report, and I think one of the problems is that we were very inconsistent in our use of language. In the executive summary and the text itself, it is different. I think the word "issues" is just way too vague. In other places, we talk about social implications or social consequences, and I think even that, if we change it consistently in the report to some word like "consequences," I think that would help.

One of the comments seemed to confuse the notion of what a social consequence was with the idea of social acceptability. It seemed to think that we were trying to establish this ahead of time, which, of course, is exactly the opposite of what we intend. So I think that that is not one that we need to take seriously. I think it was just a confusion partly based on our own language.

DR. McCABE: So we need to be very cautious as we go through the document about the use of language. Would we be happier with "consequences" rather than "issues," or can we, meaning Sarah and myself and the writer, try and look at that as we go through and do what is grammatically and semantically appropriate, but try and narrow that a bit?

DR. BURKE: I would support that, what you just proposed. We could defer that to you in terms of language.

I think in terms of responding to the comments that were made on this issue, two things, it would

be useful if we could offer a very specific and concrete example when we first bring up social issues, and I think we do in our report in a couple of places indicate what kind of social issues we are particularly concerned about, the targeting of tests to a particular community that might lead to stigmatization of a community. So that is the first point.

The second point is that I think we have to acknowledge that this will need to be operationalized. That part of the process of developing the initial sorting mechanism for genetic tests will be an operationalizing of that concept, and that that is going to be a significant task.

DR. McCABE: Thank you.

Let's move on to Issue 2. There was some confusion and some concern about lack of specificity. Some suggested adding additional criteria for test categorization. These were different by the different commentators, but they included: detection rate, false positive rate, rates dependent on what population is being tested, variable expressivity, anticipation, genotype/phenotype correlations and whether they are known or not, and the level of complexity of test interpretation.

Actually, I think a lot of that is in there, but it is probably buried and it is buried under specifics rather than some of the general. Some discussion of whether we need more specificity here?

DR. BURKE: I do think that we have captured most of those comments in our attempts to define "clinical validity" and "clinical utility."

What I think we also need to capture here is a discussion we have been having relevant to our definitions. That is clearly in categorizing tests now that we have this broad definition. Whether or not a test is being used for research purposes or non-research purposes, for example, would be very important.

We have had a lot of discussion about predictive versus non-predictive, but I think we have captured that.

DR. McCABE: Sarah points out one of the issues may also be an issue of consistency between Issue 2 and Issue 5, and that is something we need to go over carefully in the final draft.

MR. HILLBACK: I think the issue of categorization, it is very clear that all of these tests are not the same, and the more we talk even today as Wylie said on the definition, it is very clear they are not.

So, to sit here and try to define all sorts of groups and do this ahead of time, I do not think in the end we are going to be the right group to try to figure out what the classifications are.

In the public comments, we had conflicting points of view about what should be high or low, and it is just not something we are going to do.

To embrace the concept that there are going to be different classifications is important, but after that, I think we are wasting our time to try to get into the details here.

DR. BOUGHMAN: I agree with Elliott, but if we are going to include examples -- and the one comment I keep sending back all the time is the issue of multiplex testing, tests that bundle multiple, multiple tests -- those kinds of tests together need to be considered in some kind of a special category, and I am not sure how to do that.
DR. BURKE: In response to Elliott's comment, I agree completely. It might be that some of the response we had that was concerned with the vagueness in this arena might be telling us that we need to give some more specific recommendations about how the process should go forward or who should be involved in the ultimate categorization of tests.

DR. McCABE: I will take Elliott in response to that and then Reed.

MR. HILLBACK: I think this is a topic that is going to come up again when we talk about Point 5. What we have to recognize is that this process is going to take time to work out how we actually get to the mechanics of oversight. I am sure we will talk more about this when we get to Point 5.

I think what we need to do is give people a comfort level that we recognize that all these tests are not the same, and that whoever provides oversight and whatever mechanisms of oversight is provided through, recognize that, and that all the players, all the major players are going to have some input into how tests should be categorized so that we can get to a point where we can say yes, there is a general consensus, not 100 percent probably, but a general consensus that this is the way it ought to work.

So I think the report needs to stress that we recognize there are lots of differences. These are examples, but it is going to take a lot of work by a lot of people, down in the devil-is-in-the-details kind of thing, to get a working process that will work and that will be flexible to change over time.

DR. BURKE: Yes, I agree.

DR. TUCKSON: Actually, the last couple of points by both of my colleagues is what I wanted to also say.

I did find myself going back and looking at the original question which says "how." That is the very first word, how can you do this. So to punt it is to punt the entire question. We have got the criteria. How were you going to use it? It is funny that after you read these comments, the critical comments, you go back and say, "My God, we blew the first word." So I do not think we can punt.

If we want to describe the categories and then say see below for how and then we can get to our discussion later, that is fine with me, but somewhere along the line, you have got to answer the question.

DR. McCABE: I think that is an important point. Until you brought it up, I had missed the fact that we had opted out of the "how." In fact, I think we did deal with it much better in Issue 5 than here in Issue 2.

DR. CHARACHE: I think there is a limit to how clear we can make this section in any event. One, is it used for diagnostic or predictive purposes? Of course, it may be diagnostic in one member

of a kindred and predictive in other members of the same kindred. So it is a muddy thing because many of the diseases or issues that we will be looking at cross barriers. We got into that Friday in the forum group where we wanted to match the various categories that came from SACGT, but as you start to think about individual tests, if the purpose of this categorization is to decide on the levels of oversight, you get into trouble in a hurry.

You also get into trouble because one test, if you are looking at oversight, they may have parallel needs for assessment prior to use in patient populations, but they may differ all over the map in terms of the complexity of the test itself. You can diagnose the same entity with a dipstick versus a molecular test.

So I think this is very muddy, no matter how we look at it, but the concept is to look at the different issues that are associated with different events. We cannot really put things into cubbyholes.

MR. HILLBACK: I think this issue goes back to one of the concerns that I have heard from a number of people that we seem to as a committee work at the 10,000-foot level instead of at the 200-foot level. I am not sure at this level of detail that we are talking about here that we have the kind of people and the detailed knowledge that we would need to work at 200 feet.

We have two choices. We can, therefore, create a subgroup, have them do the work and report back to us and then answer the "how," or we can say we need to define some parameters of the approach and our job has been to define an approach and then we are going to expect various groups, FDA, CLIA, the laboratorians of the world, to come up with the practical methods. I think we can either do one or the other, but we certainly did not work at 200 feet which is what the "how" would require. If we want to do that, then we need to create a subcommittee of people who have a different skill set than many of us on this committee to go do that.

DR. McCABE: My view has been that we were describing a mechanism and not the details; that we were specifying the parameters that should be considered. I guess I had not expected us to get down to the very detailed mechanisms of how.

DR. TUCKSON: What I hear where we are is that we might be able to say the "how" is that there will be a subgroup that we will specifically attempt to identify that will use these categories to make these decisions on a test-by-test, case-by-case basis. The dilemma then becomes what is that subgroup, and we keep bouncing. We will either get to that discussion now or when we get to Area 5.

As we described at the end of our last meeting, Ed, you said it was us that then creates subgroups along the line that Elliott gave or it is CLIA, FDA, and these other bodies. I think that is where the dilemma becomes. Just to put an oar in the water, I guess I'm starting to see it as perhaps a consensus body of people under what we do, under our umbrella, that gets this stuff convened to look at it, as experts looking at it on a case-by-case basis. Anyway, I do not know whether that is the appropriate time to debate it.

DR. BURKE: I would concur with that and also with Elliott's comments. I think the devil is in the details, and I think we have had a lot of very good comment about that.

I think our principles are likely to hold, but there is going to be a process where people with detailed information about specific tests need to attempt to categorize those tests using our guidelines and come back either to us or I think a similarly represented body and say, "Here is what we found out." It is either here is an easily categorizeable group that don't generate concern or here is why it is hard to do that. I think there is probably going to need to be an iterative process.

DR. McCABE: I was invited to give a talk at the University of Utah, and I worked on the slide set that Sarah and Susanne prepared, but this was actually an area where I felt I needed something visual to get the point across.

What we did was we drew a three-dimensional construct. If you look at what we have, we really have high penetrance versus low penetrance among those issues that we raise, high versus low penetrance, treatable versus not treatable, and diagnostic versus predictive. And once you describe a three-dimensional axis with those parameters, then it s fairly easy to begin to see at least the extremes of where things fall and certainly which quadrant the highest concerns are expressed in.

I do not know if that would be something that in terms of the "how" if you would want us to take that slide and reproduce it for this to show at least a way that one can take what is really a list and operationalize it into how you can take one test and see how it is graded on various parameters and then see where the concerns are.

The ones that I picked out of the list, which I think actually Susanne or Sarah had identified these as being the ones that were identified really among the list of six or seven issues, but it is high versus low penetrance, treatable versus not treatable, and diagnostic versus predictive. It becomes very clear when you look at those that the ones where you are going to have the highest concerns are the predictive, where there is no treatment and there is low penetrance. And that, to me, is the category that raises, at least for me, the greatest concern.

I can also tell you that having now floated this construct on a focus group, which was the genetics community at the University of Utah, that seemed to help them understand it, and they commented on that.

DR. TUCKSON: I think that it is useful. In some ways, the "how" is also going to turn out to be the "who." And I think that it probably is premature to fully engage who takes this three-dimensional grid and applies it until we get to the data question in Issue 3. So I am prepared to hold off.

DR. McCABE: But we could recommend –. Again, we are making recommendations. We could recommend that perhaps one of the things for the Secretary to consider is that this is an area that needs more detailed consideration, and whether that is a subgroup of us or another group to be developed by the Secretary would be then the "who."

DR. COLLINS: I like the idea of trying to visualize this in a three-dimensional axis with eight categories. The only problem with that, of course, is that it assumes you are not going to have to

go beyond three criteria. Otherwise, you cannot visualize it anymore, at least I have trouble doing so.
I did want to point out, and it was already mentioned this morning, the other approach sort of using a point system that NSGC has put forward, which I think also is worth looking at. Here is a way of essentially trying to apply weighting for a host of factors which does not limit you to three in number, which then can be used to try to define what you think you are most worried about.

The trick there, it seems to me, is to figure out whether all of these criteria ought to be equally weighted or whether there needs to be quite a difference in the amount of weight that goes to some things than others. There, it seems you would develop such a discriminate index and then you would try it out on 20 or 30 conditions and see if you got the answer that made sense to you.

DR. McCABE: I agree that the NSGC document really goes into much greater detail than we have and does lay out a nice construct. I am sure that will be discussed in their comments.
DR. COLLINS: Yes. A big part of this discussion is to what extent is the FDA feeling that this is part of their job to figure out where to set the barrier and to what extent is that something that we should assign that task to ourselves or somebody else.

I do not mean to put Steve on the spot.

DR. GUTMAN: That is a very interesting question, and obviously it is challenging to play by the rules of others. We are familiar with certain constructs that are frankly different than the constructs of the peer here, but we are obviously here to serve.

DR. GUTMAN: Well, I have said this before, but I will say it again. The issue of treatment, from our perspective, we are still confused whether it really is a good idea to suggest that having a well-defined treatment makes it of more concern or less concern than having a poorly defined treatment.

We actually have in the background gone through these criteria through our own point system and through our own flow charts, and we have a tremendous problem with devices which appear to be diagnostic, but as soon as they make the diagnosis, suddenly in other members of the family, they become predictive. We have actually talked about shifting to a population base rather than a predictive test if we are trying to curtail our workload because in fact we do not see a single test we do not like that might not be predictive. That, of course, I do not think is what this committee is calling for, that we review all tests in the way that we know and love. You are looking for new models.

So, whether it is a subgroup of this, FDA obviously is interested in playing, if for no other reason, because we do intend to continue to regulate the kits, and we would like to have some parallelism in our approach. And if we end up regulating some home brews and we want to satisfy the needs of the committee, we do not want to necessarily start developing new regulatory paradigms that would be different for genetic testing than we are applying to a broad variety of other tests. Of course, we could accommodate by changing the way we regulate other tests.

DR. KHOURY: Actually, I would like to concur with Elliott Hillback's initial assessment of 10,000

feet versus 200 feet, and we are at 10,000 feet right now.

The three areas that are intimately connected is categorization, data collection, and then oversight, and the central piece of what we are trying to do here is making sure that genetic tests are safe and effective. Those three pieces are so tied together that it is very hard to separate one from the other without getting down to that 200 feet.

Unfortunately, the way we are dealing with this is at that high level, and there has to be some more in-depth analysis. Obviously, you will hear my presentation this afternoon and also from Bob Martin at CDC that there are other groups that are trying to deal with the details, and we are looking to you all for guidance on how to translate the overall recommendations that this group comes up with to actually workable solutions that would cross the bridge between FDA and CLIA and then the voluntary models of data collection.

Obviously, from my perspective, it is hard to collect data on 100,000 genes. So you have to prioritize and get down to the level of which one do you tackle first. So you will hear a little bit more this afternoon from us.

DR. McCABE: The good news is that as the Genome Project is completed, there may be only 50,000.

DR. KHOURY: I will go with 40,000.

DR. McCABE: Or 40,000.

DR. CHARACHE: I am tempted to ask how many tests those 50,000 will generate, but because Steve is sitting here, I think I will not.

I also just wanted to say exactly what Muin did. I think that perhaps the discussion by Muin and Dr. Martin this afternoon will be helpful because of the discussion that went on at the CDC-associated interdisciplinary public-private forum on Friday, and I think some of that information will be helpful on this issue.

DR. McCABE: Sarah has taken my scribble and put it onto an overhead, or Susanne did. Would this be the kind of illustration at least to say that with certain of these dimensions, one could begin to bring them together, more as an example than any final thing, but to help people see the concept? Is that acceptable to include that in the final document?

I think you can see how you begin to identify quadrants.

DR. COLLINS: With appropriate artistic expertise, you could even plot some points on here that are representative of certain examples to help people see how this fits.

DR. McCABE: Yes, which I did with the laser pointer when I was doing this. Clearly, again, that quadrant that is defined sort of in the right back of this, that is, the low penetrance, no treatment, and predictive, extreme of predictive is the one that would for me have the highest level of concern.

Whereas, if you have a high-penetrance, treatable disease for which there is a diagnosis, we are talking about PKU there really as a nice example where there can be significant benefit and where the concerns might be a bit lower.

Sarah is giving me a laser pointer, but I think people can see how that would go.

Let's do one other quick issue over the next seven minutes or so, or at least get into it. Are we done with Issue 2, then, in terms of the public comments?

Issue 3. We had a concern here. Do the first two recommendations need to be modified to more fully reflect the contribution of research, that the collection of validity/utility data prior to a test transition to the clinical setting? This came from Francis' group. I think we have discussed this, but it appears that it was not in there as explicitly as we may have wished.

Certainly, there needs to be a research arm in most of these because the data just have not been gathered. I think there will need to be research on the mechanisms. Any mechanism that we or another group establish needs to be tracked, and it needs to be determined whether or not that mechanism is efficacious.

I do not think this is new territory that will be charted. So mechanisms as well as outcomes need to be evaluated.

MR. HILLBACK: I do not have the specific paragraph whatever, but I believe this section still defines "the laboratory" as having primary responsibility for data collection. I think we need to look at how we modify that to reflect Francis' group's point and the various other points that people make about all the sources of data and all the sources of information.

I do not think laboratories are connected to the patient the way many people hope we are. I do not know how we should reflect that. I open that up to a discussion. I think if we leave it the way it is, it is not realistic. Most laboratories cannot do what is stated here, if any labs can do it.

DR. McCABE: The model that we have discussed in the past has been the oncology model where you need to have groups that come together to analyze data and collect the data. That, again, has significant funding implications, but I would agree that it is going to have to be groups that have to collect these data. It is important to collect the data.

DR. BURKE: My guess is that we will hear more later this afternoon about data collection. It may be helpful.

I think also the point Muin made about prioritization, particularly in context with what we have just been talking about with Issue 2 is probably relevant; that is, clearly additional resources are going to be needed, particularly for postmarket surveillance. It may well be the category of tests that you just underscored for us, predictive, low penetrant, treatment not available. There will be certain tests that fall out as ones of tremendous concern for postmarket surveillance and that resources could be directed there perhaps through the kind of data collection mechanisms that we are going

to hear about this afternoon.
DR. McCABE: The public had similar concerns, and while there was general support, there was a suggestion that at least one agency or one central clearinghouse handle these data and that it not be split up into multiple laboratory sites, which I think perhaps is the same comment that Elliott had. There was an encouragement of public accessibility to data and analyses, and I think that the analyses of these data is going to be a major task in that there should be a resource that is open to investigators and the public, but that is something we may want to discuss after lunch.

There were concerns raised in a number of places, but this is one of them that we may be placing a barrier to test development and implementation here. I think we need to be cautious about that. We have always recognized that this was a balancing act between the need for oversight, but not developing a bottleneck in the process.

With having discussed those, we could discuss some more after lunch. Why don't we break now. We will come back into this room at 1 o'clock.

For those who are here on the committee, we are going to meet in the Alcove Room which is just up the way. It is just off the restaurant. The hotel restaurant is upstairs, and the staff at the meeting desk also have restaurants that are in the vicinity. So we will come back into this room at 1 o'clock.

Thank you.

[Whereupon, at 12:05 p.m., a luncheon recess was taken, to reconvene at 1:05 p.m.]

## A F T E R N O O N  S E S S I O N

[1:05 p.m.]

DR. McCABE: We have set aside time now for comments from the public. We have asked each of the speakers to make your remarks brief, no more than five minutes. We really want to be able to accommodate as many people as possible. Also, we want to be sure we have time for follow-up questions.

In addition, the individuals who have signed up to give remarks today have also submitted comments in writing. So we have the benefit of your thorough written comments as well.

Our first is Wendy Uhlmann who is president of the National Society of Genetic Counselors.

MS. UHLMANN: I am going to use my time to present the concept of developing an algorithm, and what I would like to propose is individuals with genetics expertise and also people that are experts in statistical modeling get together and try to work out what the factors are that we use to evaluate genetic tests.

What I did in terms of coming up with this algorithm is just try to think in a genetic counseling situation what are some of the variables we go over with patients and what are some of the things that we weigh.

As you can see in the first category, it is just type of test, and it is weighted from 1 to 5. Whereas, 1 is the lowest ranking being a diagnostic test, 5 is the highest being a prenatal for an adult onset condition.

I then took a look at prevalence and, again, weighted it 1 through 5, the highest being if someone had a family history of a genetic condition.

Under surveillance and treatment, a lower rating was when there was a condition that had treatment that was proven versus a higher oversight would be when there is no treatment or no benefit to treatment.

Locus heterogeneity. That refers to when you are looking at a genetic condition for which there is just one gene known or whether there are several different genes that are involved. Detection rate was to help take a look at how good the test was.

Genotype/phenotype correlations. There are different genetic conditions that, depending on the mutation, will give different clinical features.

Penetrance obviously refers to the fact that someone can have the gene change, not develop the condition themselves, but can pass on the gene change to the next generation.

Variable expressivity just means that with some conditions, you can have a wide range in terms of what are the clinical features that are present.

Anticipation just refers to the fact that there are some genetic conditions, like myotonic dystrophy, for example, where you can have earlier age of onset and greater severity in succeeding generations.

And then cost is self-explanatory.
Taking a condition like Huntington's disease, in the first category for diagnostic, just to walk you through an example, it became a 1 because it was a diagnostic test. The prevalence in this case was a 5 because there was a family history of the condition. The 3 was for the surveillance because there is no treatment or surveillance of any benefit for Huntington's disease. It got a score of zero because there is no locus heterogeneity. There is just one gene change on chromosome No. 4. The detection rate is great. It is greater than 90 percent for this condition. There is some genotype/phenotype correlations. If you have a higher number of expansions, you tend to have an earlier age of onset. So that was given a 1. Penetrance in this condition is complete. Almost all individuals that have the alteration will develop Huntington's disease.

There are some variations in symptoms, but not a whole lot, and there is some anticipation when this condition is passed down through a father and the cost is pretty reasonable.

Adding these all up and these are all arbitrary numbers that I was using, and I do not want to quibble with the numbers. I just want to say that this is a model that if I could do it myself that this is something that getting a group of people together that have statistical modeling skills, I would like to think that we could come up with a doable model.

So, for here, when you do Huntington's disease testing diagnostically, it is a low oversight. However, if you go to the next column here, if you are going to be doing it predictively, that changes the type of testing from a 1 diagnostic to a 5. Now you have got a pretty high oversight condition.

Likewise, I think you can see with some of the examples here, with some of the hereditary cancers, you end up with high oversights, but for different reasons. For example, with hereditary non-polyposis colon cancer, you end up with a higher oversight because, with locus heterogeneity, I had to give out a 4 because there are several different genes that cause hereditary non-polyposis colon cancer, not just one gene alteration.

Jumping ahead, just because I know my time is limited, I just wanted to show newborn screening. Here, you get a type of test being diagnostic. You get a 1. Prevalence is low, about 1 in 10,000. There is excellent surveillance and treatment for this condition. If you catch it early, you can do diet management. No locus heterogeneity. In terms of the test, you have got a very good test, no genotype/phenotype correlations. In terms of penetrance, the rest, like I say, is explanatory. You end up with a 7 which is a low oversight for this condition, though I would say that any test that is going to be initiated on a population basis or any testing that is going to be initiated within a certain ethnic group should initially start out as high oversight, but then can be downgraded to low oversight.

I do not know how much time I have left. I think that you can see with hemachromatosis, I was trying to take something that is a very common condition that is being looked at for population screening. You can see right now, I come pretty close to the cutoff that we had generated. Like I say, it would be 17. Hemachromatosis would just make it in barely under for the low criteria.

I guess what I wanted to just say is that I think it would be possible bringing together geneticists, genetic counselors, and consumers to really come together with a model that could be used as a baseline screening by the FDA to make their initial pass at evaluating genetic tests. I think it is critical that people in the genetics community be the ones to develop this because we are the ones who have been working with the technology and know the different attributes that need to be considered.
I know we are not necessarily going to be able to come up with something that is going to be able to apply to all different genetic conditions, but I do think if I could do this that a group of us with expertise should be able to come up with something that would be workable.

DR. McCABE: Thank you, Wendy.

Why don't we have just a couple of minutes for brief questions. Does anybody have a question?

DR. BOUGHMAN: I would like to commend you on the effort and the help that it will give in actually looking at a variety of models.

The question I would like to ask you is actually on a different but obviously related topic. And that is, from your perspective in NSGC, I wonder if you could help us out in the use of the phrase

"genetic counseling", and the most minimal definition. In your written testimony, you referred to "non-genetics professionals" and so on. If in fact we make a statement that suggests that genetic counseling should go along with this process, what is your minimalist definition?

MS. UHLMANN: I guess what I would do is I would separate out "genetic counseling" and "genetic education" because those are two different but very important concepts.

I look at genetic counseling as really being the decision-making part of all this, as being able to take in all the information and helping people arrive at a decision that is going to best meet their needs, but I think that a lot of the genetic education can potentially be done by others.

DR. KHOURY: I would like to commend the Society for doing this. I think this is definitely a step in the right direction.

Without actually quibbling over all the details here, I think one can simplify some of these concepts.

MS. UHLMANN: Absolutely.

DR. KHOURY: Rather than making it to quantitatively burdensome, it might still fall into a qualitative arena.

Let me give you a couple of ideas to think about. Prevalence, for example, my tendency is to try to keep it dichotomous. The world of rare versus common. I think there is really not that much difference between 1 in 5,000 and 1 in 10,000 in terms of numbering. I think once you identify rare conditions, they might fall into a different category altogether than some of the more common conditions.

MS. UHLMANN: Right. I still think you need a separate category, though, for family history because I think that changes the dynamic.

DR. KHOURY: Then, some of the other areas with respect to detection rate and locus heterogeneity, which are analytic validity and clinical validity issues, there are concepts of sensitivity and specificity captured in only one of them.

The next three areas, genotype/phenotype correlation, penetrance, and expressivity, they are all part of the same spectrum of things you are trying to identify. Penetrance and genotype/phenotype correlation actually go together. So there might be a way to combine some of these --

MS. UHLMANN: Absolutely.

DR. KHOURY: -- and make it simpler rather than more complicated. But I commend you for your effort.

DR. McCABE: Unfortunately, I think we are going to have to move on. If we have time at the end,

we will come back and follow up with some of these.

Our next speaker is Michael Werner who is director of Federal Government Relations, bioethics counsel for the Biotechnology Industry Organization.

MR. WERNER: Good afternoon, everybody. My name is Michael Werner. I am bioethics counsel for the Biotechnology Industry Organization (BIO). BIO represents 920 companies, academic institutions, and state biotechnology centers engaged in biotechnology research on medicines, diagnostics, agriculture, pollution control, and industrial applications. We certainly appreciate the opportunity to comment on the committee's document on preliminary conclusions and recommendations on the adequacy of oversight of genetic tests.

We submitted formal written comments, as most of you probably know, but I wanted to take this opportunity to highlight a couple of issues.

BIO agrees with the preliminary conclusion in the report that more education about genetic tests is needed. That is probably something that there is consensus on around the table and in the community. We have several concerns with the report including, and I will just list a few. It treats genetic information and genetic tests differently than other medical information and tests. We believe the report inappropriately emphasizes issues such as discrimination and privacy in the social impact of genetic tests while providing insufficient discussion about the regulation of tests and the effect of different regulatory approaches on the development, availability, and access to tests.

The report recommends new regulatory schemes, even though the existing Clinical Laboratory Improvement Act, or CLIA, framework constitutes a sufficient oversight mechanisms for organizations providing genetic testing, and we respectfully argue that only a subset of the many opinions expressed by members of the public have been emphasized by this committee.

So, there are a couple of key points that I want to highlight. Genetic information from our perspective is not different from other medical information. Moreover, genetic testing provides information that is comparable to that which may be obtained using other diagnostic methods, forming part of a continuum of medical information. But unfortunately, rather than accepting this principle, the report, especially noting on page 12, says that the committee was guided by "the widespread perception" that genetic tests are different from other tests. And the committee seems to use this belief as a justification for increased oversight. From BIO's perspective, that is a fundamental flaw in the report because singling out genetic information and genetic tests for separate regulatory treatment could inappropriately stigmatize genetic information in the public's mind and inhibit the benefits it could potentially provide to individuals and society.
So, rather than providing security, this report could have the unintended and harmful effect of exacerbating anxiety in the public. Because of a perception that genetic information is different, the report argues it should be regulated differently. However, if it is regulated differently, the public could become convinced that in fact it is different, leading to increased public concern. The result of what I refer to as a "cycle of fear" would be a creation of a stigma about genetic tests. This could hurt the development of new technologies that hold great promise for patients because, armed with the information these technologies will provided, patients could make lifestyle and

medical care choices that would have otherwise been unavailable.

In addition, the knowledge gained by research used to develop new tests and the information gleaned from those tests will lead to new drugs and therapeutics to treat disease and maintain health. So an environment of anxiety or fear could stifle this critical work and delay the development of many important and potentially lifesaving products.

I want to be very clear that BIO has long supported federal legislation to ensure that a person's individual medical information, including genetic information, cannot be misused. BIO has supported the creation of federal standards to protect the confidentiality of an individual's medical information, including the results of genetic tests, and has been a supporter of national legislation to protect the confidentiality of all medical information.

We have also supported legislation prohibiting discrimination in health insurance based on health care information, including genetic information.

However, we believe that this committee's charge is to analyze the impact of regulation on the availability, quality, and accuracy of genetic tests now and in the future, and those issues are different from issues of discrimination and privacy.

And finally, just as we believe that genetic information is one type of medical information, BIO believes that genetic tests are one type of medical test, and they should not be regulated in a manner different from others.

Rather than creating a new regulatory scheme, therefore, it is essential to make sure the current system keeps up with scientific advancement, and we believe the CLIA system has successfully promoted quality in laboratory tests for many years and can continue to do so.

So creating a new regulatory scheme for genetic tests is inappropriate, especially one that establishes different levels of scrutiny simply because no safe and effective interventions are available for a disease or condition being tested as the report says. After all, we do not subject other tests, such as those for fatal illnesses, to greater regulatory scrutiny based on that rationale.

So thank you for the opportunity to submit comments. BIO members have expertise and experience in the field of development and use of all tests, including genetic tests, and we stand ready to work with you as you think through your recommendations and develop proposals.

Thank you.

DR. McCABE: Thank you.
DR. BURKE: I really appreciate those comments.

I think you have given us a very important distinction that we need to stick to, and that is, on the one hand, we have had public commentary that tells us there is a perception that genetic information is different, and that perception is there, but on the other hand, there is the issue of what kind of oversight genetic testing should have. And I think it is important to say that a

perception that genetics is different is probably not a sufficient rationale for saying oversight of genetic tests should be different.

I do want to reiterate that I think our charge as a committee is to advise on oversight of genetic tests, not on oversight of all medical tests. So, if we make recommendations about appropriate oversight of genetic tests that lead as they have to suggestions for increased oversight, I do not think we are necessarily saying the genetic tests should be treated differently. In fact, we may be identifying principles that could, by other committees, be viewed as very important principles to apply to the oversight of other tests as well. So I think it is important to just emphasize that what we have done here and continue to do is to look at what is the appropriate oversight for genetic tests because that is our charge.

I think also there has been a lot of discussion this morning about the importance of figuring out ways to categorize genetic tests and identify those that really do not generate the need for additional oversight versus those that do, and I think help from your membership would be tremendously valuable in accomplishing that task.

DR. McCABE: Thank you.

Again, I am sorry that we cannot discuss this further at this time, but we will move on and, if there is time at the end, we may come back. Thank you.

Our next presenter is Alan Donnenfeld. Dr. Donnenfeld is medical director of Genzyme Genetics, associator professor at the University of Pennsylvania School of Medicine.

DR. DONNENFELD: Thanks, Ed. It is a pleasure to be here. It is sort of an interesting position for me since I am a practicing obstetrician/gynecologist. I see patients every day. I know the committee was speaking before about being about 1,000 feet above the level of the ground, and I sometimes feel like I am at ground level, but most of the time, I feel like I am in the trenches.

I deal with genetic counseling. I deal with patient concerns every day. I also have a role as a medical director for Genzyme Genetics. I am going to speak to you with both hats on, as an obstetrician as well as a geneticist.

I had a professor in medical school who once said that when you try to convey a point, you should speak it clearly and try to promote it very effectively, initially repeat it, and then reinforce it again at the end of your talk. So this is a point that I would very much like to make.

In reading through the deliberations of the committee from your February meeting and some of the fairly contentious discussions which I thought were interesting, and I am sorry I missed them, what I would like to see the committee take another look at is FDA oversight of genetic testing.

The main concern that I have is that I do not want obstacles to develop that are going to impede good medical practice, specifically something that is going to get in the way of the patient and physician relationship and something that is going to hinder good medical care.

When I got here, I was looking through some of the information and some of the letters that were sent in, and there was on from ASHG, from Ron Worton, that reiterated my concern. He said, "As geneticists, we are concerned that too much regulation and oversight by the FDA, particularly at the time a disease gene has just been discovered and searches for mutations that are still going on, might inhibit research." I think that is the main crux of what I would like to convey today.

When a patient and a physician are dealing with a medical condition, we would like to have the autonomy of the patient and the physician would like to have the ability to make decisions that affect that patient's care without a lot of extraneous interactions that are going to impede that patient-physician relationship.

Some of those comments were reiterated in the overview of issues raised in public comments that was discussed earlier this morning. It says that of all the public comments regarding oversight, the majority of comments stated that additional oversight was unjustified or unnecessary or against FDA oversight, supported existing regulations or supported expanding existing regulations rather than recommending FDA as lead federal agency for reviewing, approving, and labeling all new genetic tests.

Just as a way of an example, I still have a patient that I care for, it must be 10 or 15 years now, who came to me a long time ago with a family history of a brother and an uncle with mental retardation. At the time, we only had fairly crude medical tests for genetic diseases, and I was concerned, obviously, about Fragile X. We did the cytogenetic analysis, but it was indeterminate.

She said, "I am not going to take the chance. I am not going to have a child because I do not want to take the chance of having a child with mental retardation. I have seen what it has done to my family."

When the research was done that identified these CGG trinucleotide repeats, I called her up. I said, "Listen, we have good analytic testing now that can identify genetic disease, and let me test you and see if you are a carrier, see if you have the expansion." I called her up, she came in, we talked about it. She decided she wanted to go ahead and conceive. She was found to be a pre-mutation carrier. I did an amnio on her, and it turned out that everything was fine. It was an unaffected male infant, and now this child is about 13 or 14 years old.

What I am concerned about is unnecessary burden of regulations impairing my ability to offer an analytic test that comes right from research and identify it, discuss it, analyze it, make sure it is valid, and then be able to use it clinically. Maybe the clinical validity studies have not been accomplished yet, but it ought to be a decision that is resting between the physician and the patient to be able to do that.

So my message, and I am going to repeat it, is I would very much like to see the doctor-patient relationship be continued very strongly without an overburden of extraneous obstacles to medical care imposed by too many oversight regulations.

Thank you.

DR. McCABE: Questions or comments for Dr. Donnenfeld?

Were you at all reassured by our discussion this morning that we do want to maintain that research is still an OPRR IRB issue as opposed to the mechanisms that we are discussing?

DR. DONNENFELD: I was reassured by that, and I like the idea that there are going to be some academic centers and some commercial labs that are going to develop these home-brew tests. Again, I do not want too many constraints imposed on them, but, frankly, I was concerned. I think one of the comments from the Adequacy of Oversight of Genetic Tests, on page 23, says that the agency, referring to FDA, should develop flexible mechanisms for review of new genetic tests that minimize both the time and cost of review without jeopardizing the quality of the assessment of test validity. I cannot help but feeling that that is kind of a naive thought.

I think that it is going to be difficult to offer flexible testing that minimize time and cost. I think it is going to be quite burdensome. That is my main concern.

DR. TUCKSON: Help me to understand. Is it essentially your point at the end of the day that the existing CLIA oversight is all that is necessary, and that the concerns of the public and others that caused this committee to be formed are essentially moot? And that as far as you are concerned, everything is okay now, this committee did not need to be formed, nothing further needs to be done? Is that your point?

DR. DONNENFELD: Not exactly, but I think you have some validity in some of your comments in that I do think CLIA is the mechanism to work with here. I think that they have a structure in place that is effective that laboratories work with.

I am concerned that I think there could be better representation of laboratorians on this committee, and to have them give you their insight because they deal with CLIA and they deal with these regulations all the time. So, instead of reinventing the wheel, I would like to maybe strengthen some of the CLIA regulations and use that as a focal point as oppose to starting something new.

DR. TUCKSON: Could you submit for us or comment now on some of those areas of strengthening in CLIA that would seem appropriate to you? Could you identify some of the legitimate problems or concerns that CLIA might do a better job of doing and that you would recommend that we use as a shield to assuage the anxieties of legitimate constituencies?

DR. DONNENFELD: I guess I do not see the difficulty, as you put it, with anxieties of the constituencies.

Obviously, there are major concerns with genetic testing, and we have heard before about there are concerns with all forms of testing, not just genetic, but all forms of medical testing. I do not want people to get the wrong impression. I do applaud the committee for the privacy and the confidentiality aspects.
I do not feel terribly comfortable commenting on exact CLIA regulations since I am obviously not a laboratorian, but I do believe that as a general philosophy, working with a structure that is in place and refining it is probably a better approach than to start with something new from scratch.

DR. McCABE: We are going to have to move on. I'm sorry. Thank you, Alan.
Our next speaker is Michael Boss. Dr. Boss is vice president for Operations at Athena Diagnostics.

DR. BOSS: Good afternoon. Mr. Chairman, members of the Secretary's Advisory Committee on Genetic Testing, thank you for the opportunity to provide public comments.

In order to keep to my time limit, I am going to abridge my comments, although a more fuller letter is available.

I am Michael Boss, Vice President of Operations of Athena Diagnostics, Inc., a clinical laboratory specializing in the field of neurology. Starting with our first test for muscular dystrophy in 1989, we now provide some 80 different diagnostic and genetic tests, all for neurological disorders.

We applaud the Secretary of Health and Human Services for chartering this committee and the Assistant Secretary of Health and Surgeon General for directing the committee to consult with the public in order for the committee to assess and advise the government on the development and use of genetic tests.

We are, however, very concerned that the committee has not carefully reviewed the public's comments and has not allowed itself enough time to evaluate, address, and incorporate these public comments into the committee's recommendations.

The committee has proposed new additional government regulation and oversight of genetic tests. However, in doing so, the committee has not addressed the impact of new regulatory requirements on research, development, and clinical availability of genetic tests. Without a full and meaningful discussion on the role and impact of additional FDA and other regulations, we do not see how the committee could come to the conclusion that both new and existing genetic tests should be subject to FDA review and approval when other clinical laboratory tests would not be subject to prior review and approval.

A review of the February 24-25 committee meeting transcripts shows that only an abbreviated discussion was held on regulation and oversight. Indeed, it is apparent from the committee chair's final comments on February 25th that he had already made up his mind that some additional regulation was necessary.

I believe the committee should remove or change its current recommendations calling for new additional regulatory oversight. Should the committee decide to keep this recommendation, we urge you to recommend that the Secretary explore the impact of new additional regulatory regimes that are based on a genetic exception.

Before the FDA or any other part of the Department embarks on the development of new regulatory frameworks for genetic testing, we as a society should know how these new regulatory strata will impact the development and availability of not only genetic tests, but also all other diagnostic tests running clinical laboratories. What will the cost be to society and FDA, CDC, or

HCFA devoting time and resources to this activity? Are there other pressing public health priorities these public resources should be devoted to? Are these recommendations cost-effective public health recommendations? Will these recommendations address society's true concern, that of discrimination based on genetic information?

We at Athena Diagnostics believe that new and additional regulatory requirements will not address the principal issue at hand, genetic discrimination. Rather, new requirements will have an adverse effect by limiting the development and access of not only genetic tests, but potentially also other diagnostic tests running clinical laboratories.

Developing any diagnostic test requires time, energy, and money. With additional regulation, genetic tests will become more expensive, and those for rarer disease in particular may be withdrawn from the market, and new tests for rarer diseases may not even emerge.

The committee's document on highlights of the February 24th meeting states, and I quote, "Many of the public comments express concern about the potential for genetic test results to be used to discriminate against people. The public comments also highlighted the importance of ensuring the quality of and access to genetic tests."

It did not call for developing a public health system based on genetic exceptionalism. The recommendations for additional and new regulatory regimes for genetic diagnostic tests are an example of genetic exceptionalism which we feel is not in the best interest of clinical medicine and the public health in the overall product regulatory system.

I urge the committee to review the transcripts that Athena Diagnostics' comments provided on January 31st and May 22nd and the other public comments provided on this subject. And kindly reconsider your recommendation for new and additional regulation for genetic testing.

Once again, I thank the committee for this opportunity and look forward to working with you as these discussions move forward.

Thank you.

DR. McCABE: Thank you, Dr. Boss.

Are there comments? Yes, Wylie.

DR. BURKE: I just want to make a comment that I think is a clarification of our discussion in February relative to your comments and the previous comments, and that is, a concern that came up, if I am understanding our conversation correctly last time, was that the CLIA process is an excellent process. I think there has been strong endorsement of the CLIA process, but CLIA process does not allow for premarket approval.
What came through in our interpretation of the public comments was a concern that genetic tests have accuracy and reliability, and where I think our recommendations came from for involvement of FDA had to do with identifying that agency as the agency with legislative authority already in existence to provide premarket approval.

In fact, there was an explicit discussion about the fact that often all that we would expect to be required would be that the same information that is required for CLIA oversight be made available for that premarket approval process. So there was not intent to involve more work on the part of laboratories bringing test to market.

DR. CHARACHE: I would like to endorse that and just further amplify it with one concept, and that is, the CLIA review occurs every two years. There could be a product that could cause harm on the market for a long time before there was any review if there were not some premarket oversight.

DR. McCABE: I am concerned that you implied that I had a preconceived concept, and I would point out that the closing remarks, which you did not quote, but, again, that we are a public organization and have a transcript that we do make public unannotated and uncorrected. The concluding remarks from the February meeting are then the very conclusion to when we would have the document submitted as a draft document to Dr. Satcher.

I guess I would question the time table that you are suggesting that we have been moving too fast when in fact there was a time table imposed by HHS and the Surgeon General. Do you wish to respond?

DR. BOSS: I think if you are talking about recommending a fundamental change in the way laboratory procedures are carried out, I think it is important to look at the underlying rationale for doing that.

DR. McCABE: I guess my question is that you are saying that my conclusion from all of our deliberations prior to the development of the draft of the document represents a preconception and, therefore, a bias in my direction of this committee.

DR. BOSS: Well, I have the quote here from the concluding remarks, which I can submit in my written comments, but that indicated reference to FDA in that conclusion.

DR. McCABE: But, again, I am pointing out that that was a conclusion from the deliberations of approximately eight months of discussion, not the beginning of those deliberations. So I think it was a conclusion and trying to assess the consensus that we had developed.

DR. BOSS: Right, but that was the first opportunity the public had to comment and participate in the process.

DR. McCABE: I would argue that that was not the case, and there has been public comment at each of our meetings dating back to June of 1999.

DR. BOSS: Okay.

DR. TUCKSON: Certainly, I would say the transcript cannot record the nods and assents, but let the record be very clear that this committee -- and if anybody feels differently, then let them speak

up, but let the record state very clearly that at no point did the members of this committee and certainly not this speaker feel in any way in this discussion that Dr. McCabe as chairperson had tried to engineer or steer our discussion or conversation in some preconceived way. To be quite frank, I am offended by this comment, and I will not let it distract me from objective decision-making, but I consider this to be doing violence to the work of this committee.

DR. McCABE: Thank you. I think we need to move on.

Our next speaker is Dr. Barry Berger who is vice president for Laboratory Medicine and External Affairs of Exact Laboratories.

DR. BERGER: Hello. I am Dr. Barry Berger as previously introduced. For a little more perspective, I have been with Exact Labs for only two years. Prior to that, I have 18 years at Harvard Community Health Plan, and I was responsible for the laboratory care directly, about a half-a-million patients. So a lot of the deliberations that this committee has gone through is something that we went through a lot with the HIV programs when they first came out.

I am going to tell a little story here, and then I am going to go through a couple areas very quickly trying to add to the conversation from what we had before. This is basically what this company does. It is doing applied genomics. And basically, we are in the acquired mutation business, something that we talked about quite extensively this morning as we were talking about definitions.

Based on the work of Dr. Vogelstein at Hopkins, we have been able to take some of the acquired changes that happen in the pathway of colon cancer genesis from normal epithelium through to cancer and turn that into a stool test for screening for colorectal cancer. So this is very practical. This is what the committee here is all about.

Basically, this is like Star Wars. We can basically find these mutations in DNA from stool. Okay, we can find the targets from stool. In doing this analysis, we found a different test that is not quite covered by what we are talking about. We actually look at DNA fragment length. So we are not looking at a specific gene, but the DNA is the analyte. and we are looking at short and long. The question is how is that going to sort out.

Basically, this is the type of profile that we do, and I want to do a little mathematics on this for us. Basically, about 85 percent of colorectal cancer is from average risk patients. It is acquired. It is not APC-related in the genetics, in the predictive sense, or HNPCC, which is about 2 percent. So, depending on the burden that we have using the screening test on the 70 million age-eligible patients who would get this test, we are very concerned with some of the issues around overall informed consent documentation and such for this type of test because this is what we are all about. This gentleman is saying, "I would have been here sooner if it had not been for early detection." So we do not want to keep him from getting there any sooner than is necessary.

So, initially, we had written comments about the issues of definitions for genetic tests. You had a very informed discussion this morning, and I am not going to go here because you spent a lot of time. I do not have trouble with the definition as long as there is categorization that will allow

acquired mutations to be easily taken out of the bucket.

Something that Wendy presented earlier, something that is very easy -- in fact, if you look at Dr. McCabe's three-point axis, you wonder where "acquired" will fall off one of the axis on that particular one, and that will actually be fine.

So, regulatory burden. We were thinking that CLIA '88 from a lab process point of view, because it is a process not a product inspection, is adequate for laboratories in that it requires sensitivity, specificity, negative and positive predictive values to be available at the time that you do the test.

The FDA regulations for sending out kits are certainly fine no matter what they are, and just the issue comes down to how are home brews going to be regulated if regulated at all.

Informed consent was an issue for me specifically. I am all for informed consent. I am a practicing clinician as well, and anything that puts a barrier from getting a patient to get a test that they could use is a problem for me. When we put a screening test in place that is going to be based on genetics that has a huge population, we are not used to addressing tests that deal with millions and millions of patients in this way.

Doing the numbers, if we take 100,000 patients that are going to get screened for colorectal cancer, an average risk, we are going to find 60 to 80 patients. It is about a .6 to .8 percent prevalence in an unscreened population. If we have to do a written informed consent process on those patients in order to find the two patients that will have about 26 and potentially have HNPCC, that is a very large burden to do, and it may keep people from getting screened because they may worry something is up.

So, when we are looking for a tumor that is already present as opposed to looking for a predisposition to find that tumor, as we do, that becomes a different category. It becomes the same as doing a Pap smear or a mammogram. We are not looking for a possibility of developing a tumor. We are actually looking for DNA from the tumor itself shed into the stool stream. So that is an issue for us. Basically, we feel that will give an additional financial burden, and it also interferes with the physician-patient relationship.

So, in order to avoid poor patient care, I think the committee has already addressed this. All tests need to be valid. All patients should know the reason that they are being tested and how they are going to be tested. That is what we do as clinicians. We should indeed have those conversations, and hopefully, we do already. And clinician training, I think, is an issue you will address later, but clinicians really need to know the limits of the tests that they are doing.

So, this is the issue that I heard in February quite strongly, and I think it is a big public concern. I think the public is very concerned about how their genetic information is going to be used, and if that is the issue, let's make darn sure that we have carefully regulated and compartmentalized this information. We went through the same thing with HIV over the last 12 years, and this is not much different as it has become more prevalent, which raises the issue, is the issue around regulating how the tests are validating come forward or is the issue around regulating the information. I think that was larger.

I am just about finished. This is the last slide. On the categorization process, my request is that whatever process we put in place through CLIAC, through this committee, is that it is easy and your test can get a quick read, this acquired mutation is stage zero or stage one out of 20 for being at a risk, and go right ahead. That would be very satisfactory to folks like us who are in acquired.

Thank you for your time.

DR. McCABE: Thank you very much, Dr. Berger.

We have time for one question, probably.

I think your last point, which you did not comment on, I would like to put it in for the record because I think it was an interesting concept, and that was that those that should have higher scrutiny should be pulled out by exception rather than all being in the bucket, the concern that they might get lost in that bucket. I thought that was an interesting comment.

DR. BERGER: Thank you.
DR. McCABE: Let's move on to Judith Benkendorf who is a senior genetic counselor and professor of Genetics in the Department of Obstetrics and Gynecology at Georgetown University Medical Center.

DR. BENKENDORF: Good afternoon, and thank you for this opportunity to make some brief remarks about the working document that we have been looking at on the oversight of genetic testing.

I want to make these remarks as a genetic counselor with 20 years experience, as both a clinician and an academician, and want to make it clear that I am not representing my current employers, which are Georgetown University or the American Society for Human Genetics or the House of Representatives Commerce Committee. I am making these solely as a person with 20 years of experience.

I want to start out by applauding the SACGT for really a monumental task over a very short period of time and for such a comprehensive report being put forth to Dr. Satcher and Secretary Shalala.

As a 20-year member of the National Society of Genetic Counselors, I have agreed to vet some of my comments with those of Wendy Uhlmann so she could go over her algorithm, and I think, together, we really all support the overarching principles. And I particularly commend you and thank you for the prominent endorsement of this committee for federal legislation to look into the prohibition of genetic discrimination in employment and health insurance.

A couple of comments, areas for future work -- that is all the committee wants to hear from us now are areas for future work when you are not quite done with the task at hand -- one is we have heard a lot about parameters for oversight of genetic testing. We have heard not as much to this point about where we are going to set the bar for all of those parameters. It is very nice to talk about utility and validity of tests, but where to set the bar still is a work in progress. I would like to

offer the technical advice of members of the genetics community and actually urge that perhaps a standing panel be formed that could work side by side of the FDA is that where oversight goes. I know the FDA does use outside standing panels in a number of the other things that they do and oversee, and I think this would be an ideal way to use genetics professionals to look at criteria and actually see some of these criteria as moving targets, as the therapeutic gap closes, as the Human Genome Project marches on over the next 10 years, between our ability to test and to actually treat genetic disease.

Also, as the medical genetics community and the basically primary care health community becomes more adept at delivering genetics education, genetic counseling, and genetic tests, as we do outcomes research, as we learn more about the psychological impact of test results, I think many changes are going to be made. By having an expert panel that can kind of parallel these things with consumer input, I should highlight, I think it would be excellent.

I would like to underscore the fact that oversight for genetic tests, I would hope, would look at the testing process, and it really must include recommendations about the minimal acceptable level of genetic education and counseling for the testing process in the different testing categories, not detracting at all or minimizing the importance of the doctor-patient, counselor-patient, professional-patient relationship, or allowing for clinician judgment or the unique circumstances of every family's and individual's situation.

I think we must remember that the entry point for genetic counseling for many individuals and families is really risk assessment, and when Wendy was at a loss of words, I think that is one of the things that genetic counselors and genetics professionals do offer is risk assessment. Just the fact that by going through this report, I just put the paragraphs together, and the benefits for genetic tests took up about 40 percent as much paper as the risks right now, and these risks are not medical risks. They are mostly psychological and non-physical risks. This really tells me that these are issues that need to be explored and really are best addressed in many situations now by adequate genetic counseling.

This is what, really, to my mind propels the informed consent process by allowing for a discussion of the inherent risk of testing versus the alternative, not testing, and delving into the personal meaning of the information that can gleaned from genetic tests, the usefulness of that information to individuals and families and the relevance of that to the life of the individual being tested.

Also, the original task force, Tony Holtzman's task force, took a risk and put themselves out on the limb and actually talked about the fact that little or no precedent exists for asking for a demonstration of competence before ordering tests that will be performed primarily in ambulatory settings, and perhaps there are some genetic tests, particularly predictive tests, where we should be a little bit more stringent in looking at provider competence when we talk about the best interest of protecting the public. You actually even go and state in this report that the clinically valid test in the hands of a poorly trained health care provider can pose as much risk as a less valid test in the hands of somebody who is properly trained.

A couple of final comments. NSGC obviously is very concerned about the informed consent process, the content of informed consent, as well as the way informed consent is garnered for

those tests where we believe that informed consent is important. As I said, the genetic counseling process does propel it.

Just a couple of last comments. One is that in its role in relationships with developers of new drugs and devices, the FDA does have a history of protecting proprietary, especially in looking at premarket information and adverse events reports. We have learned some recent lessons from the recent trials with human gene transfer experiments. We have noticed that there is a bit of misunderstanding about data to be collected by whom, to whom, what, where, and when, and I would really, really hope that any premarket, postmarket surveillance data about genetic tests involves all of the stakeholders and that everybody knows to where that data is going to go and how and when so that we can really ensure public safety.

There are many stakeholders, and the FDA does have a number of public programs. One is the Medwatch Program to look at adverse events of drugs, and I would hope that those kinds of things could be implemented for genetic testing.

DR. McCABE: Thank you very much, Judy.

We have time for a brief question or comment.

[No response.]

DR. McCABE: Thank you very much, Judy.

Our last speaker who is scheduled is Dr. Kathleen Rand Reed, who is president for Geographic Genetic Systems. Kathleen has appeared before us as an expert. She is an applied anthropologist and ethno-marketing specialist.

MS. REED: Let me, first of all, clarify, it is not "Doctor" yet, but it is coming, "coming soon" as they say in the movie theaters.

My comments are just a few, and they are specifically coming on the heels of the testimony that was given this morning about the presentation that was made by the Department of Justice.

It is a process as far as remarks, and that is that with all due respect, Dr. McCabe mentioned that a presentation before this body does not necessarily imply a tacit agreement. I would hope to offer these comments as a sort of head-off, especially coming out of a media and marketing background, to head off some of the downstream issues that are going to be coming back very quickly from the public, number one, as the social feedback loop is shortened, especially via the public reactions to certain news, and also the public oversight will be strengthened.

From a policy-maker's perspective, this view may be okay in terms of a presentation does not imply tacit agreement, but from the position of many of the communities, the record and the history of the record should and must clearly explain either refutation or the position on the issue so that it cannot be construed that an association is made or that an endorsement is rendered. Because the credibility issue comes in where people say "as presented at the" fill in the blank or

"not refuted in the record," et cetera. That becomes important, especially with the issues around the Department of Justice and law enforcement in genetics, because there are dynamic issues around communities and around testing in these communities that may come about at a later time, but that are not being reflected, especially from an anthropological point of view, not being refuted at this time.

Just very quickly, one of them is that the profiling of some of the communities out here, especially communities of color, is that often times they do not take into consideration direct migration from specific areas or long-term endogamy such that you get populations that, if you profile a few families, you may very well have profiled that entire neighborhood or that entire community.

And I say that as just one example, but these issues are going to be coming up more and more. So I think it behooves the Committee to go on record that if this is not something that you are adhering to or something that you are not in favor of that it be very definitively reflected in the record so that no one can construe it at a different time.

Thank you very much.

DR. McCABE: Thank you for those comments.

Questions or comments? Why don't you wait here Kathleen in case there are any questions for you.

[No response.]

DR. McCABE: Okay, we very much appreciate those comments. Thank you.

I would like to thank everyone for the time, effort, and thought that you have given to reviewing our preliminary recommendations and appreciate your analysis. It has been very helpful to us. We will now turn to Dr. David Feigal for a discussion of the FDA's standard review process and the extent to which it includes an assessment of a test, clinical utility, or effectiveness and outcomes data.

This question arose as we were putting our final touches on the preliminary report. In our report, we have highlighted how important the clinical utility of a test is in assessing the clinical implications of the test and its risks and benefits. We want to be sure that the FDA will be able to take some measure of the test utility or effectiveness along with the somewhat more straightforward clinical validity issues, and we have had these discussed both in the panel this morning and then from the public comments.

DR. TUCKSON: I want to make sure I understand the process here. Given that we have got a number of comments, both in writing as well as from the presentations from several speakers just a moment ago, about the decision that we made in terms of FDA, are we going to review that, or is that basically done? And as we hear this presentation, are we to be thinking of asking the FDA representative questions that may be in our minds that would help us to have that conversation? Knowing that FDA did not ask for -- by the way, we are not putting them on the spot and they did

not ask for this, but we are trying to understand better the appropriateness.

DR. McCABE: I think this would be a good time to do that. I do not know what Dr. Feigal's schedule is for the rest of the day. We have some time later this afternoon, but it might be good to try and deal with those now. That is certainly an issue that has been raised by the comments.

DR. FEIGAL: Thanks. Actually, I am here for the rest of the day, and I am sorry I could not join you all day.

At the very first meeting of this group back at the NIH, Dr. Alpert and I believe also Dr. Gutman went over sort of some of the basics of FDA regulation, and what I wanted to do with this passthrough a second time is to focus a little more on the specific issues that have come up in all of the rest of that, but also to go back because, if you did not get it the first time in terms of how things are regulated, you are not alone. I am still trying to understand HCFA. So, if anybody could explain some of these things, this will all work out.

The other comment is that many of these issues are not either/or because there is overlapping responsibilities. So one of the things that I have tried to do in this presentation with help from Dr. Gutman and others is to contrast some of the things we do versus what is done by CLIA, by the states, with the apologies that we may not understand them very well either.

This slide actually sort of goes back to the middle ages of device regulations, about 1976. Prior to that, there were some devices regulated as drugs, like contact lenses and sutures, but in 1976 when the drug regulations came into place, there was a process of taking all of the products that were on the market and sorting them by risk classification. Over time, what has happened is that these classifications are allowed to have fluidity, but they were stratified by risk. The group that had the highest risk were the Class III's, and of the old drugs, the process was to call for PMAs.

Essentially, this became the family of 510(k) predicates. "Predicate" is not a word you use very often in common conversation, but you hear a lot of that when you are talking about device regulation.

These 510(k) predicates in these different classes. Then there are basically two ways of applying for a device marketing. One of them actually is to notify us that you have a 510(k) predicate and make the case that it is substantially equivalent to a previously cleared device.

Early in '76, those were the things that were on the market by '76. Everything that comes into the 510(k) pool joins the other predicates and can become predicates for future devices, and the emphasis on 510(k) is not safe and effective, but it is substantially equivalent. Products are not approved. They are cleared because they match a predicate. There are relatively few Class III 510(k) predicates left, and the other category of products is that if it is a novel product that are not substantially equivalent to a predicate, then a premarket application is required and we will take a look at this process in a little bit.
The key features to the '76 amendments, and they are features we are still rather fond of, the fact that there was an attempt to define medical devices and to separate them as a subcategory of

drugs, it gave the FDA authority to move against violative products. In fact, it gave us some authorities that do not even exist for drugs, but it established a tiered system of controls based on risk. This is a little bit different than the approach to drug approvals. And it established the standards of evidence for marketing claims.

The tiered approach has been one way of describing those are a set of controls. There are some general controls that apply to all devices. The facility registers with us, and they list the products that they manufacture. They are required to notify us of new products unless the products are in a classification that is explicitly exempt.

Every year, in fact, of about the 9,000 medical devices that go to market, about half of them are exempt from premarket notification. Even though they do not have to have a clearance before going to market, though, all manufacturers have to follow good manufacturing practices, also called quality systems, and have to have systems for reporting and dealing with device failures. This is just a general summary, but if you ask what is in the lowest category, what is the lowest category that you would have, that would be an exempt device that has to register and list and follow GMPs. They have to submit reports to us, and then they have to maintain more detailed failure analysis within the companies.

The difference between a Class I, which is the lowest risk, and a Class II is that if the product cannot be assured to be safe and effective with just these very generic non-product-specific type of measures, then in fact in Class II, you have standards. There is a requirement for premarket review, and the standards often come from guidances or external standards.

So what happens when we get an established test, for example? First, you have to ask yourself why is the test established. It is usually established because there is current medical knowledge about what it is that you are testing. The diagnostic devices already exist, and there is the predicate for you, and that the devices are presumed to be safe and effective. So that establishes the test.

Then the issue comes up as well, is that test making an established claim. If the claim is already established by the predicates, if the new test is making the same claim, then in fact the evidence required will focus almost entirely on analytic validity.

The example we give is that if you have got a new way of measuring hemoglobin, we are not going to ask for studies that say hemoglobin correlates with a clinical condition like anemia. We are just going to say hemoglobin is hemoglobin, and it will focus on analytic validity. This would be sort of the logic of a 510(k) of an established test, even though this particular product is different than an established claim.

In the 510(k) premarket notifications, there are about 900 in vitro diagnostics a year that come through Dr. Gutman's division and found to be substantially equivalent by comparing themselves to a predicate. The type of information that is in those applications look at issues around accuracy, precision, analytic sensitivity, and analytic specificity. So that is sort of the framework for established tests.

If we move to a novel test, which is probably the next slide, you have to ask yourself why is the test novel. It is usually novel because there is not a predicate. There is not an existing diagnostic device that is similar enough for you to claim that is what it is doing. However, you are usually developing a test because there is some medical knowledge that makes the test plausible. It is biologically interesting or feasible or diagnostically important. There is some reason that you want that knowledge. If we had a test for which there was no known cause, it would be hard to say what the claim would be.

The test is also novel if the claim is yet to be established. So then the evidence is going to require the clinical validity of the claim because, after all, these are clinical claims. Often, these can be established with surrogate endpoints. The clinical outcome studies, though, are usually not required. So, by surrogate outcomes, again, if we had some novel measure of hemoglobin, we would, well, actually, I will give you an example with PSA in a moment. But one of the things that is a feature of the PMAs for a new product is sort of an intense interest in labeling.

It is instructive to look at what goes into the label because this is the kind of information that if you were clinically trying to apply one of these tests, this is the kind of information that we would be trying to provide for you through the manufacturer studies in an approved label. Next slide.

These products are the products that go through PMA, premarket approvals. You can see it is a relatively small volume of about 12 to 24 applications per year, and the evidence level set in the laws, language from the statute, is that the safety and effective evidence comes from well-controlled investigations or other valid scientific evidence sufficient to determine the effectiveness of the device. And so, usually, in that setting for in vitro diagnostic, that means looking at clinical sensitivity, specificity, and predictive values.

And if you take a look at the genetic tests, what is daunting, given the number of them, is that most of them do not have predicates. So we are looking at adding a very large number of tests to a process that currently has a much smaller volume. I think the next slide starts looking at the labeling.

So, when you have a PMA that is approved, this is the type, this is the structure, and this actually comes from the regulations, of the kinds of things that you would expect to be able to know to write a label. So, the name, that is straightforward. The intended use, that is the claim. A summary and an explanation of the test, principle on the procedures, information on reagents and instruments, information on specimen collection and preparation, these are all pretty straightforward. Next slide.

Procedures, results, limitations of the procedures, expected values, specific performance characteristics, bibliography, and some information about the business. And then the next slide. Oops, I think I was missing one of the slides.

In the labeling of this slide comes the performance characteristics which will be the clinical studies that would be required to show how the product would perform. Can I have the next slide.

So, just to give some examples of tests, an example of novel tests, the PSA test was approved in

the early '90s. The evidence was that it could identify additional tumors, but the actual performance in a clinical setting, saying if you screened a population, would you in fact have better overall population performance with this test, was something that was never established. But the product was allowed on the market with that cautionary type of labeling.

The next slide is a more genetic example in the HER-2/neu assays. There have been three approved assays. The first assays were approval-based on the limited prognostic information that was provided, but others were based on selecting patients for specific treatments, the monoclonal antibody that is associated with this marker, which is probably an example of a pharmacogenomic test. Again, the label does the job of saying what is known, but, again, there is clinical information that has to be collected to put into that kind of labeling.

One of the questions that comes up in the process of collecting this information is what is the role of investigational device exemptions and how are they used in this kind of a setting. We do have the option to waive the use of IDE in certain types of settings, and it depends on the use of the information. There are settings where research can take place where the information would not be made available to patients, and that is a setting where some of the oversight could be waived.

There also is waiver based on the issue of risk, and if it is considered to be a nonsignificant risk device, then the issues of oversight of the experiment rests entirely with the IRB. And the IRB in fact has the authority to decide in some of those that they can waive informed consent or in fact that they may want informed consent, but it is a local issue.

If it is a significant risk device, then FDA and IRB would both have jurisdiction. The kind of in vitro diagnostics that have had the higher level of oversight have been the ones that have particularly strong messages, such as HIV testing or other types of tests where the accuracy and understanding the result are extremely important. Next slide.

This is a chart where we have tried to lay out comparisons of the review process, and we have compared ourselves to the process in New York State.

Registration and listing. In general, our registration focuses on finding the devices, although we know where the manufacturing facilities are as well, but our emphasis is probably more on identifying the devices. CLIA, on the other hand, organizes their efforts lab by lab, rather than device by device. New York State does a combination of both.

Informed consent. I have discussed a little bit about how we do it, and we know that New York State from their presentation does look at this issue in some settings.

IRB oversight, again, is something that there are specific federal guidelines on composition of IRB, conducts of IRB, that when they are required that we do have oversight on that.

It is down at the area of sort of analytic and clinical and validation of clinical utility that you start to see some of the differences. For analytic validity, the FDA approach is very definitely to look at each product, device by device, in fact claim by claim within devices. Whereas the CLIA starts with the laboratory and will look at the analytic validation of specific assays as part of the process

of their oversight of laboratories, New York State's approach, again, seems to be by device.

Clinical validation for novel devices, for a device where there is not a known clinical reason to get the test, those would usually be in the PMA category and would in fact require a clinical validation. The comment that we think is correct from New York State is that, yes, they could assess this, but no one has requested a claim for clinical validity at this point. And so they have not actually had to assess that yet.

In terms of clinical utility, there are times actually when manufacturers will bring a product to us with the utility claim, but it is fairly unusual in the in vitro diagnostics variety. But again, a lot of the type of evidence that is required works backwards from the claim that is made for the product. Next slide.

Let me just, again, set this a little bit in the setting of genetic diagnosis and what are we up against and what types of tests are out there. We have put together a list that is probably an incomplete list of some of the types of testings currently used, and I think much of the focus of this conference has been on the molecular tests.

One approach would be to ask whether or not one way to deal with the large number of tests would be to have standards set for certain types of laboratory methods that would streamline any type of application process.

The next slide actually shows the difficulty with doing this. This is a slide that is unreadable in purpose, but these are the subsettings of the previous slide. So the previous slide had the broad headings that were here, but you can see that once you get down into the details, and there are probably some sub-settings below this, it is hard to make the case that this would be a simple matter of saying this is the standard way of finding a gene and, if you find it that way, that will be an acceptable way of doing this. Can I have the next slide.

This is some of the data that actually has been taken from presentations at this meeting. So this is kind of a review, but the task is that if you look at the databases that list tests available, there are about 710 worldwide, about 300 in the United States, 443 separate laboratories worldwide offering the test, and 158 laboratories in the U.S.

DR. McCABE: David, are you going to finish up soon? Because we really want to have some discussion.

DR. FEIGAL: Yes, I am almost done.

One of the things that is daunting about this, and we have cut off the numbers, the actual Fragile X syndrome starts with 84. There are 84 separate laboratories that offer Fragile X syndrome tests. The numbers go down. You can see they are above 26 even when you get to hemoglobin S. So, when you ask the clinician which test are you going to choose and what do you know about the test, this is the daunting number of different varieties of the same tests that you have available. This is just a list of the top 30. Next slide.

These are the numbers that are FDA-approved. Next slide. Six out of all of the tests that have been there. Next slide. And these are where these tests are being done. Next slide. The vast majority of them, 50 percent of them, are in the universities, 21 percent are in commercial reference labs, and 29 percent are in hospitals. This is the home of home brew, if you will.

And then, finally, as you know, there is some regulation of the analytes that go into these tests, and these are the approaches that are taken to the analytes, but this is a far step away from the type of regulation we have been talking about these tests. Is that the last slide? No, this is the last slide.

One of the approaches of FDA regulations is to try to identify the least burdensome pathway to the market. It is clear that there is going to be a need to do business differently, given the large number of tests and the way that this area has started out, but that does not mean that we should not find some way to do it, even if there are some walls and barriers that we need to break down.

Thanks very much.

DR. McCABE: Thank you.

We have about five minutes for discussion of this presentation, but other issues around FDA, and we will have time to come back to it later this afternoon.

DR. BURKE: I guess I will just make a comment. It seems to me implicit in your presentation that if we were to identify clinical utility, as we have, as an important parameter to be evaluated, that some additional process would need to be developed or some elaboration of existing FDA process.

I guess I am understanding that clinical utility is evaluated if a claim is made on clinical utility. And I think where the discussions here have gone is that we would expect tests to comment on clinical utility; that is, not wait for a manufacturer to decide whether or not to make a claim of clinical utility.

DR. FEIGAL: Clinical utility varies in how hard it is to determine. If it is for the diagnosis or confirmation of a diagnosis of a disease that you have got other clues to, you may be able to figure it out in a fairly straightforward fashion.

On the other hand, if you want to show that knowing that information, even for that acute disease, improves the management of that disease in some way, that is clinical utility. That is very difficult. Very few diagnostics have ever done that.

But I think the sense that this group has used clinical utility often has been to get beyond the point of saying: yes, that was the gene; yes, this is a genetic syndrome; how does this fit into the practice of medicine and using genetic information.

I think that the question that we would be rightfully asked by a manufacturer and are trying to do a regulatory job, if someone showed that they could measure the gene and that is all they were claiming, would we have any basis for not allowing them onto the market, and we would not.

Unless there was no plausible clinical use for that information, then in fact that would be the entry into market.

On the other hand, if the company wanted to claim that this helped predict development of breast cancer and they had no such data, they would not be allowed to say that. They could say that they had found a gene that was of some interest, but that would be one of the more difficult areas as to when those should actually come into market. Those are the things we usually take to advisory panels.

DR. BURKE: I just want to say I think you have identified an area of great concern to the committee. My sense from the conversations we have had is that we would want a manufacturer to make an argument of plausible clinical utility, that that should be a requirement. And it might well be that we all understand that sometimes that is merely a plausible argument, rather than an argument based on outcome data, and that the nature and strength of that argument influences how the test is labeled.

DR. TUCKSON: I will yield to Elliott for a minute. It looks like he has something right on this point.

MR. HILLBACK: I think you get to the point. One of the points that we have often thought about is what if we in the lab, as a lot of non-genetics labs do, just provide the data on the analyte. Your cholesterol level is 400. What that means is up to the medical community to tell the patient. We do not do it. The labs do not do it.

We could very easily say we found a mutation at delta 508. We do not have a clue what that means. Of course, we do, and we provide that extra service through our genetic counselors, through our lab directors signing out the cases. That does not solve the fundamental issue.

The fundamental issue is not FDA versus the labs. The fundamental issue is, and I want to elevate to that and hope that we can stay at that level, how do we make sure that there is useful information for the doctor to use, back to Dr. Donnenfeld's comments and many comments that are written.

We do not want to play the game of let's go play 510(k), let's go play this game that David laid out, which is all we will do is tell you we found a mutation, and the rest of the medical community will figure out how to use it, but in reality there are virtually very few tests where the lab, the manufacturer, is doing all this innovative research and deciding what the test is.

If you take the latest, and I took it the other day, the latest journal from the genetics community and go through the list of articles, 65 or 70 percent of the articles all show a correlation between a mutation of some sort and some disease state. None of those are done by a lab. They are all done by researchers. And yet, if we were asked to do that test, now you are going to say to the lab, "Now you have to prove that that is useful to do." I think this is where we get hung up that we have got to go back to the fundamentals, what are we trying to get at, that the body of knowledge that we all have is there. I think that is where you get into it cannot be FDA versus labs, It has got to be the whole body of knowledge we talked about, who generates it, and how do we deal with it. Therein lies a lot of conversation later on today, I think.

DR. FEIGAL: From our standpoint, it does not have to be generated by the lab if it is known in the literature. You would have to show that you in fact are measuring the gene that was shown in the literature, and then you can have the literature.

The problem in a lot of these fast-moving areas is the literature is pretty slow. So, oftentimes, the manufacturers actually will have data in advance, and the research community will have information that is in advance that is brought to us. Often, it is not unusual to have it come in a couple years before it reaches the literature. So I think there is some flexibility in the process. But I think the problem with clinical utility is it has so many different meanings that I think it is probably almost going to have to get down into some specific cases. I think there are some very hard situations where you can be told about the presence of a gene that might predict something. We do not know how well because we need to have follow-up, and no one has ever followed up a cohort of people with this gene before. That is a very hard situation to know what to do with.

I would agree with Elliott. It is not a real regulatory issue. I think the regulatory principle is you get to say what you know. What we are all grappling with is how do we learn what we need to know and have some process for evaluating that.

DR. McCABE: I have got three people here. Please be brief, and try to be brief with the response. Reed, Pat, and Kate.

DR. TUCKSON: Briefly. First of all, great presentation. I really was struck by the necessarily bureaucratic -- that slide that was deliberately scary was scary, and it made me really nervous about putting anything into that kind of mix.

Is there any precedent for an outside consortium developing and working on the kind of things that you just got into discourse with, with my two colleagues, that then presents some refined digested material into that mishmash that then allows for efficiency, speed, appropriately, of course, so we kind of move stuff forward? Is there any precedence in FDA for working with a consortium that predigests?

DR. FEIGAL: The easiest one to point to is the recognition of standards, and these are done by a wide variety of different standard bodies. If someone can assert that they have met some, usually they are performance standards, but there is no reason they could not incorporate something like this. If they can show that a new test meets a certain standard and asserts conformance to that standard, then that is all they have to tell us about it.

The trick is that it is hard to get the standards written, but there is a very large activity in doing that. Then the standards can be substituted for parts of the application.

DR. McCABE: There is a precedent within the federal government, and that is within CLIAC where you can have deemed status. Pat is going to speak next. So maybe you can address that, too, briefly, Pat.

DR. CHARACHE: I would like to make a comment and ask David a question, and I will speak very

briefly to deemed status.
My comment is that I think Wylie, with David's answer, has put her hands on the pulse of a very major gap in current clearance mechanisms. A lot of our problems are people who simply say they can detect a given gene, and then leave it to the lay press to decide whether that is helpful or not helpful in terms of clinical diagnostics.

I think we do have to have something in there that relates it to disease and predictive values of disease, regardless of whether anyone is making a specific claim, or else say something which is very specific that I cannot figure out.

My question for David has to do with an impact on the volume of things to be assessed. If you have a test for a given analyte, let's say a Factor 5 Leiden assay, and someone develops a new test which uses different stringencies, so your sensitivity and specificity would be different and predictive value would be different, although it is the same target, would that count as a 510(k) equivalency or would the new group have to show the sensitivity and specificity of their tests for Factor 5 Leiden assay?

DR. FEIGAL: Usually, in the 510(k) for two tests is that you want the new test compared to the gold standard, and the new test has to establish a sensitivity and specificity. It is usually done against reference samples in an analyte type of a setting.

DR. CHARACHE: So we are talking, then, about each lab that has a different master mix or different temperatures for ligation and so on, would have to show sensitivity and specificity, although less numbers.

DR. FEIGAL: Again, I think the model may not entirely apply to genetic tests, and I think that is where we have to have some flexibility. There are genes that will be useful in working up kindreds. That probably presents a different level of evidence than if you are screening a population for a more complex situation.

I think it is hard to lump all of these things together. The bottom line is that basically to label the test, you basically have to say how does this test perform, and have some information about some actually performance. That is the information that you want the labs to be giving out with the test. If not, then they should acknowledge that it is an experimental test and that it should go under the rules of how do you evaluate experimental tests, sometimes with informed consent, sometimes not. Then you are in that different kind of setting.

DR. CHARACHE: So, if they cannot say what the test means, then it would be under the IRB and not in the marketplace.

DR. FEIGAL: If they cannot see what it means because the test is still being developed, so they do not know how accurately they are saying it and so forth. That is one thing. If they cannot say what the test means because it is a gene of uncertain significance, but it is well measured, that is one of the tougher ones because its analytic performance would be great. That is one of those where you get into these dilemmas. Do you let the medical consumer and the patient consumer decide that they are willing to take well-done uncertain information. That is a different question

than a sloppy test because it has not been refined yet.

DR. CHARACHE: CLIA there does say that a laboratory director shall not do a test that is not useful for the patient population on which it is performed.

DR. FEIGAL: It is in the eye of the beholder, though.

DR. CHARACHE: In terms of the exempt and equivalent laboratories, I think that would probably be better answered by Judy Yost in terms of how HCFA enforces these things.

DR. FEIGAL: Yes.

DR. CHARACHE: Deemed status.

DR. McCABE: Maybe we can get to that later, Judy.

MS. BEARDSLEY: I just want to ask kind of an open-ended question. The last time we were here, we talked about the FDA process, and we talked about our desire to find a way to have some review of tests, but also to be able to get tests on the market in a timely fashion. You have described the FDA process today. I think you were going to go and think about how to fit these tests into that process in a way that would get us to a place where we could get some sort of expedited process.

Can you give us a little bit of a status on your thoughts about that?

DR. FEIGAL: Well, I think if you would step back and look at the vast majority of tests out there, although the volume of the testing that is being done has been gradually increasing, it is pretty unlikely that the majority of these tests have gotten beyond what would usually be considered a developmental stage. And so, if most of these were to actually tell us everything they know about the tests, we would say, "Well, you are still working on it." So then I think the question for this group gets to even though the utility question will eventually be interesting, the real question now is when does the test stop becoming an experimental test and when do you stop getting informed consent because you are using a developmental test where you cannot yet characterize the sensitivity and specificity and the prediction versus tests where you know that, but you do not know the longer-term issues.

MS. BEARDSLEY: Can I follow-up on this?

DR.McCABE: Yes, Kate, and then we're going to have to move on.

MS. BEARDSLEY: So, if I am understanding right, what we are really saying is the test would stay in a developmental stage probably for longer than we think about that happening now. If that is true, then would they be restricted in terms of the number of people to whom they could be available? I mean, would they be a standard IDE, or would there be some way in which they could be used more broadly as long as it were carefully disclosed?

DR. FEIGAL: I think it would depend on the use. The problem cases would be developing tests for screening where by its nature you would have to test large numbers of people, but I think the way that you all can think through this with us is sort of the issue of how much would you have to know about a test to say that is a well characterized commercial test. If someone cannot tell you some of the basic performance characteristics, even at an analyte level, which I imagine many of these are, then they are still under development. That is why I do not think we are looking at facing 750 PMAs.

DR. McCABE: Thank you, David.

DR. TUCKSON: Ed, at some point, can we come back? I think that what we heard is really getting us a clearer definition of the issues. I am really interested now in what the representative from BIO, for example, what does that mean, what you just said, to the normal conduct of this industry as of today. If the BIO guy at some point later can come back and tell us the implications of what we just heard, which is perfect -- thank you -- what it means, that will help me to understand a little bit better.

DR. McCABE: We will have time to do that after the CDC presentation.

We have asked Dr. Muin Khoury and Dr. Bob Martin, director of CDC's Division of Laboratory Systems, to provide updates on the public-private collaborations that are underway and the data collection on genetic tests and genetic testing processes. I have asked them to shorten their talks so that we can have time for discussion. So, if you would, I would appreciate it.

DR. KHOURY: I usually speak fast. So I will try to improve my speed.

This has been a very interesting morning so far. I have learned quite a bit myself. Although every time I hear the FDA process – oh, what happened here, we lost the Grand Canyon. We only have half a canyon here. What I would like to do is give you a coordinated CDC approach to how we deal with genetic testing assessment. We have had quite a bit of internal discussion within the agency, and certainly the leads from the laboratory side and all the programs. And we have even coined the term "GenTAP," or genetic testing assessment program.

I will give you a little bit of an update, a status of our projects, and then move more into what GenTAP would do and is doing right now.

In 1997, Tony Holtzman's report paved the way and challenged CDC and other agencies to do a number of things, and two of the areas that we were challenged to do is coordinate this data collection piece that I have been working on ever since. It does not get any smaller. It gets bigger and bigger every day.

Also, because of CDC's role in CLIA and the scientific arm of CLIA, that report challenged CLIA to beef up its recommendations. So, in 1998, we formed an HHS-wide interagency group that has been discussing the data issues which led to further two pilot projects. I will give you an update quickly. Then CLIA was doing its job in forming the CLIAC Genetic Subcommittee, which you have heard before that led to some recommendations.

In 1999, we basically worked around two diseases, cystic fibrosis and hemochromatosis, to illustrate the spectrum of adult and child conditions for which genetic tests are available, and we held these two workshops. CLIAC kept doing its work at the same time.

In 2000, right now we have two pilot projects around the data issues and, of course, the CLIA Notice of Intent and the creation of the CDC lab forum which you will hear a little bit more from Bob Martin. Next slide.

Basically, this issue of data collection is so difficult and involves so many stakeholders from all the agencies, the private sector, the lab developers, consumers, and researchers. We have begun forming these working groups around these two diseases, identified their membership, began to review both the published and unpublished literature, and began to develop the framework, if you will, the template by which we will look at analytic validity, clinical validity, and clinical utility.

The members of the consortium are beginning web-based methods of communication, and we are going to have later on in the summer and fall two meetings, one around each disease. We are still hopeful that the final report of these two efforts will be done by the end of this calendar year. Next slide.

Let me put this in the context of where we are heading with this. Because we sit at this crossroads. HHS is obviously getting advice around genetic testing issues from both CLIAC and SACGT. What is our hope right now is to begin to work with a large number of stakeholders and within HHS to develop that ultimate knowledge base. I have heard the words "what we know" and "what we don't know" several times mentioned, especially by Elliott last time. That will fill that gap between the gene discoveries and the application in medical practice.

You can think about them in four domains: one are the lab issues; the public health issues around testing whole populations; clinical practice, one on one or family-based; and, of course, the ethical, legal, and social implications. And for each one of these, there are specific data collection analysis dissemination for each one of these boxes.

What we are going to try to do is -- next slide-- begin to provide that template, especially around these two areas of traditional strength for CDC, around the lab quality assurance and the public health assessment. The two key issues here is the coordination with all the HHS agencies because all of them will be involved, from the regulatory side to the research arm, and this is going to follow a public-private partnership model. Next slide.

So what will be the goals for this effort? And the goals -- I look at them in two domains. One is developing, evaluating, and updating this accumulated knowledge base on genetic tests, meaning the analytical validity, clinical validity, and clinical utility, but also develop information on the genetic testing process. And maybe this is the first time I make that differentiation clear because genetic tests are one thing that feed into a testing process from the pre-analytic, analytic, to the post-analytic side of things. This is where the relationships with the regulatory side of things and the CLIA might come in handy, but these are the two goals of this effort.

Some of the products are still a moving target, depending on where the regulatory side of things falls, and also the categorization side, we might get started on different tests. You can start by thinking that all tests should have a database of claims. We are using the FDA model here, but anybody who claims to have a test, let them put their information in the public domain. How much of that will be reviewed, obviously the non-proprietary value of these claims could be reviewed and put forward to the public, the consumers, as well as the health care providers and the policy-makers. The consortium model or the group models of data collection analysis will continue. I will mention to you a little bit, the next date, after these two pilot projects are done.

For a small fraction of these, there were be formal technology assessments a la U.S. Preventive Service Task Force deliberations in which you take only a few of those and have a very intense discussion on the clinical utility and use for these. And obviously, surveillance data would be lab-based on the genetic testing process and how well it is going, the lab performance, whether people are getting informed consent, et cetera.

Now, what is our next step in the beginning of this GenTAP effort is an RFA that was supposed to be out on the street last Friday. I was told that it will be out either today or tomorrow in the Federal Register. It is sort of a program announcement. We would like to work with an academic institution to develop the research arm of this development of the model system for data collection. This is a three-year effort, and we would like to go beyond the two tests that we are learning about right now and do an additional three to five per year that come from different parts of the spectrum of genetic testing and, again, design a model system for data collection and analysis. And then three years from now, we will evaluate this approach to see how best to develop this model. Next slide.

Where we are right now, we are at with the beginning of GenTAP, the two pilot projects as well as the RFA that is going on. Hopefully, the work will be started in the winter this year. As an integral part of this discussion, the Division of Laboratory Systems under Bob Martin's leadership has begun exploring some of the lab issues around this area and the formation of the lab forum and how this is going to feed into this process.

So I will turn it to Bob, and maybe we can entertain questions together at the end.

DR. McCABE: Thank you. Bob?

DR. MARTIN: Again, I would like to thank you for the opportunity to present this information today. I think at the last meeting, I pointed out that it was almost serendipitous that we were thinking along the same lines in terms of what was needed in the way of a forum of an expert panel. Even in today's discussions, I would think we are back at that same point again. So I would like to tell you a little more about how this laboratory forum or expert panel will be working.

And I would like to point out, again, that this forum exists within the framework of HHS providing information back to CLIAC and to SACGT in order to deal with the issues that we have to deal with, much in the same way, for example, as you took the definition today from the CLIAC definition and incorporated it now into the SACGT definition of "genetic testing."

Again, just to reiterate what I mentioned at the last meeting, the purposes for a forum or expert panel, this is to provide a venue for dialogue for laboratorians involved in genetics testing, to provide a framework for consensus development, to establish a process through which voluntary or regulatory change could occur.

I would like to emphasize the relationship of this forum to other committees and advisory groups. Again, the forum is an expert panel that will provide support when requested by SACGT, CLIAC, or others within HHS. The forum will bring issues of importance conversely to SACGT and CLIAC and will interact with other groups such as the FDA Genetics Advisory Panel and, of course, HCFA as well.

The question was what would be the contribution of a forum in terms of the process for test assessment. One of these could be the development of specific criteria, and a second would be the development of a process for making this determination.

We just had a meeting on Friday at the laboratory forum. To remind you, there are about 20 different organizations represented at that forum, ACMG, CAP and many others, including genetic counselors. Basically, we came up with a proposed criteria and a model process we are going to tell you very briefly about. We are going to focus on heritable diseases, identify categories of intended use. Then, as Dr. Collins mentioned earlier, once that model is identified, apply that model to different candidate diseases in that category and integrate with the current pilot disease-specific data projects that Dr. Khoury is running in order to maintain that data.

So the test categories were basically the test categories that SACGT had developed, and we put some examples of tests in here, diagnostic confirmatory testing, such as Fragile X, CF, or Factor 5 Leiden, predictive tests such as the BRCA, presymptomatic tests such as Huntington's, carrier testing, again, an example of the test that would carry over to different categories, prenatal, and orphan testing such as Marfan's syndrome.

Now, the model development is going to be accomplished by having a few of our members develop this model. Dr. Mike Watson and Dr. Walter Noll are going to take the lead on this, but working with others within the group. Basically, they are going to start with a retrospective analysis of easily identifiable data sets; for example, the proficiency testing data and other surveys that might be available to them. This data would include pre-analytical, analytical, and post-analytical information.

They are going to suggest some practical solutions for the identified problems. They will be looking for the gaps in this process and, again, identifying some of the practical solutions. These, again, are laboratorians that do this on a daily basis.

So, in conclusion, again, I want to finish with this slide because I want to point out that we are doing this in the current environment of HHS, working with CLIAC and SACGT, and the process that we will develop will include the gathering of data and making available that data to the public as well.

I believe that is the last slide.

DR. McCABE: Thank you very much, and thank you for shortening your talk.

We have five minutes or so for a discussion of this presentation. I think there has been some discussion today about the need for having laboratorians involved, and it looks like this is moving ahead and that there will be specific examples that will give us some sentinels in terms of how useful such an approach would be. So I think that I am pleased to see the progress.

DR. BURKE: I agree. I think this process might go a long ways to in essence being that subcommittee process that we talked about earlier that would help us to deal with categorization, but in that context, it seemed to me that we talked earlier about wanting to be sure that we had the same kind of broad representation that, for example, this committee has. And I would think that includes consumers, clinicians, biotech industry, et cetera. So I just want to clarify whether that degree of broad representation is already incorporated in your process.

DR. MARTIN: Not in the forum itself. We have not addressed that issue. As I said, the forum to this point has been considered, more or less, an expert panel, and you will recall this is just our second meeting. The first one was basically a very formative meeting. The membership, of course, is not closed, and we would consider any suggestions.

DR. McCABE: Could we perhaps ask that for our next meeting, you bring the membership to us so that we could look at that, please?

DR. MARTIN: Yes. In fact, we can send that to you.

DR. McCABE: Okay. Or, maybe even get it to us at this meeting. I do not know what would be possible, but for us to take a look at it.

DR. MARTIN: Sure, we can do it.

DR. CHARACHE: I have been struck both by the FDA's discussion and by the discussion at the forum. One of the problems, I think, we have had has been to define who should do oversight before we got to the specifics of what we want to have overseen, such as do we want someone to market that they can detect a certain gene or do they have to say what this gene means in terms of disease if they are marketing it as a clinical test.

This, I think, entered into that list of the target analytes to be modeled. I think the concept was if we could model something that represented an orphan disease and model something that represented a predictive marker. That we then would have identified some of these issues before we get around to saying who is the best person or what is the best strategy for overseeing that that happens.

And also, I think the goal was to have this specialty working group that we have heard about four people today say should address some of these issues, and rather than reinvent an SACGT, but rather have a group that could focus on some of these issues and then bring these forth for a

discussion of a broader panel as well.

DR. McCABE: Thank you. Reed?

DR. TUCKSON: I think I like that last point and Wylie's point as well. When she says it goes a long way, it seems to me that the horse is out of the barn here. I wonder what would be the result of our recommending something different from an augmented forum that already exists. Would we be creating basically mass confusion given that you have already got a significant head start with a significant input of a number of people and to which you are willing to amend? I am just trying to think of what would be the result of recommending anything different than this group.

DR. McCABE: The reason I asked for the membership, one of the things that we will do is we have been looking at what already exists within the federal government, and that has been included in various documents.

This has been somewhat of a moving target. So, here, we have something new that I do not think is included in the document. Is that correct? I do not know that it will be included in the document that goes forth to Dr. Satcher following this meeting, but at least it would be something that we could consider in the future.

DR. KHOURY: Can I answer Reed a little bit? I think we are early enough in the process right now. What CDC has been trying to do is respond to the challenges that have been put to us, first, by the task force and, second, by SACGT. So we are early enough in the process that we can adapt to any recommendations that this committee can give us.

DR. McCABE: The other thing that I have been impressed with as I have taken on this responsibility and looked at other advisory groups, I think that it is important to have public representation on advisory groups. So I think that is another reason to look at that so that it would not be trying to create confusion, but perhaps to have some representation beyond the traditional representations on expert advice.

DR. TUCKSON: But I think you mean that in the sense that the confusion question would be is if they were unwilling to augment their already-existing activity, then we would have to think of something else, but if you are willing to augment and then we still proposed a different mechanisms for this data collection, you are not going out of business, I presume, no matter what we decided.

Thank you.

DR. McCABE: Michele, last comment, and then we are going to move on with our discussion.

DR. PURYEAR: Can FDA and CDC explain to me how they are working together on this? Because I think the reality is that these are not in conflict; that you guys are actually working together. They are being presented as two different initiatives, and I know FDA and HCFA are working with CDC for sort of a joint effort or joint modeling or a joint conceptualization of a model for oversight. Could you guys present that, what you sort of have agreed?

DR. MARTIN: I can start, and Dr. Feigal will finish up.

I am not sure what you meant by two different models.

DR. PURYEAR: Well, the FDA presented and then CDC presented, but I know in fact you guys are meeting together.

DR. MARTIN: Right, right.

DR. PURYEAR: I know they are members, but that is not coming across. I think it should be clarified that these are not necessarily two different things; that there are some joint efforts going on.

DR. MARTIN: That is correct. There is joint effort among FDA, HCFA, and CDC, all of which are members of both CLIAC and this forum as well. So you are correct.

DR. KHOURY: There is also another point. Whatever the regulatory process moves forward to, this process is needed, anyway. It is still early on in the game to be adaptable. So the data collection piece as the genetic assessment from a clinical perspective is going to go on.

Now its magnitude, its size, and how it is going to be shaped up will depend on obviously the recommendations from different groups, the available resources, and how the agencies will work together for implementation.

DR. TUCKSON: Let me just make sure I understand one thing. Your group is charged by the Secretary or is this just a group of the CDC deciding to do something nice?

DR. KHOURY: It is within the mandate of CDC to do all these activities that have predated genetics for a long time. We do surveillance. We collect data. The CLIAC group has been doing CLIA for many years now. So we did not have to get special permission.

As a matter of fact, I have a genetics oversight group within the agency that supervises what we do, and they are very excited about this being the central role of the mission of what CDC should be doing.

DR. FEIGAL: Let me just give an example of FDA and CDC in another area real quickly. Opportunistic infections in HIV both in adults and children, the CDC put together a task force. They developed rules of evidence where there were randomized controlled trials, where there were case reports, where there were expert opinions, and they made recommendations, a PHS task force-wide recommendations for how to treat opportunistic infections in HIV. They have also done it in cancer. That was a separate process from the regulatory status of the products. Some of the products were approved for those indications. Some of them were available under IDE. Some of them were available only through the CDC as the IND-holder. Some of them were even more difficult to obtain. But it was an expert panel looking at the recommendations based on the scientific evidence.

FDA's role in all of that is that some of those would be claims that manufacturers would be allowed to make because they had met the standard of evidence and others would not, but that is a different kind of a mission. So there is nothing incompatible about putting together a public access database about claims. If the manufacturers were to overly commercialize it, then that would begin violating some of the laws.

We have permanent jurisdiction over IVDs. Whereas, the CDC's mission can change the emphasis and their programs could change, although in many areas like this, there is very, very long-term commitments in these areas.

DR. McCABE: Thank you. We are going to move on now. Thank you very much for your presentations. We are going to move on now and go back to the discussion by the panel.

There were a couple of points that were raised in the public comments. There were a number of points, but a couple that I made notes on, Kathleen Rand Reed saying that there should be a repudiation of any use of genetic information for profiling and concerns about communities and how genetic information could go from being individual information or family information to community information.

Is there any discussion on that point? We discussed it in terms of social issues in the document. Do we feel that it is strong enough? Does it need to be stronger?

DR. KOENIG: I am not sure exactly what action we should take, but I just want to reinforce the notion that this is a potential use of genetic testing. Actually, at Stanford tomorrow, we are having a seminar with a whole bunch of population geneticists and others speaking to reflect -- and someone can help me with this, perhaps you can -- about a new law. It was either New Hampshire or Vermont that has proposed a law to identify Native American status with DNA testing, which raises another whole issue of the sort of non-clinical uses of genetic tests. It is those kinds of uses that I always have in the back of my mind, or that is one kind that I have in the back of my mind when I think about these kinds of boundaries. You would use the same kind of a test.

DR. TUCKSON: As I think about it more, what I would look for is while we do not want to extend our range beyond the clinical and medical utilities here, that I think one of the things we have to be clear or helpful in is to at least make a statement that will allow our recommendations to get a fair hearing in all of America's communities.

If it were known or perceived or even suspected that what we were getting at here was the use of these tests to predict criminality or those sort of things, given the experience of the African American at least as one part of the community this country has, immediately they would be suspect in all of these areas, and it would make it very difficult for many clinicians to be able to effectively counsel their patients in the legitimate medical use of these tests.

I am well aware of the furor that accompanied the Secretary of Health under the Bush administration's Advisory Committee on Violence when this issue was not clearly addressed, and

as a result the entire report was thrown into disrepute, and the motives of the panel and the Secretary were severely challenged and it added fuel to an already bad situation.

So I guess what I am getting at is I would want to make sure that given the suspicion around Tuskegee, given those kinds of concerns, that we want to be very clear to distinguish what we are talking about from these other pejorative kinds of things and also that how we phrase it is done such that the counseling around this from a medical point of view is not polluted by these other polluting kinds of phenomena.

DR. BURKE: I think Reed's comments really underscore why we introduced the concept of social issues as part of how tests would be categorized and why it is important to keep that concept within our purview even though it is going to be hard to define.

DR. McCABE: So perhaps we need to give some examples as we have done in other places.

DR. BURKE: Yes.

DR. McCABE: We can give some examples that specifically comment on the misuse of genetic information in the past, and we can try and be a little more specific. Maybe that will help this issue on the concept of social issues being vague if we put it in there.

DR. BURKE: If I could just add, I do not think it is simply a matter of good use and misuse. In fact, the law proposing use of DNA-based tests to identify Native American status clearly got passed because there were people who thought that was a potentially useful way to deal with a social issue, but that is clearly an example of a genetic test use, first of all, that may be highly controversial. There may be disagreement on that point, and it certainly has major social implications that make it a different kind of use of testing.

DR. KOENIG: I think the other thing that we could probably point out in the report that would be useful is that all of these kinds of uses, even the one that I mentioned, they are highly speculative. Most people working in this area would say it is not even feasible. Yet, violence is really the same issue.

Francis actually counseled this in one of our first meetings that, when we mention some of these issues, it makes it appear as though these are possibilities by our taking them seriously. I think we just need to point out that they are not really technical and scientific realities at this point in time. It is sort of a tightrope that we are walking on. If we mention them too much, it makes it sound as though they are real and possible.

DR. McCABE: Could I ask several of you to look back at the document overnight tonight and just come up with some examples, something that we can put in parentheses or after a colon when we address social issues the initial time, so that we can inform the reader as to what we are getting at there?

DR. BURKE: Just one brief follow-up to Barbara's comment. I think the other point which I think we have already incorporated in our thinking is that when we look at the criteria by which tests

should be judged, we look at a whole package of different criteria.

So, for example, if there are significant social issues that arise around a particular proposed use of a particular test, it is likely that we are going to conclude that clinical validity needs to be very, very high; that is, that the bar needs to be set very high when you are making certain kinds of social distinctions. Whereas, to use a noncontroversial example, a genetic test that predicts some degree of increased risk for cardiovascular disease that is amenable to certain kinds of readily available management, hypertension management, hypercholesterol management, et cetera, it would not necessarily require this same threshold of clinical validity. I think that concept of interaction of different factors has already been present in our discussion.

DR. McCABE: The other thing that Reed had brought up during the public comments was the issue about FDA and BIO. I do not think Michael Werner is here anymore. I think he may have left.

Reed, would you like to comment further on the points you wish us to follow up with in the discussion?

DR. TUCKSON: As I recall it, it became real clear that once something goes into the legitimate and well-time tested process of the FDA, there are certain inevitable results that occur. There is a chain that has to occur.

And there was almost a rate-limiting step that David sort of described. What I was trying to get a sense from those who are in the industry is, based on his comment, what would that mean for the industry at this particular precarious moment.

The point that the industry people were making, it seemed to me was over and over again and I think it has put a lot of us in a quandary here, is if you use the FDA mechanism, then you will introduce a level of bureaucratic oversight that will stifle and, although it is a little dramatic, kill this industry. You certainly will stifle discovery and innovation, and you will stifle physician subjective decision-making in the real world today and so forth. It's the point they keep making over and over again.

They keep making the point in addition that things are okay now, that if you just leave it alone and let CLIA do its thing, everything will be fine, thank you.

What I am struggling with is that when David suggested that you go into the FDA system, there really are some consequences. You put brakes on things right now that are inevitable. So what I am trying to get a sense from the industry, then, is how real are those brakes and are there then any fail-safe mechanisms, does that then influence at the end of the day whether or not we stay with our recommendation about using the FDA system. I basically just wanted to know whether or not it is true.

DR. McCABE: David, if you'd like to respond to that? Maybe also along with that, tell us how many PMAs were submitted. You told us how many were approved. So the question is, is the same number submitted that are approved or is there a huge backlog.

DR. FEIGAL: Of all the PMAs submitted in all product classifications, just as in all new drug applications, about a third of them are never approved because they never meet the standard for approval. So, no matter how much time you spend with some of them, there are applications which are never approved.

Let me phrase the question to industry in a different way because this is an industry that brings 900 new in vitro diagnostics to market every year through the FDA process. So my question would be what is it about these tests that requires a lower level of consumer protection than is required of the other in vitro diagnostic tests, and that seems to be the bar that is set.

Now, if there is a way that we need to be able to respond, to be able to deal with very rapid product life cycles, then we need to modify ourselves in order to do that. But if you look at the average life cycle in many areas of device manufacturing, the average market life cycle of a device is 18 months. So that is how rapidly they are turning over. And the approval process is on the front end of that cycle. So, if the rest of industry can do it, the question is why is it that this one cannot.

I guess I would maintain, the thing that struck me when I saw that only six out of 700 tests had ever come through FDA is that the home brew has created an avenue for development of in vitro diagnostics that are free of the consumer protections other than CLIA's consumer protections which are an every two year lab-based protection. That is a perfectly reasonable level for many things that are developmental. We just have to ask does that meet the standard for these.

DR. TUCKSON: Mr. Chairman, you obviously will not let us lose control of the meeting. I do not think it is appropriate for Elliott to have to answer this question.

MR. HILLBACK: Well, I would like to.

DR. TUCKSON: But I just want to make sure that for this transcript -- and again, to be very blunt about it, there is one person who has come in here and said some pretty horrible things to this committee. I want to make darn well sure that the people who felt so strongly about their points have a chance to respond specifically to this question that David just answered. I think you have phrased it well, and I would like to have it in my mind before I make any final decisions. But I will be darned if somebody is going to ever come in here again and make a statement like that.

MR. HILLBACK: Let me respond, but there may be other people in the audience who would like to join in as well.

First of all, I am not sure that we are arguing for a lower level of regulation. You said it yourself. Again, I want to take this out of FDA versus labs because I do not think that this is the point. I think the point is what sort of constriction point do we make around getting these tests into the market.

Most of the tests, and I would ask other people here in the room. Most of the tests, I believe, that are performed, the resulting report says the cholesterol level is X and does not say what that means from a patient point of view.

Genetic testing is different. We have, by definition, said that every lab has a pre- and post-test set, that it is personalized to the patient individually, and that part of the lab director's responsibility is to sign out a lab report that is related to that patient and that patient's family situation and make a suggestion as to what the answer is.
I would maintain that that is a higher level of information that we are requiring out of the genetic testing system than anything else.

As David said a few minutes ago, if we want to get to the situation where all the lab is required to do is to prove that we can find delta 508 or that we can find any other mutation and that that is our responsibility and we will report that out and let the rest of the community figure out what to do, we have a very easy task in the genetic labs because the methods to find mutations, known mutations, are quite simple. We are finding new mutations all the time, and it would be a very easy task for us in running labs to roll over and say, "Fine. We will just do that and let God sort it out," let you folks all sort it out, all of the geneticists and all the primary care physicians. I do not think that is what we want to do. I do not think that is good for patients, and I do not think that anybody has advocated that, although given that opening, I think there are maybe some labs that would do it.

I think the direct implication of people's response and why FDA rings a bell is that there is a certain process that FDA is known for, which is very thorough to approve things. If we are going to take tests that are done on a few hundred people a year and put them through what we perceive as the same set of rules that are for a cholesterol test that is done millions of times a year, it just does not compute.

The slide that David showed showing how many laboratories are doing CF tests or how many laboratories are doing Fragile X tests, I will have to tell you there are a few cynics that ask me, "Elliott, why do you at Genzyme disagree with having FDA review these tests so rigidly? Because it would put all the hospital labs who have no resources at all to go through an FDA approval process, it would put them out of business. And you and Baylor and Mayo and a couple of the other large labs would get to do all the testing." I do not think that is good, and it is not the way we want to go.

So I do think that we do not sit and argue, and I understand that there are points made that we should just use CLIA. I think the point is, to go back to the points earlier, 50,000 genes multiplied by the interaction of those genes with each other and all the different mutations, multiplied by the number of environmental events, the data that we are going to be looking at in 20 years time is incredible. And between now and then, we somehow have to figure out how to get that all useable.

I do not care if it is FDA or CLIA or CDC or any other individual unit. If we are going to use traditional methods to deal with an untraditional future, if we put the past on the future, I think we are going to really try to keep the genie in the bottle by putting a cork in it. I think that is where people react to FDA in the traditional sense.

Now, if what David said earlier, that FDA is committed to finding ways to be more flexible and finding ways to make those difficult compromises, then you cannot say it is an FDA problem. It is

all of us.

I will reiterate one other point, and then I will stop. Labs are not doing this fundamental research. There are very few tests that are being created by the lab. They are being created by hundreds of thousands of researchers around the world working on diseases, and hundreds of thousands of physicians treating patients and trying to figure out what is causing the disease, and we are happy when we can to develop a test that provides some information they can use.

It is not the other way around. It is not us coming up with all these really neat tests and them saying now we will foist them on the world. It is just not how we do it.
So I am happy to take the position for BIO a little bit, but I think the reaction is to a rigid system that does not reflect the speed or the number of points of data that are going to be coming at us. I think if we build a system based on history, it will be standing in the way of the future. So that is my best answer I can give for all of this.

DR. McCABE: I am going to take brief comments from Joann, Pat, and Ann. Meanwhile, I am going to ask that then we will take up to five or six comments, 30-second to one-minute comments, from the audience after those three speakers.

Joann, could you just make a list of people who might want to speak from the audience, just if you could go out into the audience and circulate a list on this point, as Reed invited?

DR. BOUGHMAN: I would actually like to ask Elliott to expand for just a moment. You said we are subjected to in fact, you believe, higher scrutiny for the genetic tests because we must do A, B, and C with regard to the results of a genetic test. By whom? Who is the scrutinizer?

MR. HILLBACK: The scrutinizer is our boarded lab director who has to sign out that test and is not going to sign out a test saying this is indicative of higher risk level of this disease if they do not have some data from the literature, from somewhere, that they have been able to make that interpretation. It is not formal. That is true. But it is not a random marketing person who says let's decide that we have got this test and maybe it can do that.

DR. BOUGHMAN: I am bringing this point out just to remind us that in fact there is another level of complexity out there because this does relate back to the professional organizations and in fact the criteria and the certification processes for lab directors as well as laboratories.

And I believe this is one of the gaps that we need to address. I believe the answer to Reed's question, we should not be asking some of these questions of the laboratories, the companies, the representatives that are in this audience. These are not the folks that, as a member of an FDA panel, I am really concerned about. It is all of those out there who in fact might not even have known about, let alone have any respect for, these processes.

And so I think when David made the comment about the consumer in general, we have to not lose sight of that basic premise.

I agree with you, Elliott. It is not the FDA versus the labs. It is especially not the FDA versus the

good labs. It is the FDA and its responsibility for safety and efficacy for the general patient and consumer population.

MR. HILLBACK: Can I just respond to one thing?

DR. McCABE: Yes.

MR. HILLBACK: I think we have to think about it not as the labs, anyway. We have to think about it as the system. The system is all of us. All of the geneticists, all the people who are treating genetic diseases are part of the database building. Without that, there is no database.

The solution has to be holistic. We have deferred all the discussion of educating the user so that they can understand how to use these tests. It is a little difficult to talk about how we are doing to do all of this work to improve the process of approving tests when part of the reason we are so worried about that is we think we have dumb users out there that do not know how to use the test, the information we give them. It is holistic. Until we get the whole thing looked at, I do not think we are really going to get to the root of the problem. I understand we have to take it in pieces.

DR. CHARACHE: I have a legal question pertaining to what the FDA is allowed to do which was raised by your discussion.

The FDA evaluates any new test based on the claims made for that test by the sponsor of the test. So that, if the sponsor says this is helpful in making a diagnosis of cystic fibrosis, you will evaluate it on that basis. But if it says that this test can show the presence or absence of Gene X and we do not know what that means, by law can the FDA say, "Come back to me when you can tell me what that means"?

DR. FEIGAL: Yes.

DR. McCABE: Thank you.

And Ann?

MS. BOLDT: I just really wanted to comment on Elliott's intimation that every single genetic testing lab does provide interpretation, and that is really not true. That is really far from the truth. There are many good labs that do that, but even good labs sometimes are providing you if the mutations there are not. If it is in the hands of a genetic professional, they can interpret that, but if it is not in the hands of a genetic professional or a health care professional that understands genetics and has a competency, they cannot interpret that. So I do not want anyone to get the false sense that there is interpretations provided on all of these genetic tests because that is really not the case at all.

DR. McCABE: We have five individuals who have asked to speak. Again, please try and limit your comments to a minute, if possible.

The first is Barry Berger from Exact Labs. There are both microphones in the audience and up

here. Feel free to use either.

DR. BERGER: Hello, again. I agree with what Elliott has to say in great measure, but I also agree with what Dr. Feigal had to say. There is no reason for the bar to be different, especially for tests which are dealing with large populations of patients, as I was talking about before.

The practical issue in timing, though, for a small operation which is starting up is if you are burning a million dollars a month and you have got a four-year process, you are looking at $48 million. You have to go back and raise some money in order to be able to do that.

So the question is one of timing. It is one of timing. So, if there is some process that we can put in place that gives us a break for a couple of years to gather that information on a home-brew process, then let's kick into the FDA process which is what we are going to try and hopefully will be here four years, and I can tell you that it worked. But that is what we are going to do. So I would put that on the table for folks to think about. Put a process in place that allows us to develop tests, get them out there with a reasonable amount of information, and interpretative information, and then go forward and get it out. The truth is we need FDA approval for big tests to get reimbursement.

DR. McCABE: Thank you very much.

The next is Mike Watson from Washington University. And I think Mike is representing the American College of Medical Genetics today.

DR. WATSON: I want to thank you for letting me have the chance to speak to you briefly, and I want to try to stay on this point.

It is not just the fact that we have a lot of home brew going on in genetics that we have taken advantage of to stay out of the system. I think there is actually another issue at FDA which is off-label use. And it is going to be exceedingly difficult for FDA under its current structure to control how tests are used since you are mandated, as I understand it, to allow somebody to tell you I am going to use it in this very narrow area and approve it on that basis, and off-label use has been one of the hardest things to control.

So I think the consortia approach is the most likely approach to be successful for a couple of reasons. The information is evolving very rapidly, and I think we need a group of people who are very much focused in understanding this information in order to keep up, without getting those bottlenecks we are talking about, which could very easily happen within an agency which is very limited in its genetic expertise at the time.

I value FDA tremendously. I hope they stay involved. I want them to keep those kits and things coming that make our tests better and safer and cheaper, but regulating the labs, I think, is going to be exceedingly difficult.

I do not want to wait until your programs develop until we get a better handle on genetic testing. So I think there are things that certainly have been going on between professional organizations,

the development of programs for proficiency testing and inspection, all of which have room to be enhanced.

One of the problems that is critical is that we do not have these standards that we need for regulatory bodies to enforce. It does worry me a little when the regulatory bodies develop the standards. I think the standards are best coming from the professional communities and are enforced by regulatory bodies or, in this particular circumstance where we want to move quickly, are developed together and perhaps enforced by the regulatory body.

I very much like the sort of multi-pronged view of clinical validity that was put on the board by Dr. McCabe, but it is much broader than that. I think you can break this problem down. It is nowhere near as difficult when you begin to think about it. There is an analytical component to testing which goes through multipole tiers, direct targeted hybridization, genome scanning. I think genome scanning for unknowns is an exceedingly complex area of testing. We are looking at our inspection programs to be able to target those areas and bring the most expert inspectors to laboratories doing those services.

So I just think that the problems that we are facing are ones that no single agency will be able to address well. I think we have to look at these models of how do we take advantage. If we talk about HHS as the oversight body, I think we are better off, and then moving to how do we take advantage of all the HHS programs to target the specific problems that we are identifying in genetic testing.

DR. McCABE: Thank you.

Next is Dr. Michael Boss from Athena.

DR. BOSS: First of all, maybe I would like to apologize if my prior comment seemed inappropriate.

As Elliott mentioned, we also work extensively with leading researchers. I think we are so worried because the words of FDA have very specific meaning, as illustrated by the FDA's talk, and a process based on a PMA application process and clinical utility labeling requirements would be well beyond the capability, I think, of most organizations with most genetic tests at this point.

Thank you.

DR. McCABE: Thank you, Dr. Boss.

Dr. Tony Holtzman? Tony.

DR. HOLTZMAN: Well, as many of you know, I was the chair of the Task Force on Genetic Testing that has been mentioned a number of times today, and I am glad that you are where you are and I am where I am now.

DR. HOLTZMAN: I do want to talk about the role of FDA. I want to recite something that you have

written that was in your conclusions and recommendations that appeared in the Federal Register in which you noted that BRCA1 is an example of a test that should have been released with disclaimers about the limited knowledge about the test's clinical validity. And it seems to me that is one example that has affected a lot of people, not always in a helpful way, that the direct involvement of FDA, as Dr. Feigal has laid it out, could avoid.

It is not the only example. Another example, if not from Athena, then from its predecessor, was the release of a test for apolipoprotein E4 as a predictor of Alzheimer's disease, in other words, no restrictions on its use at a time when there was no treatment and where the benefits of this test were questionable, whereas the risks were decisive. Again, here was a situation where a laboratory could release a test.

So I think there are those examples and other examples, some of which we mentioned in the task force report, that indicate that there is a problem out there in the premature release of tests not for the long-term concerns about discrimination, but for very short-term concerns about what a positive or a negative result mean to an individual who is being tested; in other words, clinical validity and, to a secondary extent, clinical utility.

So, with those problems out there, I cannot see when you have an organization, an agency in place that has the capability and the experience to review these issues how you can do otherwise than use it.

I think also, though I did not see the little print in this slide that Dr. Feigal showed, that, yes, there are a lot of discoveries out there. We may hit 40,000 or 50,000 genes, but that is a long way from the development of tests, a long way from the collection of adequate clinical data. Clearly, there has to be some interface between those researchers who may be collecting bits and bits of that data, but they have to eventually or they should eventually be funneling it into a laboratory or a manufacturer who is going to provide a test that will be used clinically. And it is that transitional phase that needs to be approached, and I think that Dr. Feigal's, the FDA's, idea of using the investigational device exemption is a good way to begin to bridge that gap.

So I really cannot see how this committee could step backwards from where it was and do anything but say that FDA should have a role in the regulation of all genetic tests.

DR. McCABE: Thank you.

Our last speaker is Dr. Michele Schoonmaker from Vysis.

DR. SCHOONMAKER: Good afternoon. I am standing here before you formerly as a student of Tony Holtzman and now as a student of industry. So I feel I have a healthy respect for the difficulties of all the issues that are before you.

As we deliberated on definitions, there are two definitions of industry. One is commercial testing laboratories and the other is manufacturers of kits, both of which have different regulatory pressures, different market pressures.

Vysis has the distinction of being the company with five of the six FDA-cleared or -approved tests that have gone through the market today. None of our FDA-approved tests are for particularly high-volume conditions. Vysis is a very small company. What we would like to say is that the FDA process works.

The risk-based classification scheme is consistent with the committee's idea of categorization for genetic tests. Our last PMA for the HER-2/neu DNA probe test for breast cancer went through in 180 days from the time of its submission to final approval.

I guess I would like to say that I agree with Dr. Berger's comments that there does need to be a time frame of home-brewed testing and allowance for the collection of premarket data to find out if something is even worth putting through the FDA. And that the benefit to having FDA approval is largely in not only protecting safety and effectiveness, but also in controlling and standardizing what you can say about a test, what you can tell the patient, what you can tell the physician, what you can put in your advertising that helps you secure reimbursement and widespread acceptance.

So that is it.

DR. McCABE: Thank you very much.

Reed, you really stimulated this discussion. So if would you like to comment?

DR. TUCKSON: First of all, I benefitted from it a great deal. I need to ask one question about this reimbursement issue. Is it true -- I think I am being simplistic here -- that you need FDA approval to get reimbursed by the major purchasers? Not true. It helps sometimes.
MS. BOLDT: I can give an example of FISH when we are doing prenatal testing. It is still considered an IDE, and it has for investigational use only. It does not get reimbursed by most insurance companies. There are a few, but it is very difficult to get that. That has been something that has been on the market now for quite a few years.

DR. McCABE: The issue is once you get an IDE, when you put the word "investigation" in there, then that does give an excuse for many of the insurers to question this. That does not mean that all will question it, but it does raise a red flag.

DR. TUCKSON: I do not want to take this any further, but, Elliott, let me just make sure I understand. At the end of the day, purchasers are going to have to make some choices about what they are going to pay for in this great new world of molecular revolution. Somebody is going to draw a line about what they can pay and what they cannot pay. If it does not have FDA approval, Elliott, do you think that medical directors are going to make the choice to buy these things?

MR HILLBACK: If I can, let me ask Ann Merrifield who is president of Genzyme Genetics to comment on CF testing where we do very large volumes. It is obviously not an approved test. It is home-brewed.

MS. MERRIFIELD: Most payers do not care whether it is FDA-approved or not. They really care

whether it is standard of care or not, and they look to the professional societies as much as anything. CF testing and standard of care now in certain applications, and it is reimbursed. Certainly, once something is perceived as standard of care, the legal liability of not covering it, if not a desire for high-quality clinical services, it drives reimbursement.

DR. McCABE: Wylie, and then we are going to take a break that we are overdue for.

DR. BURKE: I just want to comment that I think we have been hearing what appeared to be a dichotomy between, on the one hand, FDA approval and, on the other hand, some sort of professional organization consortium approval. I do not think those are in conflict at all.

We got to FDA in the first place because we said CLIA is great, but premarket approval should occur, and FDA was the agency that could do that. What we also said at the same time was not only did we want to work with FDA or have appropriate organizations work with FDA to be flexible as FDA has indicated it is willing to do, but that we also thought it was very likely that there would be, once we had our categorization system well worked out, that there would be tests that could be approved through FDA deeming authority to professional organizations. And I think the consortium that we are hearing developed probably represents as it develops and as we perhaps have some input into how to develop precisely the organization through which that deemed authority could act. And I think that would resolve concerns about orphan diseases and what we might all agree after a categorization effort are very straightforward simple tests.

DR. TUCKSON: David, I asked you specifically about models for that, the deeming authority. Your answer did not seem to indicate there was room for that, did it?

DR. FEIGAL: The models have been that we have taken parts of our process most typically in some of the inspectional areas. "Deeming" is not the right phrase, but, for example, mammography quality which is a certification program, 90 percent of those inspections are done by state authorities instead of by us.
The requirements that someone review these processes essentially requires that they do that as a special government employee with all of the freedom of conflict of interest. They essentially have to function as though they are one of our employees, and they would have to do it up to our standards.

When you see the number of products, for example, that the CDC is proposing to evaluate in a short period of time, three to five, I am sure the information from that will be very useful, and it may be very key in the way that the labeling could be developed around a whole class of products. To say that that group could be deemed to decide whether a specific manufacturer had complied with all of the requirements, that is less likely. So I think it is identifying the components where part of the task can be carved up and be made useful.

DR. McCABE: I think the deeming model that we have is the CAP with the CLIA, and that is what a lot of us were thinking about when we inserted the language regarding "deemed status," which is very different than what you have described.

Pat, very briefly, and then Kate, very briefly, please.

DR. CHARACHE: One important reminder. There are major problems at the present time with the research or investigational exemption. Some companies have abused that title for years of charging patients for tests in which they simply have the statement that this test should only be used by the originator of the test and that its interpretation is not yet known, but for which information is billed and information is sent to clinicians who do not know what to do with it.

Second, with that investigational exemption concept, to have time to collect more data while you are giving information to patients, if the information results are given to patients or health care providers, that does come under CLIA. Anything that is under CLIA, the analytical validity and the sensitivity and predictive value has to be known. It does not mean that you will not know more about it subsequently, but you cannot simply say the FDA has given it exemptional status and think that you could use it without knowing how to interpret the results.

MS. BEARDSLEY: I just wanted to clarify a little bit what I think is being said about the deemed status in the standards-setting. What we have been talking about are inspections, the deemed status for compliance. That, I think, is a different thing than having standards that speak to the review process. I believe, and I look to you, David, to tell me, but I believe that in those situations where FDA generally has tried to rely on standards for product approval purposes, it is usually worked best in situations where the product is reasonably well established because the standard generally follows a fair amount of experience with the product.

So, in this case, where we are talking about products with which there is not a lot of experience, I think it might be a little unrealistic to think that we could be looking very often to standards as a way to get these products through the process.

DR. McCABE: We will take a 10-minute break, and we will be back in here about five of.

[Recess.]

DR. McCABE: You may recall when we broke for lunch, we were addressing Issue 3, and we have had further discussion since that point that I think helps us address some of these issues. NHGRI had asked do the first two recommendations need to be modified to more fully reflect the contribution of research, the collection of validity/ utility data prior to a test's translation to the clinical setting.

The public's comments, some summary of them, is that a general support for recommendation on data collection, suggestions that one agency or central clearinghouse handle data collection efforts, encourage public accessibility to data and analyses, concerns expressed about delays and burdens created by requiring data collection on availability of tests -- I think that is probably "in academic" or maybe -- and academic laboratories.

First of all, we have talked about the need to collect data. We have been vague about how those data would be collected. So I would like to discuss that for just a few minutes.

I will remind everyone that we have a presentation from 5:15 to 5:30 by Pat Charache and Joann

Boughman. We were going to break at 5:30. I may take the Chair's prerogative to extend this.

Did dinner get moved? Dinner may be postponed because of a program that is on this evening that may be valuable to the membership of the committee.

Issue 3 then, data collection. Do we feel that there should be a central clearinghouse, a single authority responsible for data collection?

DR. BURKE: I think it is very hard at this point to say there is a single agency and that agency should be given that task, but I think the comment really speaks to a concern with efficient organization; that is, if one particular agency takes the lead, things will happen more efficiently.

I do not think there is any question that the kind of data collection and analysis process we are talking about needs to be collaborative. There needs to be a sort of buy-in from a lot of different groups, not just different federal agencies, but also different relevant professional organizations. I would have to say I think the presentation we heard from the CDC suggests that the beginnings of that process are already in place and that CDC is assuming a leadership of a collaborative group. So I think we already have the beginnings of that process.

DR. McCABE: At the break, I had clarified that. Hopefully, I will represent the CDC's position accurately. They are catalyzing this activity. It is really a consortium, and they are not trying to become owners of this activity, per se. Is that a fair representation, Joe? Okay. I had two different people approach me from CDC to make that point.

I think, on the other hand, I am quite happy that they are moving ahead with this because I think this will begin to develop some models that we can see how such consortium would work together.

DR. KHOURY: Traditionally, what CDC has done in other areas of health and public health in general is provide both a catalyst for the kinds of surveillance data we collect at the state level or with other organizations or at the lab level, think about surveillance for infectious disease and now expanded to chronic disease and birth defects and other areas. However, we adopt a collaborative way of doing this business.

In this particular context, there is no other way to do it. I have been thinking about this for three years, and all the agencies are involved. They fund research. They fund services. They fund technology assessments. We will be more than happy if we are pushed in that direction to continue that collaborative process, but at the end of the day, somebody has to put that information together, get the buy-in and the blessing from the various groups, and provide it to the general public, and consumers, and health care providers for comments. We will be happy to continue that work.

DR. TUCKSON: I would agree with Wylie and say that I think if our report would acknowledge that this needs to occur, that it acknowledges that there is an ongoing activity that has begun that needs to then be modified or added to by certain attributes, and if we could describe those attributes -- we have already indicated in comments around the table that the consortium be

comprised of consumers and so forth and so on, from the professional community, the clinical professional community and so forth and so on, that it meet these criteria, that we would then be able to say that it ought to go forward with our blessing.

The only question that I had, Muin, was whether or not the inputs -- it would be great if we could have a slide that had the inputs of the data feeds into your activity. Specifically, have you had any of the people from the industry refuse to give you inputs?

DR. KHOURY: Can I answer that quickly?

DR. McCABE: Please.

DR. KHOURY: There are the two processes that were described to you. The first one was the disease-specific working group model. Right now, we have the two ones at work. One is hemachromatosis, and the other is cystic fibrosis. The guy who is involved with cystic fibrosis is around this table. So we have had full industry participation in this regard. Both of these working groups involve consumers, the professional organizations, health care providers, and state public health. So we have wide representation.

With respect to hemochromatosis, the story is a little bit different because that test is a lot of flux. We have industry representation that is not sure what to do with us right now, but that to me is part of the test case.

The other effort that you alluded to which was the lab forum, which is what Bob Martin talked about, so far it has been an expert panel group that is coming together to talk about laboratory issues. I see those two things melding together in the future as we move forward with this implementation of this genetic testing assessment program. Yes, you will have to have consumers. Yes, you will have to have professional organizations. I do not see any other way of doing it, really.

DR. McCABE: Thank you.

DR. FEIGAL: Were you thinking of actually having raw data coming in on a real-time basis from all the different manufacturers to evaluate the tests? I was not quite sure what you meant by collecting the data.

DR. KHOURY: Let me describe to you in a bit more detail what these two pilot studies are doing.

The consortium members are people who either know about testing for CF or have done testing both in research and non-research setting. They might have published data or sit on top of data that has not been published. So the efforts right now are essentially developing the data framework and the template around analytical validity, clinical validity, and clinical utility, describing what should go into these data elements, and then with some ideas of standards of quality, go review both published and unpublished literature and at the end of the year come back with some summary analysis of what is out there. The idea here is not to do the full-fledged technology assessment as David Lanier and I were talking about, but really describe what we

know and what we do not know, without really a value judgment as to whether or not we think this test should or should not be offered, but actually describe what we know and what we do not know and describe the parameters around quality.

If we want to take it to the next level, then it becomes a full-blown technology assessment project, which is only half of what we have right now.

DR. McCABE: David, did you want to follow up on that?

DR. FEIGAL: Yes. Actually, I would like to point out another successful model that is actually in the process of being expanded of providing data about things in development.

For nearly a decade, there has been a database of Phase II and Phase III trials in AIDS and cancer. the National Library of Medicine has done that. The Modernization Act of FDA actually required that that be expanded to all serious and life-threatening conditions.

So manufacturers, when they submit a Phase II or II protocol to FDA, also submit data elements to the National Library of Medicine to list their trial.

It would be interesting to think about if there is anything in parallel that would be useful for describing genetic tests. What is interesting about the AIDS and the cancer trials is that they have been mandatory. Normally, investigational information is confidential trade information unless they want to open it up, and the law in this case actually open it up in that area. But it is the kind of project to look at that might be very useful to say here is a test that is available from whom. You actually take many of the elements that would be out of normal labeling and say what is known about this at this time, including issues like whether there is informed consent, whether there are recommendations for genetic counseling and so forth.

So there are other types of collections of data that I think are a little different than what you are talking about that might be useful.

DR. McCABE: But the NLM data, that is more information about the clinical trial, per se, rather than the results of the clinical trial.

DR. FEIGAL: That is right. I was proposing something different, although in the informed consent for a clinical trial, you usually say what is known about the product to date.

DR. KHOURY: Actually, that project was developed in collaboration with CDC many years ago. Tim Baker from our office was involved in that development. Actually, by the time you get to the National Library of Medicine, it becomes a repository of what is known, that becomes the ultimate database that should parallel the gene sequences. To me, I can think of the National Library as the ultimate repository, but there is a lot of developmental work that needs to be done before you get there.

DR. PURYEAR: I was just going to ask him to describe the proposed data process.

MR. HILLBACK: I just was going to actually do a follow-up because I have not talked with Muin on this in a while.

One of the efforts here was not only to get the data from the laboratories. Especially in cystic fibrosis where we are interested, because the CF Foundation and the CF Centers are so well organized, it was to try to get the patient data downstream, the long-term patient data, and start to do the correlates that we all would like to do. I wonder how that part of the process is proceeding.

DR. KHOURY: It is proceeding. That is all I can say right now, but you are right. The whole idea is to do the genotype/phenotype correlation, and there is one arm of the three arms of the CF Consortium that is looking at that.

DR. TUCKSON: While I am enthusiastic and am sort of embracing because you guys have got a head start and you are willing to, it seems, be open to our attributes of the people that need to be involved, the organizations, I wondered, do I need to ask a question about your capacity to ramp up to scale.

I am not sure that I fully understand the dimensions of scale for this recommendation to be translated into anything like what it needs to be. The question is, as you describe it now, it is a fairly small discrete activity, a pilot thing. CDC is used to, I think, doing big things, but I guess we need to ask the question and let you all deal with. Can you all deal with the scale?

DR. KHOURY: I have a name for it. I call it "huge net," human genome. It is a huge task, but when you think about utility, when you think about it, we have to start somewhere. I think if we start by developing the standards, developing the rules of the game, it would be very, very helpful, even if we do not apply it on a massive scale.

I think on the long run, though, it has to be applied on a massive scale because we want to ensure that public health does not suffer. Right now, although the scale is small, we are developing these as a pilot to see what we can learn from these efforts.

In the long run, I think all the programs within CDC and HHS hopefully will buy in because they will see that it has relevance to all aspects of what they do, be it the cancer programs or the cardiovascular or birth defects. So the disease-specific part of this will carry a long way.

If you have any other alternatives to offer, I really am open to suggestions, but we are going to proceed as far as we can right now.

DR. McCABE: Thank you. Wylie?

DR. BURKE: I just want to comment that the kind of data analysis that Muin has described to us for the pilots with hemachromatosis and cystic fibrosis is very ambitious and very valuable, but there is a more limited data analysis that I think will be necessary for virtually any test that comes forward that is also valuable. That simply looks in a systematic way, using a standardized approach for defining clinical validity and clinical utility, at what data is there. Using Muin's phrase, "what we know and what we do not know," what happens when you do that with early availability

of genetic tests is that some of the boxes are blank, but that becomes part of what you disclose.

So the point has been made, the example has been raised of BRCA1 testing. If we had simply taken advantage of published data at the time that that test first became a commercial test and without seeking any additional data or any kind of additional data analysis, just try to organize what data was in the literature, I think the point of concern about that test would have been made very clear.

So, while I think the ramping-up to do the detailed level of analysis that asks published authors to give data and re-analyze data and so on, it is not going to happen for every test. The kind of straightforward analysis of published data in terms of what it means, what we know and what we do not know about clinical validity and clinical utility, it is a very doable task.

DR. McCABE: Elliott. Oh, Muin just has a follow-up.

DR. KHOURY: I think the three levels of complexity from the more simple to the more complicated, as I mentioned earlier, the simplest way to deal with this is to have a database of what the test developers claim, and using the FDA's term. So they may claim this test is good for that. So somebody can review the literature as the test developers did and come up with filling a value-added to what the test developers said. So that can be done rather quickly from the available literature.

The second is what we are doing right now with these pilot projects, and the third would be the full-blown technology assessment which will be done only on the limited ones that are ready for prime time or ready for large-scale use, like newborn screening for cystic fibrosis, is the time ready or not.

I see all of these are part of the ultimate knowledge base of what we know and what we do not know. Obviously, we can do only so much at any given point in time, but it may not be as expensive as people think it is, especially to do the first part.

DR. McCABE: Elliott, and then we are going to move on to Issues 4 and 5.

MR. HILLBACK: I just wanted to respond to something Wylie said because I think it was particularly interesting.

You said if that had been done for BRCA1 before it had been made available, it would have clarified some of the issues. I think that is right. The question is would it have precluded making the test available in your mind or only said we will make it available, but with the caveats that, therefore, allow people to use it where it is appropriate and not use it where it is not appropriate.

DR. BURKE: The latter. I would have been very comfortable with commercial availability with a very public and, to some extent, standardized process that had a lot of backing behind it that made it very clear that there is only a small number of families for whom that test could really offer benefit, and that is really not what happened. The problem is the implication that it had more broad use then it had.

MR. HILLBACK: I understand that.
DR. TUCKSON: Therefore, did we, Mr. Chairman, just make a consensus at the end of the day? Is our recommendation clear that we are charging HHS through the CDC mechanisms that already exists with this task of that is how we are going to get this data collection done, and it has three levels of involvement, the initial level that Wylie has advocated for and Muin agrees to, the second effort that they are already doing now expanded, and third, this technology assessment component, and that it would have a committee or an effort that would have the attributes of inclusion that we described before? Is that essentially what this takes us to as a recommendation?

DR. McCABE: We need to talk about that because that would be a new recommendation. I think at the last meeting, we decided that we had talked about a consortium, and we sort of took the consortium off the table. Now we are putting it back on the table again. So I think that that needs to be a consciously affirmed position, but we ought to discuss that. So we will not move on Issues 4 and 5. We will clarify this.

Does anybody object to that construct? Because I certainly think it has merit.

DR. PURYEAR: I do not necessarily have any objections, but I think there is a reality that has not been talked about. What has been going on in the HHS data working group are developing models. I know I remember some of the first meetings where we tried to find the data. I mean, you talk about looking at BRCA1 and 2. The data was not there. The industry was not forthcoming with some of that data. There were no boxes to fill in.

So, I think you can charge HHS to do some of this stuff, but the resources are not there to do it, nor is there necessarily the willingness on the part of industry to be part of that collaborative relationship.

I would much rather see the development of these models and make sure these models are sound and go back with a proposal. We also have not engaged some of the groups that need to be engaged. Primary care is not part of this. Consumers are not part of this. This is a really focussed small working group that I think has a lot of work still to be done before it goes prime time. I think the people need to realize exactly what we are capable of doing at this point in time with very little resources.

DR. KHOURY: Can I respond quickly?

DR. McCABE: Sure.

DR. KHOURY: It is true the interagency working group was just that, an interagency working group, which had representatives from all of us around the table. The other consortia around CF and hemachromatosis had the whole thing from genetic counselors to consumers. So let's try to separate the issues.

Yes, you are right. The first time we met, we had no idea what tables to fill. We have made quite

a bit of progress around developing the framework, at least the template for what kind of data we need. So we are further along than we were last year, and we will keep making progress.

DR. PURYEAR: All I am saying is let's get that model developed and then present it before we go on, but I think there is a lot of work still to be done.

DR. PENCHASZADEH: I am not sure we have to make entirely new recommendations. When I was listening to the summing-up that Reed was making, I thought that essentially we were recapping on things that we had already stated in the document. I have the recommendations in front of me, and we already talked spoke about relevant DHHS agencies, that they should work collaboratively with researchers and test developers, and that they should be coordinated by CDC and so on and so forth.

What is new probably is CDC for the past two or three months has been moving along, and there are more things that we can grapple on, but the concept is essentially stated in the recommendation that we stated forth originally.

DR. McCABE: Yes. And Sarah corrects me. What we rejected was a consortium for oversight, not a consortium for exploration. So I stand corrected.

I think what we have talked about today, we might amend this bullet on page 21 -- it is the third bold bullet on page 21 -- to include representatives from the private sector, from various professional organizations, and the public. I think that has come clearly that those should be incorporated into these pilot efforts.

The sense that I am seeing from the body language and everything is that people are more comfortable with staying with what we have here, which is developing pilot efforts.

I think though that your points, Reed, and Wylie's that we could begin to acquire data on a broader range; that we do not have to do the intensive look at these. It might be worth also getting into this document.

So you had three points, Reed.

DR. TUCKSON: They were simply the summary of what Muin is saying. One was the use of what we now know and being able to collect that and fill out the grid to make the short assessments. Number two is the pilot project, the larger, much more intense efforts that are ongoing which we would see as this government agency would now be designated as CDC, and the bullet below the designating a government agency, which we would sort of name as CDC, the consortium is the bullet below that. So we are defining that the consortium and the government agency would be rolled into one effort. It is clearly designated. That is the second point in terms of doing this longer-term work. Then the third point that Muin talked about would be this role of technology assessment, which can or cannot be left into the proposal.

DR. McCABE: So could we include something with these as examples of the types of models and pilots that could be embarked upon?

DR. CHARACHE: The point that Wylie was making of the literature review and the information that we know that pertains to the utility of the test as a diagnostic or predictor would be and will be part of the requirements for taking a test from the research lab into patient care. That is going to be an integral part of that.

The more profound look at a group of diseases will be necessary for the other issues which Muin has been pointing out, data such as what is the penetrance, how do we evolve and make more profound our understanding of given diseases. I think it can only be done with a more intense long-term approach.
I am hoping it will be possible to get the models out fairly promptly because I know it is a difficult task, but the sooner we can get a look at what the models are and what the boxes and buckets are, the more rapidly we will be able to use some of those concepts in test assessment.

DR. McCABE: Okay, so I think we have a consensus that we will include the structure as has been discussed as models and approaches.

DR. TUCKSON: I apologize, Mr. Chairman. That consensus, I will accept.

There are two other points that came up in the comments, and I do not know whether you want to deal with them or not. One had to do with the use of the IRB in data collection. There was a strong point made about that. We can either deal with it or not.

The second point that was made in this regard had to do with the –. At least two major organizations commented on the need for access to the data, particularly the postmarketing data implicitly, and that this is not something that ought be in the proprietary domain, but allows for the opportunity for scientific knowledge and research to occur. So those points are there. We can dismiss them or not, but I just wanted to make sure that we did not run past those because they were well-made points.

DR. McCABE: My understanding of IRBs is that they approve protocols and look at amended research protocols. So they are basically gate-keepers on research. But that in fact they are not -- they maintain data or at least are repositories for adverse events related to research, but other than that, they are not really designed as a data collection vehicle. But I do not know if anybody else has a different understanding.

DR. TUCKSON: It was not so much as data collection. I think their point was more the approval of the process of data so that you have the safeguards of the IRB informed consent process. I think that was more their issue, not so much as a mechanism.

DR. McCABE: Yes. So, basically then, any pilot studies like we are proposing would need IRB review.

DR. PENCHASZADEH: We stated that already in the report.

DR. McCABE: Right.

DR. HUDSON: But isn't the data that Muin intends to collect non-identified aggregate information?

DR. KHOURY: The data that will be displayed for dissemination and analyzed are unidentified, but if you go back to the original researchers, let's take, for example, the consortium that Gary Cutting has around genotype/phenotype correlation with CF. These people know, and they have information on who has what clinical outcomes.

What we will be collecting and analyzing is essentially anonymous data.

DR. HUDSON: Good.

DR. KHOURY: But at the investigator level, there could be identifiable data.
DR. HUDSON: Sure, but those individual protocols would have IRB review.

DR. KHOURY: Absolutely.

DR. McCABE: Right.

DR. HUDSON: They would not be passing unidentifiable information to a government agency.

DR. KHOURY: Yes.

DR. McCABE: But again, that would be an issue for the IRBs to review how that was done because there is a big difference if it is completely anonymous versus if it is linkable, at least for some IRBs and for some of the professional organizations.

DR. TUCKSON: The public domain issue?

DR. McCABE: Well we addressed this to some extent, but not really as explicitly as that individual perhaps or group. I do not know which it was.

DR. TUCKSON: One was the AAMC and the other was --. I am just looking back at our notes. I will find the other one in a minute.

DR. McCABE: Page 22. Joann pointed out there are two bullets that are relevant to this issue. We do not talk about those data going into the public domain in these bullets. Do we wish to address that? Data from any of these pilot approaches. The data that would become aggregated.

DR. PENCHASZADEH: If we say that those data are essential for assessment, long-term assessment of the validity of these tests, the corollary is that those data should be made available by whoever has them; that is, researchers or labs.

DR. CHARACHE: I can see some challenges for some of the kits and devices and so on that have what is considered proprietary mixes.

If the proprietary stuff has to be revealed, then it will cause problems for the FDA and other groups. If the proprietary information does not have to be revealed, it will be awfully difficult to merge them with other technologies for the same disease.

You could say what you know about the disease, but you would not say anything about test assessment.

MS. BEARDSLEY: It seems to me there might be something of a tradeoff here. If we are going to rely on industry to provide the data voluntarily and they know that there will not be any proprietary protection once they do that, that is going to be a disincentive for them to provide the data.

DR. McCABE: I think it is important to discuss this, but I think we need to be cautious that we do not build barriers to these data that are too high.

DR. BURKE: My comment is, again, being realistic. I think there is a whole lot one can do with limited data, and I think what this data process should do as its first goal is look at what can be accomplished in the way of pooled analyses of available data granting that there are some limitations in what you get from different datasets and some issues of comparability, one dataset to another. In other words, I do not think that we should jump in and assume that we are going to ask manufacturers to give up proprietary interest in information. I think, rather, we should first look at what can we accomplish with data that is readily available, the data that is published, data that manufacturers are comfortable for releasing, and start from there. My guess is that with a systematic approach to analyzing data, knowing the answers that we are most interested in, what were the populations in which testing was done, to what degree can you have confidence about clinical validity, to what degree can you have confidence about clinical utility, that we can accomplish a lot without constraining people to release data that they would rather not release.

DR. KHOURY: I just wanted to second what Wylie said, essentially agreeing with all of what she said. Remember, the kinds of data that we are looking at range from analytic validity to clinical validity and clinical utility. While we may or may not be able to analyze lab by lab, different things on the analytic validity type of things, in terms of clinical validity and clinical utility, remember, those things do depend on penetrants and heterogeneity and sort of the biologic attributes and the availability of interventions. These should be out in the public domain.

I want to challenge this committee with a simple question. If it is worthwhile, displaying the data on the sequence of 50,000 genes to the general public to have and to see at any given point in time, isn't it worthwhile to display what we know and what we do not know about genetic tests so that the public will be informed and health care providers can be better informed? That is a judgment call, I guess.

DR. BOUGHMAN: That is a judgment call, but that is also a tremendous funding issue.

I would not question the value of these data or even the simplest analyses on the most basic data. I have a real concern about the pronoun "we," "we could look at the data," "we could do these

analyses," and I am wondering who the "we" is. You just brought it to absolute clarity, Muin, when you said if in fact the sequence is worth putting forth. I would suggest there has been a tremendous amount of time, energy, resource, and a huge staff that are putting those together. So I want us to be cautious in what we, the SACGT, expect for us or our friends to be doing on top of our other day jobs.

DR. KHOURY: Can I respond quickly to this?

DR. McCABE: Yes, quickly. Then we do need to move on.

DR. KHOURY: Quickly, if we as a nation have decided that sequencing of the human genome is worth the millions and billions of dollars that we put in, I think it is a small leap to try to close that gap in our knowledge and invest, a comparable investment, even a fraction of that investment into how do we begin to use that information to improve the health of people.

So, I am challenging us as a society, not as a community, because we all agree on the value of that information. We all agree on the difficulty in beginning to assemble that information, but I maintain, and I say, that this information is collected in bits and pieces here and there in a very chaotic way. It really would not require a huge effort to begin to put it together.

If it is the beginning of an investment for our nation, I think it is a worthwhile investment, but I am in public health and I try to help people.

DR. McCABE: Let's move on to the issues raised by both the members and the public about Items 4 and 5. They have been melded in the public comments.

Issue 5. Let's look at the issues for discussions raised by members. Pat, you had a comment regarding recommendation for evaluation of tests already on the market for evaluation of clinical efficacy and development of guidelines about their appropriate use. I was not sure exactly what it --. It needed some clarification from the way it was summarized here.

DR. CHARACHE: I was concerned about the tests that were already on the market. Our recommendation had been for a subsidiary unit that was not really like the FDA, that did not have the skills in knowing how to assess tests, to give a look at the tests that were already on the market.

I did not want to recommend that we have a very superficial -- or that the tests that were already out there received a second-class type of review. I thought it should have the same kind of review as the tests that are coming onto the market because there are some bad things out there. I would not want to have them have a poor first assessment and then with the stamp of approval that they are okay when they really were not.

So my recommendation was that we take a look at the tests that are out there according to whatever standards and criteria we think should be appropriate for new tests, and if they have been out there a long time and there is a lot of data available and it is clearly a good procedure, then it will go through very quickly, but some of them probably will require more attention.

DR. McCABE: This is page 26, the bullet under Review of Tests Already on the Market. Is that what you are dealing with?

DR. CHARACHE: That is right. It was suggested that this be some other type of review process, under a different agency which did not have specific experience in doing this.

DR. McCABE: One of the things I have looked into is trying to understand the USPSTF and what they do. It is actually a very rigorous and very time-consuming evaluation and requires published data. So, in fact, if we are concerned about bottlenecks, I think it would have to be an organization like this and probably adapted to this purpose because this organization takes typically three to four years to make decisions.

What they look at is they have a methodology, and I think that may have been the lesson that David was trying to have us learn from that. They have a very rigorous and routinized methodology that is required for their deliberation.

DR. CHARACHE: Yes. I think my thought was it should be whatever our standards are for new tests. It should be a parallel approach.

DR. McCABE: Okay. Kate?

MS. BEARDSLEY: I was going to say it seems to me we should give some thought to whether this review process ought to be all in one place. I cannot really understand why we would want to develop these expertise in two separate organizations. It seems to me that if FDA is going to be the review agency for new tests, FDA probably ought to be doing whatever is going to be done on existing tests partly so we only have the expertise in one place and partly so that we are not applying different standards to different tests. And thirdly, because I think there are a lot of practical problems in distinguishing between what is a new test and what is a test that has already been in the market, that is been historically a very difficult task when FDA has tried to do it in the past. So I would propose that we think about that.

DR. McCABE: So it is the recommendation that we strike this section, then, from the document?

DR. PENCHASZADEH: We should say something about tests that are already in the market.

I would second both Pat and Kate in the sense that if we are going to appoint one agency to look at all new tests, that same agency should probably have the same expertise to look at tests already in the market and subject them to the same standard.

DR. McCABE: I think one of our purposes here was to evaluate what the USPSTF does, is develop an evidence base. So it was, I think, as I recall, that we were trying to say let's evaluate what is on the market and determine the evidence base for it as opposed to risking with a regulatory agency like the FDA having tests that are out there and functioning, now becoming locked up in a regulatory process. So we need to be very cautious, I think, that we not lose a significant part of the armamentarium that is already out there. It needs to be evaluated, but

looking at models like Muin has described will allow us to examine those models. Using the FDA mechanism could have them taken off the market.

DR. CHARACHE: I am wondering if we cannot come up with a strategy that keeps things uniform, perhaps take advantage of the models -- the FDA could take advantage of it, and the forum group could look at them as well -- that exists through the other agency, but perhaps give a period of time during which this has to be accomplished. In other words, that these tests are to be reviewed within a three-year period, whatever the period is, and can continue to be used until such time as that has been completed.

DR. McCABE: Okay, one of the things we could do is edit what we have here rather than deleting it. If we are concerned about developing two loci of expertise, we can take out the second and third sentences here and we can modify or even eliminate the bullet that is here.

DR. PENCHASZADEH: I think what we should state in this paragraph and bullet is exactly what has to be done with tests already in the market, and not necessarily who should do it. Who should do it is also important, but essentially what should be done. We want to assess whatever evidence is there after they are used of their efficacy, their clinical validity, their clinical utility, but then it says at the end of the bullet development of guidelines about the appropriate use. The problem that I see with that is that will have essentially no regulatory teeth whatsoever.

Someone will develop guidelines, but the test is already in the market. It will continue to be used or not, according to any criteria that has been used until now. So I think that we should clarify what we want to do with the test already in the market and then who should do it.

DR. BURKE: I think with an appropriately constructed body that has representation of stakeholders, guidelines could have a tremendous impact on what is reimbursed. So I agree that it does not have regulatory authority in quite the same way. Yet, it might be a very powerful force for appropriate use.

I would propose that we keep the bullet, but simply strike out the first phrase and start the sentence at the end of the first line by saying "a multidisciplinary body set up or given deemed status for this purpose" and leave it as is.

DR. CHARACHE: May I comment on that? I do not think that answers the problem that we then will have two standards, one for the older test and one for the newer ones.

There are problems. Remember, there are tests out there in which they are just saying we can detect this gene and not saying what it does or does not mean in terms of Huntington's chorea or whatever else it is.

DR. BURKE: Could we add a phrase that says "using the criteria developed for evaluation of new genetic tests"?

DR. CHARACHE: No. I would rather not say who should do it. I think I would suggest that what we might want to say is that they need to be reviewed within a set period of time.

DR. BURKE: So we want to say "existing genetic tests should be reviewed" --

DR. CHARACHE: According to the principles.

DR. BURKE: -- "according to the"--

DR. CHARACHE: "The principles that are used for new tests, but may continue to be used for a reasonable period of time," and we could define what that time is, maybe three years, five years, whatever the review body thought was appropriate.

DR. BURKE: My thought was if you did not declare what the body was, it could end up being the same body.

DR. CHARACHE: I think it might be helpful if it was the same body that did the new test, but there has to be a time period in which they are not out of the market until they get around to it. They have to continue to use it until there is a chance to review it, and then most of them will be fine.

DR. McCABE: One of the things I was struck with was the FDA and the throughput in the FDA currently and what we could potentially be asking them to do. So that while one would like not to have two loci of expertise, there may actually be some advantage of parallel processing in this situation.

If we strike "a body similar to" and just, again, say "a multidisciplinary group could develop methodology that emphasizes," we could insert at the end of that, but right before the bullet, "This group could be similar to that which has been designated for new drugs," but leave it open. I think there still is a risk at the end of five years, they might not have gotten around to it.

DR. CHARACHE: I am thinking that the FDA could ask a body to do it. It would still be under their control, and they can do that according to the Modernization Act. They can choose another group to evaluate them.

I am not presuming the FDA would do it. I am presuming we should not tell the FDA how to do it.

DR. McCABE: The other advantage I see of having something like this construct is that it might allow you to then also look at the off-label in the future. It is not an FDA regulatory which has its own issues about off-label, but it is an evidence-based approach which would allow you to address the off-label uses.

Is there other wording that anyone can recommend here? Kate, did you have your hand up?

DR. BURKE: I think it is just worth noting that a properly constructed body has tremendous power to set standard of care, and that is really what we are talking about here.

DR. McCABE: Right, right.

If we make this "multidisciplinary," do we want to insert wording that this could be a group similar to that for new drug analysis or designated by that group?

DR. CHARACHE: I would rather not since we do not have those standards yet. That is what is being developed are those standards. So I think they are going to exist, anyway.

DR. McCABE: So we will modify that with these thoughts in mind. Do you have them down enough?

What I would do, then, just for the record to clarify this, we will strike the second sentence of the introductory paragraph. It will now start "A multidisciplinary group could develop methodology that emphasizes systematic." That is what is already there, but we just struck "such" and made it "a multidisciplinary group."

Then, in the bullet, we have struck most of the first line at the end. It starts, "A multidisciplinary body set up for this purpose. The issue is" -- and we struck "or given deemed status." Do we want to leave that in? Because if we leave "or given deemed status," that allows it to deal with a group designated by the FDA.

DR. CHARACHE: I am going to suggest truncating that a little bit so that it might read, "A multidisciplinary group given deemed status for this purpose."

DR. McCABE: Okay. Is that comfortable with everybody?

[No response.]

DR. McCABE: Okay, Ann?

MS. BOLDT: Was there some discussion earlier, when I was not here yet, about an advisory group to the FDA? Was that discussed as well, or would this fit into this discussion here about an expert panel being an advisory group to the FDA?
DR. McCABE: David?

DR. FEIGAL: There actually is an advisory panel on this topic to the FDA already.

DR. McCABE: Further discussion on this point?

[No response.]

DR. McCABE: The second point from the members on Issue 5 is that FDA noted that "SACGT identified predictive tests as requiring the most strict scrutiny. Issue 2 suggests that there may be other types of tests that also warrant more careful oversight. Does the concept in Issue 2 need to be explicitly integrated into the recommendations for oversight in Issue 5?" We discussed this, this morning. I think there are a number of places where Issue 2 and Issue 5 are not in sync. We could go back and try and get those into sync, but I think that is going to be hard to do here. But we will work on that. Let’s finish the members’ --.

DR. TUCKSON: Is one of the major issues that we will get in sync the research issue?

DR. McCABE: No. I think it had more to do with the parameters. I think we stated it this morning fairly clearly, but perhaps not.

DR. TUCKSON: What we stated earlier was that we were not looking at this to be in the research domain.

DR. McCABE: No. The IRBs will still have responsibility for research. I think what became a little blurrier this afternoon was that the line between research and clinical practice with the discussion about the IDEs, but, again, I think the details of the mechanisms perhaps do not belong in this document.

DR. CHARACHE: Just one peripheral concept that i do not want to lose in terms of looking at regulatory oversight requirements. What we discussed this morning in terms of Issue 2 and what was covered by some of the discussants all had to do with the medical implications of a given test, medical and social implications.

One of the criteria the FDA also looks at and that we should not lose is the complexity of performing the test procedure, the laboratory component, because that impacts on the reliability of the information that comes out, whether it is a very simple test that it is hard to make a mistake, such as a waived test, or whether it is a high complexity test that needs added attention.

So I think that we appropriately concentrated on the other issues, the clinical issues, but I do not want to lose track of that one altogether as we look at needs for oversight.

DR. McCABE: Additional recommendations. "SACGT recommended that written informed consent should be obtained for tests used for predictive purposes. Should informed consent be required or only recommended?" "Should" is recommended. "Must" is required. I think there were some public comments about this as well. Should it be limited to predictive tests? So what are our thoughts on this?

There were a number of people who had this issue.
DR. CHARACHE: I think it is either "must" or "need not." Either it is a test that requires it because of the nature of the test or it need not be there.

DR. PENCHASZADEH: I cannot conceive of anyone ordering a predictive testing without full consent on the part of the patient. To me, that translates into an informed consent, which means not simply a piece of paper signed, but the whole process of the education of the patient.

DR. BURKE: I would just add that I think written informed consent is really just a symbol for this is the kind of test that you need a detailed informed consent process. I mean, the written form itself is symbolic rather than accomplishing the goal.

And I think that the final decision about what must require informed consent probably will come

out of our categorization. At this point, the one thing that we have been consistent about is "predictive tests of limited penetrance with no treatment" fall in that category. It seems to me when the work has been completed on categorization, there are likely to be some other tests that fall into that group, too. I think we should limit written informed consent requirement to those tests.

DR. PENCHASZADEH: Sorry, a follow-up. To those which not only then are predictive tests, you would open it up for categories of high risk?

DR. BURKE: Potentially, yes. I think we probably need to look at the categorization work before, but it is going to be those high-scrutiny tests.

DR. PURYEAR: I would caution everybody to remember that the great majority of newborn screening programs in this country do not require informed consent, which does not necessarily mean that is the way things should be. Certainly, the Newborn Screening Task Force, their focus was not on informed consent, but on the education process and that that really needed a bigger focus and a bigger place than is currently happening with the newborn screening programs. But the formal informed consent process should not necessarily be there, as long as the tests were of proven clinical validity and utility.

DR. BURKE: And I think that is key. I think there is a general consent that you want to use newborn screening tests when identifying an affected individual leads to a treatment which results in an outcome difference. If you apply that standard to choosing tests for newborn screening, then you have got the other end of the pole.

DR. PENCHASZADEH: I just want to say exactly the same thing as Wylie. The very definition of the requisite to set up a particular condition for newborn screening, the benefit of the test has so much weight and you are dealing with a newborn baby. That really, you can forsake the informed consent of a parent.

DR. McCABE: We need to know what we are going to say. Do we want to strengthen the education part and make sure that that is very strongly in here and leave it "should," or do we want to make it "must"?

DR. PENCHASZADEH: My reading of the consensus is that it should be "must." It must be “must.”

DR. McCABE: Let's have a discussion.
DR. PENCHASZADEH: But for the high-scrutiny tests.

MS. BOLDT: Actually, that is what I was just going to say. I think informed consent goes hand in hand with genetic education and counseling. You cannot have informed consent with that. So I almost think we need to almost meld those two. No, I know that is the next point, that we are going to discuss as well, but I think we need to actually bring that up and discuss it together.

I would almost possibly suggest that we consider making this an overarching principle as well. It is almost like this additional recommendation at the end is an almost like an afterthought. It does

not really show the weight that we really want it to have.

DR. BOUGHMAN: At the same time, I would encourage us to use the term "informed consent," judiciously, and I think that after our discussion in the next couple of days, people may think slightly differently. Even if we used "informed assent" to a test or something, I just think we need to be very careful about use of terminology that certain groups and/or agencies use very, very strictly.

DR. McCABE: Again, the comment was made before, the most important thing is education. I think sometimes "consent" is used as a poor surrogate for "education," and we need to be very careful that we do not lock individuals into getting a written consent and avoiding the education.

MS. DAVIDSON: I just want to concur that if we are going to make a recommendation, then it should not read as "should." It really should be required. Otherwise, it does not pull any weight at all, and it does not have any meaning.

The other thing, just to throw another term into the bucket, the term that we are using at the Alliance now is really "informed decision-making." I think this, then, kind of pulls together "education." It also reorients us from the process of informed consent, which has a whole different context and meaning.

DR. McCABE: So, could we take that bullet. This is the bullet on page 27 which says "written informed consent should be obtained for tests used for predictive purposes." We could change that to "informed decision-making should be required for tests used for predictive purposes and other high-scrutiny" --

DR. CHARACHE: I was going to suggest one word change. Can we make it "informed decision-making must be documented"?

DR. TUCKSON: First of all, Mary, I appreciate the concept. It makes sense to me. It is the right thing. The reader of the document will not understand it, even if you explain it. "Informed consent" is understood in all of its connotations in today's world, and I just would urge you to use that language, if that is what you mean, and we will educate people to ramp up to informed decision-making. But "informed consent," people know what you are talking about.

DR. McCABE: Again, Michele's point that 4 million tests are done every year, most of them being done in an informed dissent approach.

MS. DAVIDSON: Actually, part of my concern is that people do understand informed consent, and it does not describe from my perspective as a patient, as a consumer, it doesn't really describe an educative process. It is something that is given to you, and you have got 15 seconds to sign your name. In fact, that is one reason I think we should be using a different term would highlight the difference in the process.

DR. BURKE: I wonder if your concern is best addressed in the bullet on the previous page where we are talking about "Individual and family members considering a genetic test should have

access to appropriate genetic education and counseling to ensure their ability to make an informed decision about being tested." I mean, doesn't that address the point you are concerned about?

MS. DAVIDSON: Yes, yes. I am the last one. I am not going to fight over terms.

DR. McCABE: But we need wording on this other one.

DR. BURKE: We could make it "informed decision-making" and sort of restructure the sentence, but it seems to me that is where we are making that statement.

MS. DAVIDSON: Right. I think that rather than using the term itself, but just using it to describe the process and putting more emphasis on education.

DR. BURKE: Just to follow up on that, I would say the only way in which that additional bullet about written informed consent adds anything in my view is if we think that a requirement for written informed consent serves as a red flag, which I would propose it does in the clinical setting.

When clinicians know that they have got to get written informed consent, that is like a buzzer going off. This is a major deal. I think the purpose, then, for written informed consent is not to assume that it covers everything that we want it to cover. Really, that previous bullet is the more important point, but it is just a way of signaling tests that are much more complicated and require much more careful decision-making than other tests.

DR. KOENIG: I agree with Wylie, and I also agree that the most important point in a way is covered by the bullet about genetic education and counseling in terms of the overarching principle, but that also in the clinical setting, it is an important flag. I think there are categories where we do want to require written informed consent, but perhaps we do not want to limit it just to predictive tests, but to, again, tie it to the whole process and to the particular categories.

DR. McCABE: So would we want to say "written informed consent must be obtained for tests of high scrutiny or requiring high scrutiny"?

DR. KOENIG: I would support that.

DR. McCABE: Anyone who disagrees with that wording of this bullet?

MR. HILLBACK: No, I do not disagree with that. That is in the system, you are talking about.

DR. McCABE: Right. This is not IRB.

MR. HILLBACK: This is not necessarily the piece of paper that is sitting in the laboratory.

DR. McCABE: Right.

MR. HILLBACK: This is the physician somewhere in the system this is happening. I just wanted

a clarification.

DR. McCABE: What I am hearing as the sense of the committee is it is a documentation of the education. I think we need to make sure that we make it clear that it is not a surrogate for education.

DR. CHARACHE: Your idea was better.

DR. McCABE: Thank you.

Okay, so then let's go to the next one. "Should reimbursement for genetic counseling services be linked with genetic test?" Did we discuss this previously?

What about the issue of the "overarching"? Do we want to move these into the "overarching" so that they are not stuck as an appendage? We will do that, then.

So, the last two bullets from the members are as follows. "Should reimbursement for genetic counseling services be linked with genetic test?" "SACGT has recommended that genetic education and counseling resources be accessible but not required for individuals and family members considering a genetic test. Should genetic counseling for genetic tests of high scrutiny/complexity be required?"

Thoughts?

DR. PENCHASZADEH: I think that that point is addressed in the bullet that we just read of the recommendation of appropriate use, genetic education and counseling.

MS. BOLDT: But I think we can strengthen that by adding an additional sentence basically saying what we are saying for the written informed consent that any test of high scrutiny it must be required that there be genetic education and counseling.

DR. HUDSON: Also, in the text following that, it says that the test provider should be encouraged or required. So it would be striking the "encouraged."

DR. McCABE: So we will strike that "encouraged" and then add -- do you see where to make that other change? Do you want to give us that sentence again, Ann, please? "For any test of high scrutiny" -- that is where we left off. It was the first bullet.

MS. BOLDT: That would remain as it is, and then add an additional sentence, something to the effect, "Any test of high scrutiny" -- how would we say that? You can even use "Genetic education and counseling must be provided for any test of high scrutiny." You can work on the wording.

DR. McCABE: We have not specified and the comments also asked for clarification of that point in terms of who is responsible for this.

DR. PENCHASZADEH: Appropriately trained professional.

DR. McCABE: The issue is, is it the model that there is a genetic counselor on call to the laboratory, like the HIV model, back when HIV screening. There is an 800 number that you can call and get someone. Or, is it that the laboratory will refer to a clinical genetic service, and how specific do we want to get here?

DR. CHARACHE: Currently, there is a requirement under CLIA that every laboratory have a clinical consultant available. That is beefed up under the recommendations of the Notice of Intent. It does not exist here.

That person would be involved only if the clinician who ordered the test requested that the service be provided. This goes another step and says the service should be offered whether or not it is requested by the ordering physician.

DR. BURKE: I think we should be very cautious about any language that implies a specific professional group. I think we may have circumstances where we want to say that a certain test should only be given in the context of appropriate counseling and education. We can say genetic counseling and education, but I do not think we want to say that it has to be given by a member of NSGC or ACMG or anything that specific.

DR. PURYEAR: I agree with Wylie. There are many places if you look towards the future where maybe engaging in genetic testing with a genetic counselor where a geneticist is not necessarily available. They may be on call, but they are not going to be there for the direct counseling or education that needs to go on. I think a physician or nurse practitioner is certainly capable of doing it, with some help, certainly capable of doing that kind of counseling.

MS. BOLDT: I understand that we may not want to say specifically the National Society of Genetic Counselors, the American College of Medical Genetics. I think it is still appropriate for us to say that there are specifically qualified geneticists that have board certification in these areas. If we want to have open-heart surgery, we are going to go to a cardiovascular surgeon. Why are we so worried about making sure everyone knows that there is geneticists that do this?

I also think we can also put a plug in for the NCHPEG. At least I downloaded it from the web, and they still have draft recommendations in terms of the basic competencies for individuals. I think we should also include that. I have no problem with that, but I think we need to make special note that there are board-certified professionals that can provide this, especially when you are talking about predictive testing.

DR. PENCHASZADEH: This is a complex issue because, if we stick to the board-certified genetic professionals, we can guarantee that most of the people needing genetic testing will not get close to any of those professionals.

I would agree with Wylie, and let's see what you have to say in a minute, Wylie, that we should not be that specific. We should state, however, that professionals providing education and counseling should be properly trained and qualified, but I can imagine, as Michele was just saying, a variety of scenarios from now for the next 10 years in which you will have primary care physicians, nurses, or whatever, quite properly trained that are not board-certified in genetics, but

are properly trained to counsel. That is the way it will happen. So I would try to find the right wording to simply state that there should be some training and some qualifications.

Now, I have a problem with "genetic counselors" or "counseling laboratory-based" because you can conceive that laboratories are in the business of making lab tests and providing lab tests, diagnostic tests, and sometimes -- and I have had experience with some counselors at our laboratory base that the type of counseling that they give is quite perfunctory. So I do not think we should support or encourage laboratory-based genetic counselors. Genetic counseling should be part of a medical interaction between a health professional and a patient and should not tied to the lab that will make the test.

I would like to go back to the bullet of the "informed consent."

DR. McCABE: We still have to finish this bullet before we move on to the other one.

DR. PENCHASZADEH: Okay.

DR. McCABE: Kate and Wylie, briefly if you could, because I really want to focus back and get the wording that we are going to agree on for this bullet.

MS. BEARDSLEY: I was going to just suggest that I can see that you cannot have a certified genetic counselor every single time, but it does seem like there ought to be a way in here to recognize the special qualifications, perhaps by saying that preferably you would have a certified genetic counselor where that is possible.

DR. BURKE: I will just reiterate. I think we want to tread very carefully here, particularly in the area of genetic tests coming into mainstream use in primary case. I think a primary care physician who follows someone longitudinally may be the very best person to give pre- and post-test counseling in many instances. So I do not think we want to lock ourselves in here.

DR. McCABE: Sarah has been taking notes here. So I am going to ask her to read what she has crafted. This would be for the paragraph above the bullet. Is that where it would go?

MS. CARR: Wouldn't it be part of the bullet?

DR. McCABE: Okay. So it is going to be part of the bullet.

MS. CARR: Part of the first bullet, "individual and family members," and then it would say, "Genetic education and counseling must be required for any test of high scrutiny. Professionals providing education and counseling should be appropriately trained and qualified."

DR. BURKE: I think "qualified" --

MS. CARR: It must be "appropriately trained." Is that your modification?

DR. HUDSON: I was going to ask a question. Did you say "must be provided"? There is a

difference between "must be provided" versus "having access."

MS. CARR: "Genetic education and counseling must be required for any test of high scrutiny," and then, "Professionals providing education and counseling should be appropriately trained" or "must be appropriately trained."

MS. BOLDT: Trained in what? Trained to do what?

DR. BURKE: I think this is a tough issue. This is exactly what is tough about this issue. If you start defining it, you start boxing yourself in. Just speaking about the NCHPEG competencies, the NCHPEG competencies for primary care include the possibility that primary care docs would acquire all the skills necessary for genetic counseling, but they do not involve any kind of credentialling process, any kind of formal certification of training.

So I think a primary care doc could argue that he or she has gone through some appropriate CME and now feels confident to do this, and we would be hard pressed to say that they should not.

MS. BOLDT: What I am saying is should we just leave out that phrase because, if you do not finish it, you are not really saying anything.

DR. McCABE: I'm sorry, we really do have to wrap this up. If we are not going to agree on it, then we need to agree that we are not going to agree and move on.

Do you want to read it again?

MS. CARR: "Genetic education and counseling must be required for any test of high scrutiny. Professionals providing education and counseling must be appropriately trained."

Okay, is required.

DR. McCABE: What about the second sentence?

MS. BOLDT: Personally, I would recommend that we drop the second sentence.

MS. CARR: So we drop "professionals providing education and counseling should be appropriately trained."

DR. McCABE: We are saying "genetic education and counseling" in the first "is required for" --

MS. CARR: -- "any test of high scrutiny."

DR. McCABE: Okay, is that –. Yes, Elliott.

MR. HILLBACK: I just have to tell you that this is deja vu all over again because, three years ago in the task force, we spent the better part of a day debating the issue that we were going to put all sorts of new rules and regulations on laboratories, but were not going to put similar rules and

regulations on those people interpreting the test. Hopefully, tomorrow, when we talk more about education, we will see where that is going. It is interesting that we are still dancing around that issue for those who will deliver the information, but it is easy to regulate labs. It is an interesting observation. That is all.

DR. McCABE: Wylie, did you have something?

DR. BURKE: No.

DR. KOENIG: Just on my other point which people may think is insane, the issue of should reimbursement for genetic counseling services be linked with the genetic tests, I may have said this in the previous meeting. Would we want to state as a general principle, not as a requirement, that third-party payers, insurers, HCFA, and other agencies making decisions about reimbursing clinical genetic services should seriously consider linking paying for the test itself with paying for counseling, and that we might even want to state as a principle that paying for the test and refusing to pay for the associated counseling of a high-scrutiny test is perhaps unethical?

DR. McCABE: So not linking it with Victor's concern. These were not necessarily be employees of the laboratory, but that it is important that because we feel that education and counseling are so important, they ought to be reimbursable as --.

DR. KOENIG: An essential feature of the service.

MR. HILLBACK: I think on this point, you will find that a lot of physicians who do not get reimbursed for the genetic counseling pay for that out of there "profit" that they have in seeing this patient, and some labs do that. The genetic counselors end up quite often holding the bag. So I think there is an incentive that if we are going to make counseling or education a required part of the test that we should not allow payers to separate those two.

DR. McCABE: Okay. So we will recapture that from the transcript and build it in here.

MS. BOLDT: I guess it comes back to the question of properly trained individuals and possibly just putting in a comment in terms of the work force as it is now. I know we are going to be talking about that tomorrow, but putting in there that we need to address that issue, too. Right now, there is only about 3,200 certified geneticists and certified counselors and that there needs to be efforts to train additional professionals in this area, as well as all the other health professionals to meet the NCHPEG-based competencies. I think that also needs to go into this document that we do recognize the need for more trained individuals.

DR. McCABE: Does anybody disagree with this to put in a comment regarding work force?

[No response.]

DR. McCABE: Let's move on to the comments from the public. I think a number of these, we have already dealt with, but let's run through them.

My goal is I want to finish these. We still have a 15-minute presentation by Joann and Pat. We are going to break.

The schedule for tonight, just so you know that there is a light at the end of the tunnel, I think that we can be out of here by 6:00 or 6:15. There is an HBO presentation at 7:00 to 8:00. It is called "King Gimp." I will let Joann tell you about it.
DR. BOUGHMAN: It is a 37-minute film, a short documentary that won the Academy Award this year for short documentary, chronicling the 12 years of the life of a young man with cerebral palsy. It is an absolutely powerful film, and tonight is the showing on HBO.

DR. McCABE: There is a room that will hold 15 individuals, so first come, first serve, I guess. Embassy Suite 104. You go to the lobby, walk up the steps. It is on the left. Walk up the steps on the left and go to room 104. They have set up a TV in there for us. That is from 7:00 to 8:00.

Then we will have dinner at Bertucci's Brick Oven Pizzeria, 1218 Connecticut Avenue, Northwest, is at 8:15. So the dinner got moved from 7:30 to 8:15. We will meet in the hotel lobby at 8:00 and walk over then.

DR. TUCKSON: And what is your plan --. We are going to do Issue 4 tomorrow?

DR. McCABE: No. I think we can do Issues 4 and 5 tonight. If not, they will go on tomorrow, but I would like to leave that time tomorrow for wrap-up and general issues.

MS. BEARDSLEY: We had said earlier today that we were going to talk a little bit about the difference between germline and somatic mutations and the different treatment of those. When does that fit in?

DR. McCABE: I had actually thought we had had that discussion.

MS. BEARDSLEY: Oh, we have? What did we decide?

DR. McCABE: In dealing with the definition, I thought we had dealt with that issue, but perhaps I am wrong.

MS. BEARDSLEY: We said in the definition that we thought it should be in the definition of "genetic testing," but I thought we said, as to oversight, there might be some differences.

DR. McCABE: Okay, if we could put that in for tomorrow. I want to go back and catch those kind of loose ends tomorrow, if possible.

Go to page 2, "Rationale of Proposed Increased Oversight/Consideration of Implications. Several concerns were expressed about the implications of proposed recommendations for additional oversight on development, availability, and access to tests, and lack of discussion in this report." And I think we have dealt with that.

I thought that we had said in the report that mechanisms should not become limiting factors, that

that is why we needed to develop creative approaches. I think we have discussed that a lot more today. Is there more that needs to be put in here?

[No response.]

DR. McCABE: Okay. If there is no discussion of that, we are going to move on.

"Criticisms regarding justification of singling out genetic tests for additional oversight." We dealt with that this morning by saying that we will try to explain that we are not proponents of genetic exceptionalism, but our charge was to deal with genetic tests. I think the other points in that bullet, we have discussed.

FDA Review of All New Genetic Test. Comments are divided, but the majority favor FDA as the lead agency.

Existing CLIA/FDA regulations. Two comments that existing regulations are adequate.

Expansion of CLIA regulations. Almost total support for expanding CLIA regulations with the exception of the CAP and the Association of Molecular Pathologists.

Does anyone wish to discuss those exceptions?

DR. CHARACHE: I would just say that we have urged those two groups to comment on the Notice of Intent and have been trying to provide some educational information to them which would perhaps help their deliberations.

DR. McCABE: Any further discussion of that point? Again, there was, on the balance, agreement.

IRB review of genetic testing research protocols. General support for this. Concerns regarding ability to implement recommendations, ability of the IRB to assess genetic testing protocols, and definition of "identifiable."

If you go back to the professional organizations' document, it is very clear what they mean by "identifiable." On the other hand, we will get into a discussion tomorrow about family history, and I think that for many of us, the concept of an identifiable individual is changing based on the discussion of OPRR and the family history.

DR. CHARACHE: I would like to ask if we could add to that section on the IRB a precise definition of a patient-care test because that confuses IRBs and I think it should be in here. That it is no longer covered by the IRB if the results are given to a patient's family or health care provider. I keep repeating that because it is missed, and it has been missed in some of the discussions here today.

DR. BURKE: Isn't it fair to say, Pat, that it is no longer solely covered by IRB?

DR. CHARACHE: That is correct. That is right.

DR. BURKE: I mean, IRB oversight is still in place, but CLIA oversight is added.

DR. CHARACHE: Yes, but I think that point should be in there so that the IRBs know when they are not the only one.

DR. McCABE: Well, is this the place for it? It is in the CLIA regulations.

DR. CHARACHE: It is missed very badly by IRBs. We are just learning the extent to which that is the case because it is felt by the researcher that if he is still doing research or he is not charging the patient, then it is not a patient care test.

DR. BURKE: I agree completely, and it may actually even be part of how IRBs should review and agree to disclosure of results; that they are agreeing that the results can be disclosed, assuming that it can be done from a CLIA-certified lab.

DR. CHARACHE: That would do it very well.

DR. KOENIG: That is the point I wanted to bring up, too, the issue. I think that we could make a real contribution to the whole IRB review process by pointing out this very complicated issue of when results are given to research subjects as such an important issue because I do not think it actually happens out there in practice.

DR. McCABE: There are a number of commentators on this. We had decided to park this issue until after this document was done, but this is where it rears its head, and that is the rare disease.

So we could specify on page 25 something about when information is reported back to an individual that testing should be done in a CLIA-approved laboratory -- must be carried out in a CLIA-approved laboratory. You recognize that once you say that, that you will shut down more than half of the types of tests that are done immediately. I know that CLIA has said this. Excuse me?

MR. HILLBACK: You sound like me.

DR. McCABE: No, I am just saying the cost of those would be prohibitive in a commercial lab. There is only one laboratory in the country right now that is doing that, and it is doing it at the cost of $2,000 or $2,500 per test.

There are others of us who have worked out deals on our campus with our local DNA diagnostic labs, but they are all taking a loss on that where we have done that.

I know this is an issue that you have grappled with and done very effectively at Hopkins, but that model has not proliferated. I am happy to put that in there, but there are significant ramifications to that statement.

DR. BURKE: So do we need an organ disease exception? Orphan disease exception?

DR. McCABE: We have parked the rare disease and said that we were not going to deal with that until after the document because this is an issue. Now we are dealing with it summarily.

DR. CHARACHE: One comment and a thought. The comment is that this is one of the reasons why one of the models that was chosen to work on with the forum was a rare disease, and that is why we chose Marfan's, so that we could look at these issues and define some criteria for them. That is coming, of course, back here for editing and thoughts and amplification.

My thought is, then, could we be perhaps less specific and simply say that if a result is provided to a patient, patient's family, or health care provider, it becomes a patient care test and not go any further than that?
MS. YOST: I cannot speak for all research or rare disease testing, but in a lot of cases, much of what a researcher does will actually already meet CLIA provisions. And I think that is a missed perception that a lot of folks have.

I know, Elliott, you can shake your head because you know what they do.

Between the IRB protocol and between all the testing and retesting they do to make sure that their test is working and that it is accurate and so forth, with all of that stuff, you can meet many of the CLIA quality requirements, even for proficiency testing. There is obviously not PT available for those tests, but they do check the accuracy of that test multiple times. So that will meet that requirement.

Quality assurance. They do a lot of the things within quality assurance, but they may not have a formalized plan. Well, that is not a big deal as long as they are doing it.

Same thing with quality control. They have got to do something to monitor that the test system is working, and that meets CLIA quality controls. No, it does not meet a CAP checklist, but it sure does meet CLIA quality provisions. I think that is an important thing we have to remember.

There may be some places that do not do all of that to that extent, but clearly I have one excellent experience actually at a government agency that I will not mention. He was doing well beyond anything that we would have asked him to do under CLIA, without any knowledge that he really was meeting that. Just as we walked through, "What do you do in your lab to assure quality?," as he explained each piece of that, it met the requirements.

DR. McCABE: How specific do we want this sentence to be, then?

MR. HILLBACK: It is interesting because we had the same discussion on the Task Force on Genetic Testing, those who were there. Steve Goodman from Colorado was there and made the same comments, and he got the same feedback which was most of these labs can meet CLIA. They just do not think they can.

Again, it is very difficult to figure out a gerrymander that says, well, if you're only doing a few tests

or doing --. Most of the genetic labs in the country do not make a profit, including many of the commercial ones, despite what everybody thinks. So, if you use profit or if you use number of patients, I think you are going to find most of the time, CLIA will not be involved, and will make the exception for FDA. Then no one will be involved, and where do we start?

If we are going to put CLIA and FDA into this, and CLIA certainly is and we can still debate FDA, I hope, you have got to do it. I do not see how you cannot.

DR. McCABE: So how would we write the sentence, then? "When test results are reported to individuals, families, or health care providers, the testing must be performed in a CLIA-approved laboratory."

MS. DAVIDSON: Again, I just want to stress that what I am told, by our member organizations, many of the tests for their orphan diseases are not CLIA-approved. Since they run on a shoestring, it is asking a lot of them. I guess that is part of my question is if it could be tied to technical assistance from CLIA. Then it is a whole different situation.

DR. McCABE: Is there a way to say because of the CLIA requirements that tests reported to individuals, families, or health care providers should be performed in a CLIA-approved laboratory? Technical assistance should be provided to those laboratories in which there are rare disorders to achieve this goal. Is that acceptable?

DR. CHARACHE: I like that, but I think that the technical assistance should also come from within the institutions.

DR. McCABE: Okay.

MR. HILLBACK: I think where we went the last time was to say these tests must be done in a CLIA-approved laboratory, and it is a horrible situation if these tests are not done. And therefore, it's similar to the orphan regulations related to therapies, there are all sorts of assistance that should be provided. So I think we need to reflect that.

DR. McCABE: Here, we will be acknowledging the regulations, we will be acknowledging the reality, and we will be trying to effect a transition. So is that a reasonable way to go?

MR. HILLBACK: The only other thing you could do is say to CLIA are there pieces of the regulation that do not need to be applied, if you want to introduce the idea of flexibility to CLIA, as we have asked the FDA to be flexible? I do not know how CLIA would respond to my suggestion, but we did state in our previous document -- I am not sure strongly enough yet -- that we are asking FDA to be flexible about how they do things. Should we, could we, ask CLIA to do the same?

DR. McCABE: Two brief comments. Ann and then Barbara.

MS. BOLDT: The other thing we need to do is address possibly international genetic testing. As David had said, there is a lot of genetic tests across the seas that are not subject to FDA and CLIA.

So we need to make some comment in terms of that availability for patients. It is listed in GeneTests. So we do make those calls and send those samples.

DR.McCABE: Okay.

MS. BOLDT: I am talking Switzerland. We might use a lab in Switzerland because it is listed in GeneTests, and if they are the only ones doing it --

MS. YOST: But if it is a U.S. person that they are doing the test on, it is covered by CLIA.

DR. McCABE: Yes, but, again, if this is the only lab in the world and the Swiss lab says we are not going to do this, what is the option for the individual?

DR. KOENIG: I am actually concerned about another dynamic. I just want to make sure that we somehow send a message to IRBs that it is appropriate to hold firm on the idea, and maybe orphan conditions excluded, but that it is okay to hold the line about not disclosing results in research situations where it truly is research.

Because my experience of dealing with IRBs is very much the opposite. There is an increasing pressure with arguments made that, for example, if the only information that might have clinical relevance comes, even if it is not a CLIA lab, all those things, that researchers experience an obligation to disclose results, and that we need to provide guidance to the IRBs that it is okay. You really should hold the line and actually put that firmly in consent forms that you are not going to give out results.

DR. McCABE: I think that is a general issue. I think that is probably dependent on the IRBs. In fact, the move at our place is not to give results. They are moving more and more not to give results, even when there might be some benefit in giving the results. But I think that is a general issue, again, not genetic.

DR. KOENIG: Then perhaps we do not need to cover it. I do not know.

R. McCABE: I really think it is a general OPRR thing about giving results, but it is up to you. We can include it in here. I see it coming up in our IRB for all kinds of things, not just genetics; in fact, more on other things.

We will do one more, and then we will break and finish up tomorrow. Well, we will have the 15-minute presentation.

FDA review of predictive tests. There were only two comments on the specific recommendation. I think we covered this in terms of review of tests for predictive purposes. So we will finish this page off tomorrow, page 3.

Why don't we have our presentations by Joann Boughman and Pat Charache. These are our representatives from the FDA Medical Devices Advisory Committee and the CLIAC.

I am not sure which of you were going to go first. Pat, do you want to go?

DR. CHARACHE: I am going to sit here, and I will be very brief.

CLIAC met in April. It was updated in terms of the initiatives from this group, and we discussed a little more about the Notice of Intent, voting unanimously to urge that it get out from the interstices of HHS into the Federal Register, which it did.

I think the next meeting of CLIAC will be in September. It will be to discuss the information that was generated by the forum and also to review the comments made from the public on the Notice of Intent and decide where to go in terms of formatting, making recommendations on regulations, which will come out of that Notice of Intent.

We are also in CLIAC very interested in soliciting people to comment on those, and I think there is a lot of details which are substantive and impact greatly on the decisions of this body. So I hope this group will get a good look at it between now and July 3rd when the comment period closes.

DR. McCABE: Joann on the MDAC?

DR. BOUGHMAN: I do not have a great deal to report because the committee or the panel has not yet formally met and in fact is not completely empaneled as of yet. However, we did have one fairly open training session.

Like other FDA advisory panels, this panel has an executive secretary in Dr. Peter Maxim, who has been at each one of our meetings all day, every day, but left just a few moments ago. I will point him out again tomorrow morning.

On the FDA side, the executive secretary of the panel is an extremely important point person in pulling these groups together.

In a moment of obvious insanity, I did agree to chair this panel and actually wrote my name at the bottom of the paper. There will be, as with other panels, six voting members. There is a consumer representative. There is an industry representative that has not yet been selected from among the nominees, and that is being looked at.

In addition, not unlike other advisory committees and review groups, ad hoc members are selected from time to time to look at either an issue which in fact can be dealt with in at least two kinds of forums, one in the writing of a guidance document or one, in fact, in a firmer document that may lead to a standards-setting process.

The panel, also when asked, will review a 510(k) or a PMA, and both of those processes were briefly discussed earlier. Let me just reiterate that in the review either of a 510(k) or a PMA in an FDA panel for those of you who have not been involved in this, it is an incredibly data-intensive review process. And in fact, the process revolves around the ultimate approval of the labeling that the organization putting forward the 510(k) or the PMA sets down. That at first blush sounds somewhat elementary, if you will, but if in fact you realize that the claims, the protocols

themselves, the ranges and the standards that go along with those ranges, the expectations and the exceptions to the tests must all be included in the labeling of these processes, so that when a new lab purchases that box, the label has to tell them everything, it becomes the appropriate focus for these panels.

The mind-set, as David reminded us earlier, is the protection of the consumer. So, in order to review these appropriately, you put yourselves in the position of a relatively naive laboratory, selecting from a catalog or purchasing via mail, this new test, and from the label that comes with the test, now be able to give it to the appropriate technician, technologist, or whomever and in fact implement the test in your laboratory. That is your laboratory whether you are in the middle of the high-tech sector in Boston or whether you are in Timbuktu, Alabama, or North Dakota.

So the process comes back repeatedly to documentation to wording to details, and anybody who has served or has been to one of these meetings realizes that these can be very intense processes. They do have the public comments, and it can be very difficult for one of these panels to separate the issues. It can be a relatively tension-filled situation. When you recognize as a panel member that to have a test do what you and/or the company want this test to be able to do, is different than your reviewing the materials and data put before you to document whether the submission does what you or the submitter wants and expects it to do. It is a very interesting process.

The FDA, believe me, has not been dragging its heels. They have been doing a great deal of discussion internally, and I think that it is a balance of the materials that are being brought up and fed to them from this group and from the CLIA side so that, if and when this panel does get started, then we are started on the right foot.

It is absolutely critical that when we pull together this group, that will be an interdisciplinary group as FDA panels are, that the group have enough direction that they can take the next steps logically and appropriately because we do not want to blow it.

Once we get it into the regulatory aspects, we have got to have all of us pointed in the same direction. So we are taking notes furiously, and we will hit the road running, hopefully.

DR. McCABE: Thank you very much.

Our plans are now that we will break. Those of you who are going to dinner, we will meet in the lobby at 8:00 to walk over to Bertucci's. Remember, tomorrow morning, we start at 8:00 a.m., not 9:00 a.m. We are starting at 8:00 a.m.

I am told that you can leave materials behind in the room. Do not leave any valuables behind. Having had many experiences in hotels, even though we are assured we can leave things behind, do not leave anything important behind because I have had it disappear too often after somebody made the announcement I have just made.

Oh, and Suite 104. Come to Embassy Suite 104 if you want to watch the HBO movie at 7:00.

[Whereupon, at 5:55 p.m., the meeting was adjourned, to reconvene at 8:00 a.m., Tuesday, June 6, 2000.]