SECRETARY'S ADVISORY COMMITTEE ON GENETIC TESTING

Ninth Meeting

Wednesday,
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Conference Room 6C-10
Building 31
31 Center Drive
National Institutes of Health
Bethesda, Maryland

FRIEDMAN & ASSOCIATES, COURT REPORTERS
11923 Parklawn Drive, Suite 203
Rockville, MD 20852
(301) 881-8132

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

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

ANN HAPP BOLDT, M.S.
Genetic Counseling Consultant
13987 Springmill Ponds Circle
Carmel, IN 46032

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

WYLIE BURKE, M.D., Ph.D.
Chair
Department of Medical History and Ethics
University of Washington - Box 357120
1959 N.E. Pacific, Room A204
Seattle, WA 98195

PATRICIA CHARACHE, M.D.
Professor, Pathology, Medicine, and Oncology
Program Director
Quality Assurance and Outcomes Assessment
Department of Pathology
Johns Hopkins Medical Institutions
600 North Wolfe Street, Carnegie 469
Baltimore, MD 21287

IN ATTENDANCE:

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

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

REED V. TUCKSON, M.D.
Senior Vice President
Consumer Health and Medical Care Advancement
UnitedHealth Group
MN 008-T910
9900 Bren Road East

Minnetonka, MN 55343

Ex Officio Members

Agency for Healthcare Research and Quality

DAVID LANIER, M.D.
Acting Director
Center for Primary Care Research

Centers for Disease Control and Prevention

MUIN KHOURY, M.D., Ph.D.
Director
Office of Genetics and Disease Prevention

Food and Drug Administration

STEVEN GUTMAN, M.D.
Center for Devices and Radiological Health

IN ATTENDANCE:

Health Care Financing Administration

JEFFREY L. KANG, M.D., M.P.H.
Director
Office of Clinical Standards and Quality

Health Resources and Services Administration

MICHELE LLOYD-PURYEAR, M.D., Ph.D.
Chief, Genetic Services Branch
Maternal and Child Health Bureau

National Institutes of Health

FRANCIS COLLINS, M.D., Ph.D.
Director
National Human Genome Research Institute

Office of Human Research Protections

IRENE STITH-COLEMAN, Ph.D.
Senior Policy Advisor
Assistant Secretary of Health, DHHS

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

C O N T E N T S

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

DR. McCABE: Well, good morning, everyone. Welcome to the ninth meeting of the Secretary's Advisory Committee on Genetic Testing. The public has been notified about this meeting through an announcement in the Federal Register on April 12th and a posting on the SACGT's Website. We appreciate the public's interest in our work.

We have four major goals for this meeting. First, we will continue deliberations regarding FDA's development of a premarket review process for genetic tests. We will also learn more about FDA's labeling authorities as they pertain to genetic tests. We are looking forward to hearing from members of the public during our public comment periods today and tomorrow about your views on the approach FDA is taking. Individuals interested in making comments on the FDA plan or any other relevant issue, please sign up at the registration table outside the meeting room.

Second, we will be briefed by CDC on interagency efforts to develop voluntary integrated systems for the collection and dissemination of information on genetic tests. As you know, in our oversight report to the Secretary, we made recommendations about the importance of gathering and disseminating data to advance our understanding of the clinical utility of genetic tests, and we are looking forward to hearing about the Department's progress in implementing this important component of advanced oversight. We hope to learn more about the scope and feasibility of integrated systems and how coordination of efforts across the public and private sectors will be achieved.

Our third goal relates to the development of clinical guidelines, another critical element in assuring the appropriate use of genetic tests. We want

to understand various models for clinical guideline development in genetic testing, with an eye toward assessing whether there is a need for a "points to consider" document that would set forth general procedural and substantive content recommendations for guideline development. If we determine that such a document would be useful, we will then consider whether this would be an appropriate undertaking for SACGT.

Our fourth meeting goal is to review the progress of the five SACGT work groups. We will review specific proposals from the data group and education group for convening two outreach meetings to help advance their important work in identifying the data elements to be considered in different stages of test development, and in assessing the extent of efforts to provide genetics education in a wide range of health professions and disciplines.

Before we begin, I also want to report on the status of the recommendations we made last fall on gene patenting and licensing and secondary subjects of research. As you know, in November we transmitted a letter to the Secretary about concerns we were hearing from some academicians, professional societies, and patient groups that certain commercialization approaches were having adverse effects on access to and the cost and quality of genetic tests. We recommended that further study by appropriate experts might be warranted to determine the scope of these practices and their overall impacts. Dr. Art Lawrence, Acting Principal Deputy Assistant Secretary for Health, has notified SACGT staff that the matter is still pending.

With regard to third parties in research, we looked into the issues raised by a decision of the Office for Protection from Research Risks that indicated family histories could not be obtained in a research study without the informed

consent or waiver of informed consent of the family member. We wanted to understand the decision and its ramifications for genetic testing research. So last June we convened a panel of experts and held a roundtable discussion of the issues. After further reflection, we decided that because the issue went beyond genetic research, we ought to defer further consideration of the issue to a more appropriate body that could take account of the broad scope of research in which information about family members and other third parties is obtained.

In a letter last December to Dr. Satcher, we recommended that the National Human Research Protections Advisory Committee, or NHRPAC, be tasked with reviewing current federal policy regarding the regulatory requirements for informed consent of third parties. NHRPAC advises the Secretary, the Assistant Secretary for Health, and the Office for Human Research Protections, or OHRP, on a wide range of human subjects issues. Dr. Satcher conveyed our recommendations to Dr. Greg Koski, OHRP Director.

We understand that NHRPAC considered the issue at a meeting held on April 9th and made a decision to form a working group to explore the regulatory definition of "human subject" with respect to information collected about third parties in research. We appreciate that our recommendation, the substance of which was reinforced by others at the meeting, including Dr. Francis Collins, is being acted upon, and we will follow the progress of NHRPAC with great interest.

Let's now turn to Sarah for her important reminder about ethics rules and conflicts of interest guidance to us.

MS. CARR: Thank you.

Being a member of this committee makes you a special

government employee and thereby subjects you to rules of conduct that apply to government employees. The rules and regulations are explained in a report entitled "Standards of Ethical Conduct for Employees of the Executive Branch." You each received a copy of this document when you were appointed to the committee. At every meeting, in addition to reminding you about the importance of following the ethics rules, we always like to review the steps we take and ask you to take to ensure that any conflicts of interest are addressed.

As you know, before every meeting you provide us with information about your personal, professional and financial interests. We use this information as the basis for assessing whether you have any real, potential, or apparent conflicts of interest that could compromise your ability to be objective in giving advice during committee meetings. While we waive conflicts of interest for general matters, because we believe your ability to be objective will not be affected by your interests in such matters, we will also rely to a great degree on you to be attentive during our meetings to the possibility that an issue will arise that could affect or appear to affect your interests in a specific way. If this happens, we ask you to recuse yourself from a discussion and leave the room.

If you have any questions about the rules of conduct or conflict of interest, our committee management officers, Claudia Goad and Mary Nuss, will be happy to address them. Thank you.

DR. McCABE: Thank you, Sarah.

We're now going to have our update from FDA, and this will be by Dr. Steve Gutman.

At our meeting in February we were briefed by Dr. Feigal about FDA's plans for implementing a regulatory process for genetic tests provided as

laboratory services. He outlined a phased-in program that involves registration and listing, test classification, development of review templates and standards, phased-in review of all tests, and implementation of premarket review. We also heard about the preliminary approach FDA was taking with an application process.

You'll recall that Dr. Gutman outlined the elements of a draft review template using Fragile X as an example. As presented, the template would require, among other elements, data on analytical validity, clinical validity, quality control and quality assurance, and clinical interpretation.

We were impressed with FDA's initial efforts to develop the review process but wanted to withhold definitive judgment until we saw how the template would be applied to other types of genetic tests with different intended uses. We were also interested in the outcome of review and in understanding what methodologies or thresholds would be used or applied to determine whether a test would be approved.

Since our last meeting, FDA has continued its efforts to further develop the review template. Additional test examples were applied to the template, and a working draft "points to consider" document was prepared to provide guidance to test developers in completing the proposed template. These materials are in Tab 2 of the briefing book. Today we have asked Dr. Gutman to present additional examples of how the template will work in practice and to discuss issues associated with outcomes of review. He will present four new examples, as well as discuss a revised Fragile X example.

We will then turn to Dr. Natalie Solomon from Abbott Laboratories, who has kindly agreed to present a pharmacogenetic test example.

A copy of this test example, which was developed through a public-private collaboration involving FDA and industry representatives working on pharmacogenetic products, is in your meeting folder.

Since we recognize the important role labeling will play in helping to ensure appropriate use of genetic tests, we will come back to Dr. Gutman for a briefing on FDA's label authorities and the extent to which FDA can require labels to contain warnings about unapproved uses of tests. We hope that the discussion that follows will help FDA continue to refine the steps that they have taken thus far.

Before we begin, I would like to extend our condolences to Dr. Gutman and his team at FDA on their loss of a valued and dedicated colleague. Dr. Peter Maxim worked at FDA for a decade, for most of that time as Chief of Immunology, Hematology and Pathology Branch. Molecular diagnostics and FDA's genetics efforts were housed in his group, and he was very active behind the scenes in supporting the program. He was also the Executive Secretary for the FDA Genetics Panel, which Dr. Boughman chairs.

Dr. Maxim worked intensely in support of and to prepare the foundation for FDA's emerging role in the regulation of genetic tests. His work in the area of tumor markers and molecular diagnostics for FDA was without peer, and he was respected by both academicians and industry for his fair, balanced, and scientific approach to regulation.

In addition to a profound professional loss to the agency, Dr. Maxim's death has also been a deep personal loss for his colleagues. Again, we want to extend our condolences to his colleagues and his many friends.

Dr. Gutman.

DR. GUTMAN: Thank you. You set me up nicely, but I intend to be a little bit more general.

As Dr. McCabe has just suggested, FDA regulatory activity, the so-called preliminary action plan, was put on the table at the last SACGT meeting by Dr. Feigal. That plan calls for registration and listing, for medical device reporting for adverse events, for the development of guidance templates and standards, for establishing a public database for presentation of key informational facts and data regarding tests, for test classification, and finally for phased-in test review.

A central tenet underlying all the activity was adherence and promulgation of a central focus in premarket review for FDA; that is, an assurance for truth in labeling as a mechanism for helping health care providers and patients to ensure that they have appropriate information in place to determine when to test and how to interpret a test result.

Based on ongoing discussion both within the agency and with outside partners, the direction of this plan remains unchanged, although incompletely formed. There is lots of opportunity to continue to mold it. There is a deliberate objective to maintain flexibility and focus in this plan. Nonetheless, the plan remains firmly in place.

A central tool for both voluntary and future data-gathering efforts that might become regulatory is clearly development of the SACGT-initiated data template. FDA, working with outside partners, has developed a number of additional examples explicating potential use of this template. They're in your briefing book, and I presume they're being shared with the public. We have also developed a very rough draft, a first draft glossary of terms, largely

derivative, actually, from terms that had floated in the background of this group and Dr. Holtzman's group. We also have an early or a rough draft on instructions on how to fill in the blanks for the template.

Although we believe this is a very reasonable start, it is quite obvious, and it will be obvious to anyone who looks at the glossary, to anyone who looks at the instructions, or to anyone who looks at the examples that there is, in fact, much work to be done.

I want to, in particular, credit an inside group, people I know and love even though you might not have seen in the public, and that is Refina Carlos, Maria Chan, and Angel Torres-Cabasa, who have been sort of an operating unit who have helped put this background material together and who have done a lot of thinking internally about how we might actually apply this both on an interim basis and on an ultimate basis in terms of renewed, voluntary, or compulsory regulatory activity.

Since the last SACGT meeting, there's been wide interest expressed in use of the template. An interested scientist at NIH was kind enough to provide us an example of potential use of this data, a demonstration device based on her actual experience with a research-based test. The Pharmacogenomics Roundtable has actually developed two formal models for use of this test in a slightly different setting than one we've actually talked about here before, and that is in predicting drug behaviors. In fact, it's so beguiling that I'm going to cede a few minutes of my time at the end of this general discussion to Natalie Solomon, who is going to very concisely present how the template might apply to that particular interesting and important product line.

Finally, FDA has had both formal and informal discussions on

template use for a number of interactions, interactions with Wylie's working group, interactions with the Professional Genetics Roundtable and one of their working groups, and also interactions through the Interagency HHS Working Group. What is clear from multiple efforts is that the boxes tend to look different as different players attempt to experiment with it. It's sort of like beauty is in the eye of the beholder. So the same scientist taking the same template and filling in the blanks come up with at least different, sometimes startlingly different results.

Hence, our desire to write an instruction manual on how to fill in this thing. Maybe the instruction manual will give you more than one choice. Maybe the template will give you more than one choice. But there has to be clarity in terms of expectation for entry, or else we're working with a potentially disastrous document here.

So there is a rough draft in place on instructions. It was put together on the fly. You'll see there are typo errors and some actual intellectual errors, but it's a wonderful start, in my view. I appreciate the group doing that, and we certainly would like this group to weigh in on it. We'd particularly like Wylie's subgroup to weigh in on it. We think it's probably important enough. It's worth a special call, a special meeting, a special discussion. It's certainly beyond the context of what we can do this morning.

The potential uses of the template, of course, are twofold. The first is that it's a vehicle for pure dissemination of information as an exercise in public health and, frankly, as an exercise in marketing of the test. It's important for people to know where these tests are and where they're available and the intellectual base on which they're being founded. Obviously, the second, perhaps FDA's particular interest, might be long-term or short-term in use of this template

in some regulatory context.

It is our hope, of course, that the two activities are not mutually exclusive, that they build off of each other. Defining and developing and coordinating work around this template, even as much as we've already done, will be challenging for both uses, and will be resource intense.

As a matter of principle with regard to the interagency HHS plan put on the table by Dr. Raub at the earlier SACGT meeting, in principle all three major players, in terms of data gathering and data interest and data regulation -- that being HCFA, FDA and CDC -- believe we can work off of this unified template, at least use it as a starting point, and are interested in seeing it enter the public domain, and are now considering in what format and at what location. I suspect Muin may be discussing that, as Dr. McCabe suggested, later.

There are a variety of potential locations. You have to realize you're hearing from an FDA-egocentric person and that certainly one public database would include or would be the FDA Website. We could create a Website. Another database, frankly, could be a CDC-based Website. But one comfortable and highly visible location would be the NIH-sponsored GeneTests Website at the University of Washington, which of course is already a somewhat highly visible place to go. Several interested outside parties who are, in fact, in the room have either discussed that with me or have discussed that with Dr. Pagan at the University of Washington.

Since everybody else was talking to Dr. Pagan, I took the audacious liberty of talking to her myself and actually had an 11th hour call. Bonnie and I talked last Friday, in fact, about whether she might be game, whether she might be willing to use the GeneTest base that she has so brilliantly and

eloquently and definitively developed, and she was certainly receptive to the idea of having discussions on making that a central place certainly for a voluntary effort to get information into the public domain, and if we're thinking far enough out of the box, who knows, maybe FDA may even be able to piggyback off that voluntary effort.

The template, as you have gathered, is growing in complexity and richness, and its use has potential to be quite nuanced. One would expect interest by laboratorians, by health care providers, both those with and without knowledge of genetics, by consumers and patients, and certainly, last but not least, by regulators. We're all interested in this damn thing.

As I said before, beauty may be in the eye of the beholder, and the importance of the template to a certain extent will depend on who might be scrutinizing it. For the laboratorian, there might be a particular interest in the methods used in ensuring proper information, on the clarity of procedures, and on information on techniques applied to assure the validity of the analytical and clinical signals being generated by the test.

For the health care provider, there's obviously less interest in methods and in the specifics of quality control and assurance and more interest in what's up with the test in terms of the use in a potential patient or a set of patients. The logical information the health care provider might want is when to use the test, in whom to use the test, what caveats need to be taken into account in test use, and what special considerations, such as special needs for informed consent, special needs for counseling, or special needs to provide access to support groups, might be appropriate for a given test.

In the process of deciding whether to order a test in a patient and

in deciding how to interpret test results, the strength and meaning of the test signal, the test results themselves, are obviously of critical interest, and it's of critical interest to understand the analytical and clinical limits inherent in the test, and the potential limits that might occur if an incompletely characterized test were in fact made available because we thought that was an intelligent public health thing to do.

The consumer or patient in this new millennium, as you surely all realize, tends to be an active player in analyzing his or her own disease and his or her own test results. Even my sister-in-law will surf the Net if she thinks somebody in her family is sick for consumer information similar to that provided to the health care provider. But obviously, to maximize access and understanding, terms should be crafted to allow complex scientific principles and issues to be communicated to the lay user. Consumers would likely be particularly interested in other issues, issues of cost, issues of reimbursement, and issues of what resources are available to provide support, treatment, assistance, maybe even access to clinical trials when they find that they have an old or a new, a usual or an unusual genetic disease.

There is, in fact, a very interesting model of consumer access to medical information here at NIH, and that's in the database used at NCI to support information on the clinical trials it sponsors. For any of you who have used this database, you will surely note that each protocol listed in that clinical trial comes in two alternative versions, one for patients and one for health care providers. Both are highly accessible, and there is free opportunity and access for both versions to be seen by either intended audience. So a sophisticated consumer can take a look at what's offered to the health care provider, and a health care

provider who is either not sophisticated or who would like to see what information is shared with patients has access to that as well.

Last but certainly not least, for regulators, at least at FDA, evaluation of design, data, and labeling, as I'll subsequently tell you, is a common and ubiquitous fact of life. The template, as presented, provides the core of what we would expect in a submission, although in critical areas, particularly the areas of analytical validation and clinical validation, we would normally expect that there would be more information and more support, that there would actually be a comprehensive description of how information is generated, how information is analyzed, and how conclusions are statistically or descriptively drawn.

Guidance on key elements actually already exists on these issues in a variety of forms, most notably in a series of relevant NCCLS documents, some of which have been recognized by the FDA as standards for use and/or for conformance, and NCCLS actually continues to work on a beguiling set of documents. They're looking specifically at molecular diagnostics, and our job in applying the template to review would be in working out the details of how to assure that the data on which the analytical and the clinical validity boxes rest is fairly and realistically presented.

So for a presentation of performance, you have to recognize that for us it can take a variety of forms, and that can range from characterizing results in terms of fairly weak clinical associations to explaining results in terms of actual estimates of sensitivity and specificity if you are fortunate enough to have insight into a gold standard or a diagnostic truth. In some cases, most definitively, you can actually generate results to develop likely predictive values in modeled or in real populations. That's the exception. We don't often do that, but we have the

capacity to do that when we're really hung up about a test.

In any case, there's a need to understand what populations have been studied, what inclusion or exclusion or selection criteria have been applied, how data has been analyzed, and what either standard or novel statistical tools have been used to derive conclusions. In some cases, summaries of data with clear explanations of data derivations will suffice, and in other cases the agency will probably choose to look at the raw data itself. We often cover the raw data itself. That's the nature of the process of our review, and that may be more opaque than you want, but in order to actually go through it, you're going to have to clear yourself and work with us for a couple of weeks to actually watch how that works, because it is an acquired taste and you just can't come off the street and do it, at least in my view.

The preliminary draft put together as a starting point for explaining how to fill in the blanks of this template is intended to do nothing more than initiate discussion on either public or regulatory collection of data. The key areas of analytical and clinical validation are actually somewhat blurred and obviously either need more extensive referencing or, in our hands, of course, probably more appropriately and more intensely detailed expansions.

Two key considerations from our perspective are important in moving forward with these instructions. First, the instructions should be as user-friendly and flexible as possible. Second, they should make it possible for us to avoid or at least minimize the intense review that we tend to do. So we want flexibility, but we want it to be straight and narrow enough that we can actually rely on information as it flows into the template.

We covet specific guidance on how to use clinical or published

literature. We are very keenly aware of the problem that you deal with in publication bias. We're also looking for how to link a particular test under review in the template with existing literature. Consideration must be given on how to handle unique issues related to testing in this world, and those unique issues would be things like informed consent when applicable, advice on counseling when applicable, and/or information on test use and selection.

Establishing links between analytical performance in a lab and clinical studies was an issue actually raised sort of at the tail end of the last SACGT meeting. I don't remember if it was raised in the formal discussion or the informal discussion, but it was raised at the last meeting of SACGT. It was an issue discussed, frankly, at the recent Pharmacogenomics Roundtable, and with or without regulatory considerations, whether we exist and are interested or not, it's a key scientific issue for labs to deal with.

Genetic testing in terms of both analytical and clinical behavior will be challenged by the interesting problem that you need to link the analytical and the clinical behavior between a particular test, and that's compounded in complexity by the fact that desired endpoints may be difficult to address because of rarity of conditions, because of the heterogeneity of conditions, and because of the unique interest in using genetic information to predict the likelihood of an event that might not occur for five or ten or twenty years. It would create a very interesting clinical trial and review challenge.

Again, without approaching these issues with maximum flexibility, the template could be viewed as an obstacle rather than as an opportunity for information and light-handed regulation.

The most interesting challenges with regard to use of the template

as a regulatory tool, and perhaps even for use as an information tool, occurs when you move to the edges of what FDA would consider its usual sphere of oversight. That's in the area of informed consent, of counseling, and of educating users in proper test selection and interpretation. That's not been a core mission for us. It may be at the edge, so it may require some very special consideration or attention to determine what our role might or might not be.

Our center has, interestingly enough, embarked on a strategic plan to broaden our approach to meeting our core public health mission, which isn't to review products but actually to protect public health, and we hope opportunities will occur in the context of this mission to allow expanded programming to help in these unusual dilemmas or areas presented by this template.

Currently at FDA there is legal discussion about how to proceed with an initiative for registration and listing, and there are draft concept papers and guidance in the process of being developed. Following advice from the Professional Roundtable, we're considering trying to use a unique approach to this process, if possible, which would be to have registration and listing that would be electronic rather than by paper, or at least it would offer an electronic option rather than by paper.

We're looking to report different information than has been traditionally asked for in registration and listing. In particular, we've been talking to the Professional Roundtable about asking for information on a couple of the key, up-front areas of the data template, as expressed perhaps in the first three or four boxes, because we think that might be a particularly relevant and important and appropriate data set to be put into a registration and listing program.

To us, the most important corollary to development of a registration program -- this is no secret, this was also discussed at the last SACGT -- is the need to insure that when device failures occur with significant negative consequences, laboratories, like any other manufacturers, would have the obligation to report the failure to FDA and to work with our agency to find appropriate public health remedies. There are a wide range of remedies, from fixing whatever is wrong with the test to recalling test results to sending out warning letters to producing education material. A wide variety of remedies are possible.

Classification is, as I suspect you may already be aware, but if not, I will remind you, is for FDA a well established and formal process, and it will require one or more panel meetings by our new genetics panel, chaired by Joann. She clearly has her work cut out for her. SACGT input into this process would, of course, be welcome.

Inherent in the current preliminary classification is the notion raised by SACGT at the last meeting that the template would inform decisions, and we're exploring opportunities to classify these tests most broadly as Class II products subject to special controls. We're actively exploring what kinds of special controls might be relevant. Special controls could be special labeling, they could be special data requirements, maybe parts of the data template. A special control could be either an existing or a modified CLIA requirement, or there are other forms of special controls, and we're looking at what special controls might make it feasible for us to, in a credible and legitimate manner, make these home-brew tests by and large Class II products.

We certainly intend the right to reserve the opportunity on an as-

needed basis to up-classify particular tests of concern and to treat tests that might be a particular worry, tests that have unusual issues with regard to safety and effectiveness or unusual public health impacts, treat those as Class III products. It's theoretically possible that there may be tests that are of significant enough interest that you might go in the other direction as well and down-classify.

Any program initiated would have a careful and probably long-term phase-in, as Dr. Feigal clearly signaled you at the last SACGT meeting. This doesn't come fast, this doesn't come easy, and that's because of the immense potential workload and our clear desire not to chill technology and not to disrupt the workplace.

At the last Professional Roundtable there was a lot of discussion about sharp edges floating around and any kind of regulatory foray into this area. It is unrealistic to expect routine laboratories to meet the good manufacturing practices or quality system regulations now in place for commercial manufacturers. The average laboratorian, and that includes me, actually doesn't really know and understand very much about design controls.

If FDA does focus on new tests, it will be challenging to decide operationally how to define new versus old. This could be done based on calendar date. It could be done based on test novelty. It could be done based on a formal classification. We can ask Joann and her crew to help. Or perhaps it can be done using new and different mechanisms. If anybody has any ideas, please don't be shy.

Defining the transition from research to clinical use has been a relatively easy but imperfect matter for commercial kits and systems and has been abetted by labeling caveats and marketing considerations. This transition may be

more challenging to operationally define and control for home-brew tests. Developing boundaries and balance for this program is likely to present interesting problems.

Finally, the science, as you all surely know, is challenging because of the explosion of information, the explosion of technologies, the broad nature of new applications, and the intense commercial and public interest in this area.

We are looking forward to an August meeting in which we hope to further vet the documents that appear in our briefing book. We hope to produce some kind of finalized drafts in the fall. If we plan to use these for FDA purposes, they would need to be submitted through a very formal good guidance practice in which we would actually publicly make them available, at the minimum seek public input, at the maximum again ask Joann to actually call on FDA to seek FDA-specific input. So we clearly, since that is an intense process, would like to start that sooner rather than later. It is in our best interest and I think in the best interest of everyone to maintain collaboration and to look for leveraging opportunities.

Again, there are a number of people in this room from outside groups who have been kind enough to come and talk to me about potential collaborative opportunities. I am quite upbeat that that will be possible.

The final disposition of this program is unclear. The full extent of both any voluntary or regulatory product are unclear. Certainly, FDA's involvement is likely to be phased in and potentially imperfect. Hopefully we will fix the imperfections.

We are looking for incremental improvement. We don't plan to solve all problems by the time SACGT meets in the fall. We believe that the

agency and division are up for the challenge because we do have a lot of people outside expressing interest and because, in the context of our strategic planning, we are clearly being asked to look out of the box, and there are clearly opportunities here for us to be at the edge or out of the box.

I don't know if I ran over or ran under, but I'm going to ask Natalie to come up and show you something that we never imagined when the SACGT first dreamed up its template.

DR. McCABE: Thank you, Steve.

Now let's turn to Dr. Solomon. Dr. Solomon is manager and principal scientist of new molecular markers at Abbott Laboratories in the diagnostics division. She's been with Abbott since 1989. Dr. Solomon received her Ph.D. in molecular biology from Northwestern University.

DR. SOLOMON: Thank you.

The first slide here is just an indication of the number of people that have worked on this particular template. I understand that in your booklets you've got several prepared by the FDA, and one that was worked on by this group of people prepared for PhRMA, and we presented that at a joint meeting with some of the members of the FDA a few weeks ago and have revised it. What I'm going to do this morning is to present just a few sections of that template that are relevant to pharmacogenetic testing, as opposed to some of the other templates that are present in your booklet.

I did want to mention, first of all, that this is a hypothetical assay that we created for this purpose, and I would also like to mention that you're going to have to follow along in the template because there are only a few of the sections that I'm giving you here.

DR. McCABE: Just to clarify for everyone, this is the hypothetical CYP2D6 template that's in the blue folder.

DR. SOLOMON: Correct.

The first section that I want to address is the intended use section. What we've stated in that section is that the CYP2D6 PM Assay is a pharmacogenetic assay used to detect cytochrome p450 2D6 alleles that will identify individuals who are poor metabolizers of drugs that are extensively metabolized by the CYP2D6 gene product debrisoquine hydroxylase, also known as cytochrome p450 2D6.

Now, the key things that I want to mention about this, once again, is that this is a hypothetical assay, and there are technical issues that are addressed in that template, some of which are kind of glossed over because of the hypothetical nature of this.

What it does here is identify common non-functional genes. So, as with many genetic assays, there are numerous genes, I think with CYP2D6 up to 53 genes that have been identified. But this particular assay only looks at five of those genes. Those are the most common. Each assay I think is going to have to make some compromise between what is feasible for a test and what includes everything that is known.

In addition, there's no positive identification of functional genes here. So this is a positive identification of the five mutations that are well known, and that is a limitation that I think you will find in many of the genetic assays, which is why I wanted to bring it up here.

The second key point with this template is in the indications for use, and specifically the purposes or uses of test section. What we say in here is

that routine clinical testing to predict the lack of efficacy or possibility of increased toxicity of drugs metabolized by debrisoquine hydroxylase. Drugs excessively metabolized by this route include Drug X, which would be a hypothetical drug, a prodrug created for this template; codeine, another prodrug; and then several other drugs are listed that have in their labeling an indication that they are metabolized by this pathway.

Some of the highlights for this section is that this is a predictive test for patients that currently do not have symptoms relevant to the particular variation being assayed. What that means is they would only show symptoms if given a drug that would not be metabolized. So that is another differentiation for many of the genetic tests that will be seen, where just having the genetic mutation itself would cause some symptoms in the patient. In this case, the particular genetic variation would not be manifest until a drug would be administered that is metabolized.

Now, the results of this test would indicate to the physician that certain drugs, prodrugs, would not be converted to an active form, and in that case the patient would not presumably get any benefit from the drug because they could not convert it. Or the drug could accumulate to potentially toxic levels because they could not metabolize it and clear it from their system. So those are really the two issues that this particular enzyme deficiency would cause.

The clinical validity section is quite long, so I didn't project it here. But the unique thing about this section is that the results are taken from the literature. So here several papers were cited and briefly discussed, and at the end there is the full reference for each of the papers. The feeling here is that the existence of published data on clinical utility should help obviate the need for

additional clinical trials when a test like this would be presented, since there's already clear information in the literature that the particular mutation is causing a problem in metabolism. So that's one thing that you should be aware of.

What is expected to be presented when a literature summary is completed are the allele frequencies in the poor metabolizer group in this case, or the affected group in any case, and concordance between genotype and phenotype, which are certainly some of the things that you would expect. And, as was mentioned earlier, there may need to be some bridging strategy to make sure that we can do a fair comparison between these.

Finally, the last section I want to discuss is that this test is used to determine if the patient is a poor metabolizer of drugs that are extensively metabolized by the CYP2D6 gene product, debrisoquine hydroxylase. This is essentially a restatement, but once again hammering home the fact that the patient is not suffering from a disease, per se, but that this mutation, this variation is only manifested once a particular drug is administered.

That's all my comments for this morning.

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

We appreciate the cooperative spirit that you, Dr. Brian Spear, director of pharmacogenetics at Abbott, and your colleagues at Glaxo have shown in working with FDA in the development of the template. It's been one of the principles that we have discussed at SACGT, that there should be these private-public partnerships, and we're very pleased to see this occurring.

We'll now go back to Dr. Gutman for a presentation on FDA's label authorities and the extent to which the FDA can require labels to contain warnings about unapproved uses of tests, and I'd ask you, Steve, to try to move

through this relatively quickly so that we have some time for discussion at the end.

DR. GUTMAN: Okay. I'll truncate it.

As I've said before, there are a variety of kinds of FDA submissions. There's Class III, there's Class II, there's Class I reserved and there's Class I exempt, a light motif. All submissions are subject to, actually, formally defined regulations in 809.10, which have also been included in your briefing book and that explicitly define the obligation manufacturers have to label their products in a particular way.

There are 15 components. These labeling regs actually preceded the '76 law. They were actually cooked up by folks in drugs who were grappling to try and have better labels. I had nothing to do with them, but as a biased clinical pathologist, I think they're pretty good, even after 20 years.

They are, in a nutshell, the requirement that there be a proprietary and established name, that there be intended uses, that there be a summary and explanation of tests, and that there be principles and procedures; that, when appropriate, there would be information on reagents, information on instruments, and information on specimen collection, preparation, handling and storage; that there be information on the actual procedure to be performed, that there be information on how results are generated at the end of the procedure, and that there be a discussion of the relevant limitations, limitations being either analytical or biological limitations.

Last, but certainly not least, that there be information on expected values -- that's the term they actually use for reference ranges in health and disease; that there be information on the heart and soul of the test itself -- that is, the analytical and, when appropriate, the clinical performance characteristics;

that there be a bibliography, a place to locate the business, and a date so you know whether this is current or old labeling.

I won't actually go beyond this. I will point out that these are mandatory. It doesn't matter what product you make, and it doesn't matter whether FDA sees or doesn't see them. These are required for products that are being marketed in the in-vitro diagnostic device. What you folks are probably particularly interested in -- I'll pick up from Dr. McCabe, and I will show one more slide -- the critical feature for us is the intended use. That drives everything.

The data requirement, the type of submission, and the thresholds of data are all based on the claim, and what is very important to us with a claim is that while we can certainly have a very keen perception of not crossing over into the actual practice of medicine, if a test requires confirmatory testing, if it requires testing in a narrow population -- children but not adults, adults but not children, pregnant women, and PSA should probably be ordered in men but not pregnant women -- we do try to provide information in the package insert that draws attention to the focus of the use. Some people would suggest we're obsessive about it. In some instances, we will actually try to link that focus through the intended use itself, or we'll try to black-box or bold-letter intended uses.

But I have to tell you that even as I assure you that we do everything possible to maintain consistency in labeling and truth in labeling, it is a very colorful medical marketplace. There is a wide and diverse and colorful literature on which to base use of test, and there are many iconoclastic physicians. The deal here is that the FDA does not practice medicine. If somebody wants to use BRCA1 to diagnose Alzheimer's disease, that may be a big problem from their state's point of view, it might be a problem from SACGT's point of view, but it is

of no interest to FDA at all.

DR. McCABE: Thank you very much.

Before we go on to the discussion, are there questions from the members around the table of any clarification for Dr. Gutman or Dr. Solomon?

Dr. Solomon, why don't you join us at the table here for the discussion, if you would, next to Dr. Lewis. Brian, too, why don't you, since you were very involved in this, if you could join us.

Yes, Wylie?

DR. BURKE: I have a question for Dr. Solomon. Before I ask my question, I just want to comment along with Dr. McCabe, express my appreciation for the work that went into producing the template, which I think is extremely helpful for us.

One of the issues that comes up with pharmacogenetic tests is the possibility that some of them will provide extraneous information; that is, information about risks or clinical issues beyond the actual metabolism function that the test is designed to assess. I'm going to ask a specific question about that and then follow it with a more general question.

The specific question is do you think it would be appropriate to expect in a pharmacogenetic test a box or part of the clinical validity statement being "this test does or does not provide additional clinical information"? Let me just add my general question and let you answer both at the same time. My more general question is did you find in developing the template that there was any information about the test that you felt you would not need to know in any case? That is, did the template ask you any information additional to what you would normally feel you needed to know in order to responsibly provide the test?

DR. SOLOMON: I think that as far as saying whether or not the test detects other applications, it's first of all going to depend on the particular marker that you're looking at. Some of those might be obvious. In the case where I think there's obvious literature around a subject, it probably would be beneficial to mention it one way or the other. But I think if you're talking about the potential for some future indication that hasn't been discovered yet, I would say that no mention of that would be required. So I think it would really be very dependent on that.

I think as far as filling in the template and finding that there was extraneous information, we had a very good discussion a few weeks ago with the FDA at the meeting that we had, and I think that a lot of the issues that had come up during trying to fill this out were clarified in that situation, and I think that the modification that you see in your packet today has been modified based on those discussions. I think it was much easier to fill it out at that point and address the issues that were there. So I think that the document giving indications on how to fill that out, and plus seeing how for different assays it already has been filled out, is very instructive as far as that goes.

So we took some judgment at some points and said what really would be appropriate for this test that, of course, we were making up, but trying to fit ourselves in the mindset of what really we would be trying to submit in an instance like that, and I think we were able to come up with something for most of the boxes. Where we had trouble, I think there was mutual discussion and I think things are changing to make it more obvious and more straightforward for what each section would have.

DR. McCABE: Elliott, is this a point of clarification?

MR. HILLBACK: Yes. I just wanted to follow up to Wylie. Were you getting at asking the developer of the test to think about what else could be done with it? Because that seems like an open-ended question which I'm not sure how you satisfy totally. You can satisfy it to some degree, saying, well, based on what we know, this is what it could be. But it's sort of a Pandora's box.

DR. BURKE: I'm actually very satisfied. I think the issue that I was raising was addressed fully by Dr. Solomon's reply. That is, if there is a robust literature about something else, it should be at least acknowledged.

But the second point, if I could just follow up a little more on it, I'm really interested in the burden involved in filling out this template. So the question, if I could rephrase it a slightly different way, I understand filling out a new form is always a burden. I'm not going to minimize that. But the question I'm really interested in, does the form in its version that we're now working on represent information that one ought to know anyway in offering a test, or is this template asking manufacturers to do things above and beyond what they would need to do responsibly to prepare for the offering of a test?

DR. McCABE: Dr. Spear?

DR. SPEAR: In preparing our template, it seemed that the information that was requested was appropriate to a test of this sort, and there was very little that sent us off searching or, in this case, hypothesizing information that we would not have had available anywhere.

To address the question on ancillary or collateral information, I think on a test of this sort, where you're looking at metabolism of a group of drugs where the test is primarily of a pharmacokinetic nature, there is going to be information derived from that that might be applicable to other drugs. So in this

case, we listed a representative sample of drugs that might be metabolized. The sort of collateral information that we would be concerned about is if we were expected to have an exhaustive list of all drugs that would be metabolized, especially as new drugs are introduced from time to time that may also be metabolized by the same pathway, then we wouldn't want to be responsible for keeping that list updated.

Alternatively, when there are genetic responses which are specific to a drug rather than to a metabolic pathway, the information that would have been developed for the test would have been through clinical trials for that drug, and to expect the manufacturer, then, to develop information on a wide variety of other drugs outside our clinical experience I think also would be a burden that we could not carry.

DR. McCABE: Joann?

DR. BOUGHMAN: Speaking to the other side of the equation, if you will, I wonder if Dr. Gutman could comment on the burden related to this vis-a-vis the FDA as examples might come forward and the ability to answer questions and give guidance early in the process. Dr. Solomon, having said that sitting at the table and actually having an interaction at that time was very helpful, have you thought about the ways in which this might be facilitated? Because this committee might wish to make some clear comments about that.

DR. GUTMAN: Sure. There is certainly a notion that it will be helpful to have a central way of presenting information and to have instructions about how to clarify that information. There are, of course, you have to recognize, immense nuances in the different products. You can only go so far in general guidance, and then when the rubber hits the road is when some creative person

comes up with something you didn't anticipate. The agency has a real commitment -- and, actually, Joe Hackett, who is in the room, has actually created an environment where we're bringing in lots and lots of people with lots and lots of ideas very early and trying to be very visible in terms of companies that are interested in diagnostics and companies that forgot that they need a diagnostic to use their drug or therapeutic, trying to remind them when they visit drugs or biologics that maybe they want to visit us as well.

I have to be honest with you. I was actually just at a workshop in Orlando the last two days by the Infectious Disease Society of America that was talking about something that maybe you all know and love, but it's the use of both genomics and proteinomics to diagnose either infectious disease and/or host resistance, and it is a daunting, frightening area. When we talk about job security, the greatest thing for public health and the worst thing for my division would be if all of these people with all of these ideas all arrived next Saturday.

DR. McCABE: Muin, and then we're going to open up the discussion to more general issues and not just clarification.

DR. KHOURY: My question is relevant to the pharmacogenomics example. It's really very nicely done, and it elicited two reactions in my mind. This is a point of clarification, and this is Barbara's question. Are all these data fabricated? This is all hypothetical, with all the references? Am I misunderstanding?

DR. SOLOMON: The references are not fabricated. Those are bona fide references in the literature.

DR. KHOURY: Okay. So these are real references, but the claims of clinical validity and utility are fabricated.

DR. SOLOMON: Correct. We took what we knew from the literature and made guesses at what the actual data would come out to look like.

DR. KHOURY: Because I was reading it -- I mean, I didn't have it beforehand, and I'm still left unclear, even after reading the numbers. Maybe I need to read again what the clinical validity and utility of this is. If you look at the clinical utility box, the question is specifically what happens if you don't test, if you don't use that test before you give the drugs? I didn't see any data on whether people get sick, how many get side effects. There's just genotype-phenotype correlation with respect to levels of the drugs. So what's the value added of the test? If you don't use it, what will happen? That, to me, is the ultimate clinical utility question, and I didn't see it represented in the box.

The second question, which is sort of a more generic question that applies to everything else, is as more data keeps coming in, it looks like this is a sort of summary form, but the actual elaboration of the literature -- and this could be exploded into pages and pages of descriptive stuff. So this is a more general issue that I have, that perhaps what goes into the ultimate summary of the template could be a little bit more condensed, versus a bigger version of the actual data and a description of the patient population, et cetera, et cetera. But that's a more general discussion.

Would you like to respond to that, the claims for clinical utility of this test?

DR. SOLOMON: What we did with the claims for clinical utility is rely on the literature. There is literature that's partly cited, and certainly, as you mention, the large body of literature that was not cited in this instance, where trials have been performed and some small percentage, some percentage of the

patients have indicated toxic side effects, sometimes those are done where they can actually monitor levels in the blood to see if the toxicity increases or can monitor and see whether prodrugs have been converted or not.

Part of the thinking here is that since the literature is so extensive in this area, you would not really want to do a trial where you could knowingly subject a patient to high toxic levels of compounds that you knew beforehand they could not metabolize. So that's one of the key things here with being able to use literature and having an appropriate bridge between the data in the literature of what has happened when drugs have been administered without knowing the patient's genetic background versus now that the genetic background is known, you really are going to be hard pressed to be able to give a patient a drug that you know is going to affect them adversely. Is that addressing your issue?

DR. KHOURY: I guess I was looking for that data that you just now said. Maybe I don't see it. Maybe if you can point it to me, that actual summary of what you just said about toxic effects. I mean, I'm not looking for a controlled clinical trial.

DR. LLOYD-PURYEAR: It's on page 1 under "Target Population."

DR. KHOURY: Yes, but I was looking at it under "Clinical Validity and Utility." Maybe it belongs there.

DR. LLOYD-PURYEAR: That's what I'm reading, what you're talking about.

DR. GUTMAN: I actually think that's a really good point. If Muin can't find the basic message in the clinical validity, then we need to modify it, because he shouldn't have to hunt. So we have to figure out a user-friendly way to

convert clinical validity into a signal that Muin looks at and five seconds later he's got it right. So that needs to be fixed.

DR. KHOURY: Maybe I'm dense this morning.

DR. SPEAR: If I could comment, though, at the same time, I think our expectations should not be that we can show clear statistical evidence for specific adverse events due to intoxication as a result of poor metabolism of a drug. So in trying to reach an appropriate clinical utility here, the determination we came to is we're trying to determine those people for whom drug levels will be higher than is expected and may be at risk for intoxication, rather than stating what the effect of intoxication will be.

DR. GUTMAN: And the notion here is that it's an appropriate claim, but Muin shouldn't have to hunt to figure that out.

DR. SPEAR: And that's exactly right.

DR. McCABE: Wylie, follow up?

DR. BURKE: It seems to me this discussion points to the fact that there is clinical utility information in this template but in the target population, and it could be either taken out or repeated in clinical utility. But I think another implication of this discussion that is worth our thinking about is that it seems from this example that it's going to be very reasonable to expect test offerers to tell us what they know about the test, and it may not be a reasonable expectation for us to have them tell us what we don't know. What we need to do is say what we know and what we don't know.

What might be reasonable, though, is for us to clarify that if it's not here, we don't know it. In other words, that the person who is suggesting the test will tell us what they know about the test, and if they haven't put the

information in the template, then we don't know it. So in terms of Muin's comment, we don't know outcomes. We have hypotheses about what the use of this test might do in terms of predicting drug toxicity, but we don't have outcome studies.

DR. McCABE: Elliott?

MR. HILLBACK: I agree, except I don't think we want to totally let us off the hook in terms of saying what we don't know. I think we may want to say we ought to tell everyone what we know, and what we know we don't know, but there are things we don't know we don't know.

(Laughter.)

MR. HILLBACK: I think I got that right.

So I don't want to take us off the hook on what we don't know, because I think there are a lot of things we don't know on a lot of these tests, and we can say that clearly, and then a caveat that says there may be lots of other elements, but we haven't heard about them up at Harvard yet.

(Laughter.)

DR. McCABE: The only thing I didn't hear you say, Elliott, is it would be an iterative process, learning what we knew we didn't know.

(Laughter.)

MR. HILLBACK: Well, that's in the record for this meeting, then.

(Laughter.)

DR. McCABE: Yes, Pat? And then Ann.

DR. CHARACHE: One other thing on the clarification issues. I think under the "Quality Assurance, Quality Control" section, essentially

everything there is quality control, and I think there should be a little amplification of the quality assurance as per the glossary, and I will make some suggestions separately.

MS. BOLDT: Just really a question in terms of the review templates. There was a lot of references to registered geneticists, so I'm just curious what that means. Do you mean certified?

DR. GUTMAN: I haven't got a clue. Please give us some suggestion what the language should be. I have enough trouble with pathologists.

DR. McCABE: Sorry. We were just notified that there's going to be a fire drill at 10:30 that will last about five minutes. So I've made an executive decision that we're going to take a break at 10:25 and people can go down and get some coffee and take it outside or whatever during the fire drill. So we will be breaking at 10:25 to give us ample opportunity to prepare for the fire drill. I'm sorry, but we are all required to exit here, so I apologize to our guests.

DR. CHARACHE: Do we have to use the stairwell?

DR. McCABE: Well, if we leave before it starts, then we can get down to the first floor using the elevator. So that's part of the goal here. I apologize for breaking into the discussion, but I think it's probably best that we do it that way.

Ann, did you have a comment?

MS. BOLDT: He said he doesn't know.

DR. McCABE: Okay.

DR. GUTMAN: No, no. You misunderstood. I said fix it.

PARTICIPANT: He wants you to give him the language.

DR. CHARACHE: I just wanted to, again, compliment the FDA

and their various groups on this. I found it extremely helpful, and I actually tried to see what would happen if it were applied to a different discipline and framed up what would happen if we used that template for detecting herpes simplex virus and encephalitis, and it works very well.

DR. McCABE: Okay, we're going to move into the general discussion. Just before we do that, I'd like to make a comment, and that is that in the "points to consider" document, it appears that there was an emphasis on DNA testing, and certainly that is a lot of what we're considering, but there are other genetic tests beyond DNA testing. So I'd just like to make that comment as you move forward with this.

Francis?

DR. COLLINS: I, too, would like to compliment the FDA on a very transparent process that you're proceeding with here to keep us informed about your thoughts, and I think the availability of the specific examples is very helpful in getting a real sense of what this would look like.

My question relates to, when you're preparing these templates, how many different indications do you try to cobble together in the same one? Because when you look at the examples provided, say, for Canavan or Tay-Sachs, it seems to include both testing to confirm a diagnosis or prenatal testing, where you're looking for a homozygote, but it also mentions carrier testing in both of those instances. Interestingly, it mentions carrier testing in the context of a positive family history. It doesn't seem to include carrier testing for Canavan or Tay-Sachs in a broader population sense, even though that is now being carried out in some Ashkenazi communities.

When you look, then, at the evidence for analytical and clinical

validity, it seems to be solely focused on testing where you expect to find an affected individual, and obviously the positive predictive value is going to change a bit if you apply that in a different population. Particularly, if you're trying to tell the difference between a homozygous individual and a heterozygote, the analytical characteristics could be quite different, notably would be quite different, certainly if you're using an enzymatic test, for instance.

So how do you envision this actually playing out? In reality, would you have to have a separate template for each and every indication and you've sort of cobbled them together here?

DR. GUTMAN: I inadvertently deleted a slide that actually addressed the fact that the templates are telescoped in terms of intended use. They're bundled with multiple intended uses, because we would consider from a regulatory standpoint each of those a different intended use, and they're actually also telescoped in terms of technology. If you noticed, several of them will have more than one analytical technology.

The balance is between simplicity and completeness, and probably the more historical trend for FDA would be to generate a separate template for each intended use, every intended use, with the expectation that as you move further and further away, it's probably easier to establish a relationship between diseased patients and the gene when you do the study in prenatal diagnosis. Even the Fragile X example that we first introduced last time, how in the world do you figure out what's actually going on with relationship to the prenatal testing and the clinical outcome? I mean, there may be some literature, but at some point it reminds me of CKMB, which never was studied adequately in terms of its relationship with heart attacks, but, in fact, became so associated with

heart attacks that you defined MIs through CKMB.

But any thoughts on that would be welcome. We telescoped them, frankly, because we did this quickly in preparation for this meeting. A more conventional thing for us to do would be to create a maze, which would be to break them out into four or five intended uses, and each intended use could theoretically have a template with each analytical technology. So we can make this as complicated or as easy as you want.

DR. COLLINS: I guess my point would just be that if you are going to try to telescope them together for simplicity, then you have to be sure that the data that's being offered as far as performance of the test is relevant to that intended use. One set of data may not necessarily extrapolate to the other intended uses.

DR. GUTMAN: The point is well taken. But before we worry about that issue, I guess it would be interesting to get feedback, either from this group or from Wylie's group, from the standpoint of just public information. Let's say we never regulate it but we talk to Bonnie Pagan and she says, great, we're putting it on our Web. How would you like it?

DR. McCABE: We have three comments, and then I'm going to break it off. I may break it off even before we're done, though, so that people can exit conveniently. So please try to keep the questions and the responses brief.

Jeff, Michele, and Elliott.

DR. KANG: This is more of an observation, and I just feel like I need to get this on the table. I'll try to keep it quick.

It's interesting that when Steve presented his overview of the FDA regulatory activity, the 8th slide on the template for multi-audience appeal, you

had laboratory users, health care providers, consumers, patients, regulators. Notably, what's missing is the health care insurer or the payer or the purchaser, and this is an issue that the access committee, quite frankly, has to wrestle with. I actually think this recent discussion that we had on the pharmacogenetic test and the clinical utility issue is kind of emblematic of some of the problems here. By not having health outcomes as more of a biologic outcome, that raises a question whether an insurer will cover it.

There is an argument here, and I see a lot of nods here, that one of the treatments -- in using these drugs, usually the standard of practice is to start low and go slow. So you start at a very low dose and titrate up. You hit a toxicity point and then back off. The question really would be about the actual treatment. Would the knowledge of this test make any difference in terms of how you managed a patient? So I'll just put that on the table. I think the access committee has been in the throes of wrestling with this very issue, and I just wanted to notify the committee.

DR. GUTMAN: That was certainly not deliberate, but you have to recognize that in our thinking, you're talking about a very parochial and narrow-minded -- well, not narrow-minded hopefully, but a focused person, and the outcome piece was clearly something we had relegated to CDC. It was our notion that as they collect large-scale data over time with public health epidemiologic surveillance, that they were going to determine the outcomes. We couldn't possibly do that in premarket review.

DR. McCABE: Michele. Briefly, please.

DR. LLOYD-PURYEAR: Just a comment and a question. The comment is about focusing on just DNA-based testing. Just for your information,

we have funded -- although I can't say what -- two large, multi-state projects around newborn screening, and specifically tandem mass spectrometry, and we are using the FDA template at our first meeting. I will ask FDA, actually, to come and present this template. So we'll see how well it works with that technology.

But secondly, I have a question about your regulatory authority for looking at or enforcing informed consent counseling and education. I know you said it's in your public health mission, but do you --

DR. GUTMAN: Well, no, no, no. I didn't say that. I said that our public health mission is to promote -- our core mission is to promote public health. Informed consent for a non-investigational test is a place we've never been. I'm not suggesting that's good or bad, but it's different.

On counseling, the most we might have is some effete labeling that suggests it might be a good idea. Again, it's not very directive. We really are focused on the issue of performance characteristics and carrying us over thresholds for substantial equivalence or safety and effectiveness. I guess in a very Catholic, broad view you could say, gee, counseling is a safety and effectiveness issue, but you're really pushing our model hard in a place it has not historically been.

DR. McCABE: Okay. With that, I'm sorry, Elliott, we aren't going to get to your question.

Please take your purses, any valuables. The fastest way out is the elevators down to the B3 level. That does not get you coffee, however. That is on Level 1 in the cafeteria if you wish to go that route, and then you can exit through the front door onto the dropoff circle, the A Level.

Thank you, and we'll resume as soon as we're allowed back in the

building.

(Recess.)

DR. McCABE: Let me tell you what our program is. We've cut into the time for public comments. I apologize to the public who were scheduled to comment. I'm going to ask, however, that you really try to keep these as brief as possible. If we had time at the end of the public comment, we would reconvene the group that was discussing before we were interrupted by the fire drill and try to continue that discussion.

I want to really thank Dr. Solomon and Dr. Spear for the effort that you've put into this, and to FDA for working together with industry. I think this is a very important model as we move forward.

But I do want to now move to the public comments because individuals may have other time constraints on them. But if we can get back to this discussion that we were having with FDA and pharmacogenetics, we certainly will.

So the first individual that I have -- and if people are not here, we'll just take them out of order if they're still waiting for elevators -- is Dr. Debra G.B. Leonard, who is director of the molecular pathology laboratory at the molecular diagnosis core facility in the Department of Pathology and Lab Medicine at the University of Pennsylvania Health System, and is past president of the Association for Molecular Pathology, and Dr. Leonard is representing the Association for Molecular Pathology.

Dr. Leonard.

DR. LEONARD: Dr. McCabe and members of the committee, thank you for the opportunity to provide comments on the genetic test review

template and review process. My name is Debra Leonard. I am an associate professor of pathology and laboratory medicine, and director of the Molecular Pathology Laboratory at the University of Pennsylvania. I have medical training and am board certified in pathology, and have doctoral and postdoctoral training in molecular biology.

I am here today, as Dr. McCabe said, as the past president of the Association for Molecular Pathology. AMP is a society of more than 600 medical professionals engaged in the practice of laboratory testing for human molecular diagnostics, as well as translational research in molecular pathology, molecular medicine, and molecular genetics. Many of our members are physicians or doctoral scientists who direct clinical diagnostic laboratories that perform molecular genetic testing. Therefore, the changes this committee is recommending for oversight of genetic testing are of great interest and concern to the members of AMP and to me.

I asked to speak to you today because I have taken an active role in meetings between the FDA and professional organizations which resulted in the development of the genetic test review template that Dr. Gutman presented earlier. I would like to emphasize that AMP chose to work closely with the FDA not because we are in agreement with the proposed FDA oversight of genetic tests, but because we want to have input into changes that will greatly affect our membership if they are implemented.

The review template is an outline of information needed to assess the analytical characteristics, test reports, quality assurance programs, and clinical validity and interpretation for genetic tests. This review template is thorough and represents an excellent guideline for laboratories developing, validating, and

performing any type of clinical test, not just genetic tests.

During the meetings between the FDA and professional organizations, this review template was actually developed with the intent of augmenting the existing clinical laboratory inspection process administered by HCFA under the authority of CLIA '88 since time for review of test development and validation is limited during these inspections. However, the mandatory requirement to submit this information for all in-house developed tests by all clinical laboratories in the U.S. will be an administrative nightmare for both the laboratory and the reviewing agency.

The proposed FDA oversight of genetic testing is redundant with existing regulations that already provide sufficient oversight of clinical laboratory testing through HCFA and professional organizations like the College of American Pathologists and the American College of Medical Genetics.

AMP is concerned that the proposed additional oversight by the FDA will greatly increase the administrative burden for laboratories, delay implementation of new tests due to review delays, limit patient access to genetic tests, and increase testing costs without improving the quality of genetic testing services. If this committee does move forward with the implementation of genetic test review using this template, AMP strongly suggests incorporation of the template into the existing clinical laboratory inspection process administered by HCFA under the authority of CLIA '88 rather than creating a new regulatory process.

As with all clinical laboratory tests, AMP believes that guidelines for the performance, interpretation, and clinical use of genetic tests are best established with primary input from medical and laboratory professionals who

have the required expertise to judge the accuracy and validity of each test. AMP welcomes the support and facilitation by government agencies of professional efforts to establish genetic testing guidelines and standards through the establishment of a genetic testing consortium. AMP is eager to work with other professional organizations and government agencies to formulate professional standards for genetic testing.

I would like to address one additional point. AMP remains very concerned with the broad definition of genetic tests being used by this committee, which includes testing for both inherited and acquired disorders. Acquired changes in the DNA of non-germ-line cells, such as occurs in cancer cells, are not inheritable. Most of the issues raised by genetic testing focus on the ethical and social concerns surrounding genetic tests, such as informed consent, genetic counseling, and implications of test results for other family members. Tests for acquired mutations, although potentially complex in performance and interpretation, raise no more concern than other diagnostic laboratory tests. Appropriate regulations for acquired disease testing already exist in the CLIA regulations.

If this committee's concern is the fact that both types of tests are developed by laboratories without the use of commercially produced and FDA-reviewed test kits, then this issue should be addressed separately from genetic testing issues. Applying genetic testing requirements to acquired disease testing is not only unreasonable but will create problems for laboratory implementation. The bottom line is that a genetic test has to be defined based on inheritance, not on the fact that nucleic acids are being used as the testing material. We urge you to narrow the definition to include only testing for germ-line inheritable genetic

disorders.

In summary, AMP asks this committee to work through the existing regulatory agencies and mechanisms for inspection and licensing of clinical laboratories to achieve any additional oversight specific to genetic testing that it deems necessary. The addition of another regulatory agency for genetic testing oversight is unnecessary since existing regulatory mechanisms for clinical laboratories already assure the high quality of laboratory testing we have today.

Thank you again for this opportunity and for your attention.

DR. McCABE: Thank you.

Are there any brief questions for Dr. Leonard?

Yes, Dr. Puryear?

DR. LLOYD-PURYEAR: Are your concerns the FDA working draft that's in the template? Specifically, if the template focused on numbers 1 through 3, you don't have any problem, do you?

DR. LEONARD: I know it intimately because I was involved in the development of it.

DR. LLOYD-PURYEAR: If the template focused on 1 through 3 and 9 through 12, would that alleviate your concerns?

DR. LEONARD: I'm looking at the number of tests I have in my laboratory, and many of the things that are required in this template are already in my procedure manuals in how my laboratory operates. But just administratively putting this together for 30 to 50 tests for one laboratory, and then having multiple laboratories submitting this to a reviewing agency, I don't see how this workload is going to be handled either by individual laboratories administratively, for which we will not be reimbursed for any of this work, or by

the reviewing agency receiving this information from hundreds of laboratories for tens of thousands of tests, if you count each test in a laboratory as an individual test.

DR. LLOYD-PURYEAR: Because it seems to me that the delineation here that I think you're trying to make is between analytical validity and clinical validity and utility. No other regulatory agency is looking at the clinical validity and utility. That's not part of what is currently going on. They are focused on the analytical validity. That is under CLIA.

DR. LEONARD: However, CLIA regulations are being revised, and much of what we do as laboratory directors is in the pre- and post-analytical interpretation of test results and use, and that's a lot of what we do in the clinical laboratory. The analytical parts are pretty much set when the tests are developed, and our ongoing practice as physicians and laboratory directors is just in that, clinical validity and utility.

DR. McCABE: Pat, and then Elliott very briefly, because we need to move on.

DR. CHARACHE: I think Debra is pointing out the reason that I've been concerned over time at trying to address an oversight of all genetic tests. It will be tens of thousands of tests, but that I think is the strength of the current approach in which people will know and should know through their IRBs ahead of time what information needs to be collected in order to have a valid test. As Debra Leonard has pointed out, she has this data because she establishes good tests.

Now, I think there is a challenge, because not every laboratory offering these tests has gotten the level of information which permits them to interpret the results.

In terms of the oversight function, you are correct that HCFA in their reviews, and CDC in their definitions, have not emphasized the pre- and post-analytical phase of testing, which has to do with clinical validity, and that is now changed as a result of the Notice of Intent in terms of the regulations now being written, and I'll comment on this more tomorrow. But I would not assume that these will not be addressed in future regs.

DR. McCABE: Elliott?

MR. HILLBACK: Dr. Leonard, I enjoyed your comments. It sounds very familiar to me. I wanted to ask, though, you talk about really two issues with the templates. One is filling them out. I understand that, certainly at the start of any process like this, there's the backlog of everything that already exists. So I'm curious, is it really the filling out of the template, since, as you said, most of the data you have to have already to do the test, or is it what FDA will do or try to do with all this data and the depth of review that leads to your concerns about cost and delays and tests not being available? Is it the preparation or the use of it?

DR. LEONARD: The preparation is daunting, but doable. My concern is, having looked at New York State molecular diagnostic colleagues who have to submit information to New York State for review before actually starting tests, they never get answers back. They can never start their tests unless they start them without the approval. So my concern is also in the delays with the review process and how this will be done.

DR. McCABE: Thank you. I would encourage you to continue to be involved, both individually and with the Association for Molecular Pathology, because I think we need to address these issues in an ongoing fashion.

Did you have some comment?

DR. GUTMAN: Well, yes. I just wanted to make a comment that Dr. Leonard has been a real star in at least FDA expansion of this template, and I want to publicly and personally thank her for her involvement. If anybody is ever looking for a chair of a committee, nobody can navigate rough waters better than she can.

DR. McCABE: Thank you.

Our next speaker is Dr. Walter Noll, who is from the Department of Pathology, Dartmouth Hitchcock Medical Center, and is here today representing the College of American Pathologists.

Dr. Noll.

DR. NOLL: Dr. McCabe, members of the committee, good morning. My name is Walter Noll. I am Professor of Pathology at Dartmouth Medical School, and I'm a board certified pathologist and a board certified molecular geneticist. I've had nearly three decades experience in the laboratory, in laboratory medicine, including more than 15 years experience as the founder and director of a molecular genetics diagnostic laboratory. My special interest has been multiple endocrine neoplasia type 2, a heritable cancer syndrome, and I have tested and personally counseled hundreds of adults and children with this disorder, both prior to and after the availability of accurate genetic testing.

I am very familiar with issues of genetic test sensitivity and specificity, the need for counseling and education for individuals at genetic risk, and the possibility of health insurance and employment discrimination that affected persons may face. Over the past 10 years or more I have been active in several professional societies, public organizations and government advisory

committees in matters relating to genetic testing, particularly quality assurance. Today I am here as a representative of the College of American Pathologists.

As you know, the CAP is a national medical specialty society representing over 16,000 pathologists who practice anatomic pathology and laboratory medicine in laboratories across our country and in Canada. Genetic testing is a growing part of the testing services we provide, and the College is committed to working with SACGT as it continues to explore genetic testing issues.

The CAP has provided comments on previous activities of the committee. My statement today comes in response to the committee's request for public comment focusing on the need for regulatory oversight of genetic tests.

First I would like to take this opportunity to reiterate the CAP's recommendation that SACGT narrow its definition of genetic tests to include only those tests which deal with heritable disorders or predispositions and which generate information that warrants genetic counseling. We all understand that testing for acquired genetic disorders, such as cancers, is technically similar to testing for inherited conditions.

However, this latter category of tests does not generate information that has any relevance to concerns of genetic discrimination or privacy; that is, long-range predictive value or information about the genetic constitution of other individuals in the patient's family. By including acquired and heritable disorders in the same category, the committee has unnecessarily increased the complexity of the discussion.

Second, CAP does not agree that there is a need for additional government regulation in this area, such as FDA oversight of in-house developed laboratory tests. These proposed regulations risk costly administrative burdens,

stifling of test improvement or new test development, and restriction of patient access to care. Current federal regulations administered by the Health Care Financing Administration under the authority of the Clinical Laboratory Improvement Amendments of 1988 already regulate all laboratories which perform genetic testing for diagnostic or other patient care purposes. These laboratories are registered, pay fees, are required to maintain personnel and quality assurance standards, participate in proficiency testing, undergo on-site inspections, and are accredited by HCFA or other organizations who have been granted accreditation authority by HCFA.

The CAP is one of the organizations that has been granted accreditation authority by HCFA. For decades, the College has been the premier laboratory accrediting organization in the country, operating a program of on-site inspection and proficiency testing founded upon compliance with established performance standards, professional peer review, and education. In the early 1990s, CAP joined with the American Society of Human Genetics and later with the American College of Medical Genetics specifically to develop performance standards, on-site inspection tools, and proficiency testing programs to meet anticipated needs in genetic testing, including standards for the validation of in-house developed tests.

This quality assurance and accreditation program is robust and rapidly growing and has strong support in the laboratory testing community. During the coming months, CAP is committed to a full-scale review of its genetics program and the current CLIA/HCFA regulatory model, with the intent to develop a comprehensive description of the genetics program in its entirety and to identify areas for improvement.

CAP understands the challenges that we face to assure high quality genetic testing, and it is absolutely committed to that end. We look forward to working with the committee and regulatory agencies in this matter, and in particular we would welcome the opportunity to present our approach more comprehensively at a future committee meeting.

DR. McCABE: Thank you, Dr. Noll.

Questions for Dr. Noll?

(No response.)

DR. NOLL: May I make just one more comment?

DR. McCABE: Sure.

DR. NOLL: You asked Dr. Leonard about her concern about whether the registration was a burden or was the laboratory community concerned about what the FDA might then do with the information. I think my personal concern would be more with how the information is used, what will happen as a consequence. The way I see it is that the FDA is proposing to use standards which are currently applied to test kit manufacturers and extend them to the laboratory testing community for their in-house developed tests.

I'm wondering why that is a valuable thing to do, and just follow me for a minute here. I'm a clinical chemist. That's what I've done for almost 30 years. When I started clinical chemistry, we had lots of home-brew tests. All of us did them. They were not regulated. They were not standardized. What one lab did was not often what another laboratory did.

Clinical chemistry right now is almost all standardized, with FDA-approved kits, FDA-approved instruments, and integrated systems which do the testing. That has led to a great increase in precision of testing, accuracy of

testing, and the result that I get in my lab is pretty much the same as anyone else is going to get in their laboratory.

Now, I think people anticipate that this might happen with genetic testing, but it's not happening right now. If we had test kits, uniform reagents in genetic testing, a lot of the issues that we're talking about today and that the laboratory fusses about would be made a lot easier to deal with, or might even go away. But I know for a fact that there isn't a single test kit manufacturer in the queue at FDA to have any kind of a kit that deals with genetic testing, heritable disease testing, for approval.

So I wonder if you might not ask questions of Dr. Gutman and other folks at the FDA about why is that the case. I'm just wondering. I don't know. I'm just wondering whether or not that process is too costly or too cumbersome or what it is. But it seems to me that if that process could be facilitated, made better, streamlined or whatever, so we could get uniform reagents, FDA-approved, out there that we could use, it would go a long way towards addressing our concerns about in-house developed tests in laboratories across the country.

DR. McCABE: Thank you.

Just a comment to put in perspective. Please stay at the podium, Walter, because I know there are other questions for you. But we were asked and charged by Dr. Satcher with speaking to the public and identifying what their concerns were, and I can tell you that they were very surprised at the lack of standardization and the lack of oversight on the home-brew test. So this is an issue that I think people have come to expect standardization in other areas of clinical chemistry and are a bit surprised why it hasn't occurred. So I think your question

or your comment is well made, and it's certainly worth additional exploration.

Dr. Burke?

DR. BURKE: I would just add something else, another element that's been an important part of discussion in this committee but didn't come up in your discussion of premarket review. It becomes increasingly apparent that some systematic and complete way of labeling tests may be a very important part of ensuring that they're used properly. I think one could easily find examples extant of tests that are available where the labeling is, in fact, not complete the way we're beginning to define completeness here. So I think that is a very important function that a premarket review might accomplish.

DR. McCABE: Any comment, Walter?

DR. NOLL: Dr. Burke, maybe one of the most important things in this statement is the comment that says we'd like to come back and show you what our thoughts are and what the plan is. When I'm not talking to you and I'm talking to my colleagues in the CAP, I have a different kind of approach, as you might expect. I'm arguing from a different perspective at that time, and I am finally personally convinced that there is going to be a sea change, that this is going to occupy a larger attention in a very large organization.

I always talk to people about this is what the CAP worries about, and right now this is how much genetic testing occupies their attention. Well, that's going to increase. So what we're committed to right now is to look at the entire program and try to draw out from that entire program those elements which pertain to genetic testing that we think you and other people are concerned about so you can see it in its entirety and don't have to look for it.

I think when you do that, I think when we do that, I think what

we'll find is that there really is a structure there which gets at so many of the things that have been discussed. I mentioned this to the committee a couple of years ago when I described the CAP program. The inspection checklist, for example, requires many of those issues that you're talking about in terms of the pre-analytical information and the post-analytical report, basically. I mean, it says it's required of the laboratory. It's a maximum deficiency if you don't do that. You have to state clearly what the intent of this test is and to whom you're going to apply it, which gets a long way towards what our concerns are, about not doing a genetic test in the wrong person or for the wrong reason.

And then the reports, they clearly require an interpretive report that's understandable by an average physician, if you read the commentary on the inspection checklist, and in some cases by the patient himself. Now, I'm not saying that any of that is perfect, and I'm not saying that the inspection program as it's now constituted can get at all of these things. But the framework is there, and I personally think it's worth looking at to see whether or not that can't provide the program that is going to be sufficiently reassuring to you and others that we can use the existing regulatory framework and systems in place.

I find what we're proposing to give to the FDA to do to be such a daunting job for them that I'm flabbergasted. I can't get my mind around it at all.

DR. McCABE: Elliott, very briefly, because we need to move on.

MR. HILLBACK: I think one of the issues, if you go back and think why don't we have kits coming, gets to the fundamental difficulty we had in this group, which is to find a balance between all the knowledge possible and enough to get this done. I think where it seems like we are today is really a combination of a front-end common template that allows FDA to be sort of the

facilitator of that template being created, but then we're not talking about throwing out CLIA. CLIA is still there with a crucial role in this whole process.

I think if the way FDA applies this template is to apply it as they would apply it to a kit and go through the full level of review, then you're right, Walter, they don't have the people to do it, and we're back to the fundamental problem that we've been debating for two years in this committee and several years in the previous one, which is that will freeze, that will stop the development of a lot of tests.

So I thought the compromise we were trying to get to was some common template, some common information which most laboratorians I think would say they have to have anyway, but a review process that wasn't like a kit but was somehow different and tied to CLIA.

DR. NOLL: We have that information.

MR. HILLBACK: We do.

DR. NOLL: If you're a good lab and you write your tests up right, it's there.

DR. McCABE: But again, I would point out what Dr. Burke said, and that is that we've also got to do this in a way that makes the information available to the individual being tested and to the health professional ordering the test.

DR. NOLL: Education, education, education.

DR. McCABE: Thank you very much.

Our next presenter is Vivian Weinblatt, who is president of the National Society for Genetic Counselors.

Ms. Weinblatt?

MS. WEINBLATT: Thank you. It's nice to be here again. As you said, I am the president of the National Society of Genetic Counselors.

I have something really nasty in my throat at the moment.

We're an organization of nearly 2,000 providers, most of whom provide at least some degree of direct patient care. We've appreciated the opportunity to speak to this group in the past and will continue, I'm sure, to comment.

In the interests of time, I won't address the issues that were already raised in the group, but there are a couple of things that I thought, in review of the templates themselves, that bore more discussion. The first really just addresses the clinical utility of the test, and I know that when we spoke in February of this year, there were issues about the review template and issues about something called a provider summary, which I know I got muddy about some back in February.

What I would suggest with regard to the clinical utility -- and I appreciate Dr. Khoury's comments earlier this morning -- is that clinical utility from our perspective really is as key as analytical validity. So there really must be something that this test will be utilized for in order for it to be available clinically.

I also think that when you talk about clinical validity, when you look in Section 9 of your template, you'll find that it talks about issues of sensitivity and specificity and positive and negative predictive value. We would suggest that in the actual test reporting, which is in item 6, the example reports that are discussed, that those issues really need to be included in the reporting, because I think that what will happen is that tests will become available and clinicians will then need to be able to interpret that information. So I would encourage that that

also be required in the actual examples of what a report might look like.

I also wanted to talk just a little bit to some of the issues that were omitted from the methodology but I was glad to see were discussed in many of the presentations already this morning, and it won't surprise you to know that some of those issues are things like genetic testing and genetic counseling and their association, as well as issues of informed consent, the genetic discrimination issues, and the psychosocial impacts.

I think that the actual placement of where this information must be in the process is something that really needs to be clarified and that it should be consistent. If you look through the templates, for instance, genetic counseling is required in the Huntington's example, and in other examples it's offered. So I think that we need to understand a little bit more clearly how those kinds of determinations get made.

I also know that there is a working group that looks at informed consent, and I think that it's really critical, either in the education process in these provider summaries, in some kind of Web review that was already discussed perhaps associated with GeneTests, or with the professional societies, to help people to understand what that really means. I have to tell you from my practice of primarily prenatal patients that there is, according to many of them, an international conspiracy that their cells, which are retrieved from their pregnancy, are actually grown somewhere and tested or done something to. So I think that patients really need to understand what it is they're consenting to when they consent to individual tests.

We would be happy to be of more assistance with regard to provider summary issues. Perhaps some of this will go in the labeling process for

FDA. Those really are the issues that I thought were important for us to discuss, and we appreciate being here and the opportunity to comment.

DR. McCABE: Yes, thank you for being present again and making public comment, and thank you for your brevity.

Are there questions for Ms. Weinblatt?

(No response.)

DR. McCABE: Okay. Our last individual who is registered for public comment this morning is Neil Holtzman. Dr. Holtzman is from the Johns Hopkins University and was co-chair of the task force that preceded this committee.

DR. HOLTZMAN: Good morning. Thank you for the opportunity to talk to you once again. I have made comments before, and if you look at the relative length of the comments that I've submitted on two or three previous occasions, I think you can plot them as going down in length. Either this reflects the fact that I'm getting tired and older or that the job that you guys have set out to do is getting accomplished to a great extent, and I think it's the latter that accounts for the brevity in my comments and in my presentation today.

I think that the template which I received with the one example of Fragile X really goes a long way towards assuring the safety and effectiveness of genetic tests, which, as you know, was the title of the task force that Mike and I chaired.

I think it's important to point out, and the committee certainly knows this, that there are aspects of genetic testing that are extremely important, particularly for predictive tests -- namely, the clinical validity and clinical utility -- that are not addressed anyplace else. If, in fact, the requirement that laboratories

providing services, as well as manufacturers providing kits, have to demonstrate clinical utility and clinical validity, if this does deter the availability to the public of tests that do not meet those standards, perhaps that's not such a bad thing. We already have many examples, not only in genetics but in other areas of testing, where tests have come out, largely through clinical services, which after long use have proven to be ineffective in some instances, and in some cases unsafe, leading to wrong diagnoses and to wrong therapeutic interventions.

So it's a difficult task but one that I think is needed to assure the public's safe and effective genetic testing.

I have only a few comments -- some of them were addressed by Dr. Gutman this morning -- regarding the template. The first was, as I read it, that the template omitted the kind of information that a test sponsor would make available to potential users, both health care providers and consumers, in marketing the test; that is, before the test is ordered. If you look back at the report of the Task Force on Genetic Testing, in one of the appendices, Mildred Cho and her co-workers and myself looked at the quality of information made available by both commercial and academic laboratories marketing genetic tests, and there was a tremendous amount of misinformation and omissions in information.

Now, Steve addressed this a little bit in terms of labeling, but I think it is critically important that the FDA give guidance as to what information should be available in the labeling, the premarket availability of the test. Of course, this will again depend on what use the test is intended for.

On the matter of intended use, I think this is where my major concerns are, because it seems that any laboratory, any manufacturer who submits to FDA could indicate what its intended uses are for a genetic test, but there are

other uses, and Francis Collins this morning actually pointed out some deficiencies in regard to uses of tests for carriers and for carrier screening in particular. In fact, the example of carrier screening is omitted from the examples given in the FDA template.

So it seems possible to me that, knowing the different levels of stringency that FDA will use, a test developer could say that its intended use is the one that's likely to require the lowest level of stringency, and that once made available by, say, FDA approval, that that test could then be used for other intended uses that require more stringent scrutiny. In the drug field and in some of the test fields, this has been sort of thrown off as off-label use, which the FDA has a very difficult time regulating.

I think that the issues that come up in genetic testing are of such great concern, particularly for predictive testing, that the FDA has to explain how it's going to avoid this problem of off-label use and to require from its own expertise an indication of all the possible intended uses of a test given the methodology that the developer sets forth, and to require some indication of how these other uses, how the public will be safeguarded from these other uses of the test.

Very briefly, under laboratory quality, there was no mention there, in proficiency testing for instance, or in the sharing of samples with established laboratories, of whether this testing should be done blindly or not, which seems to me to be another preferable way of assuring the quality of the laboratory; that is, blind testing.

Finally, in terms of clinical validity, understanding that many times this will be drawn from the literature, that developers must assure that the

data that are collected reflect the kinds of populations, the kinds of groups in which the test is actually intended for use. So going to another country or another subpopulation that is likely to be quite different from the one for which the test will be marketed I think requires some explanation and probably the collection of additional data.

As I've said many times, and it's not addressed in the template, it does seem to me in terms of not to hinder the development of tests unnecessarily, that there needs to be some provision for what I've called, and FDA in other contexts has called conditional premarket approval, where a developer can be given permission to market a test, indicating that it is still under investigation so that additional data on clinical validity can be collected.

Those are my comments, and again I compliment the Secretary's advisory committee and the FDA for fantastic progress in this area.

DR. McCABE: Thank you, Dr. Holtzman.

Muin, and then Elliott.

DR. KHOURY: Just a couple of comments here. Your points are well taken, Tony.

I thought where the committee was leading to was that at this early phase of premarket review that the manufacturers put in this template what they know and what they don't know, and then they leave the rest for a postmarket type of analysis. Certainly, the clinical utility piece, which is always the trickiest, would be nice to have, and I think this is one of those evolving features of SACGT that has, in a way, broken the deadlock around the stringent review earlier, where you collect some data, you have truth in labeling, and then you leave some of that for the postmarket phase as long as you tell people what you

know and what you don't know, to borrow Elliott's favorite phrase.

So I think some of your comments reflect perhaps a regression towards the earlier, more stringent discussions that we had on the task force.

DR. HOLTZMAN: Thank you, Muin. First of all, let me say that I think even the inclusion of clinical utility is a remarkable step forward, because something in earlier iterations, if you will, that FDA said this was something that was not in their purview.

My only concern, Muin, is that this template, which is quite articulate in many earlier points, does not lay out in sufficient detail how this postmarket procedure will be followed, and it's that that I think needs to be much better and more precisely articulated.

DR. McCABE: Elliott?

MR. HILLBACK: Actually, this goes back, Tony, to the discussion just before the fire drill as well. I believe if we go back to Wylie's committee, those of us on that committee from all walks of life, including the labs, felt that each intended use, or maybe a family of intended uses, because there may be some that are close together, was going to be treated separately rather than in this telescoped or collapsed mode that Steve talked about. That's how we have to operate in the laboratory. In order to sign out a test, you have to know which test you're doing.

I think what will drive people to the "one use and everything else will be off-label" conspiracy theory is if we go back to a very formal, long review, if we go back to clinical validity and end up like kits, where no one will do it because the work is too onerous. If we stick to the proposal that Steve and Dr. Feigal and others are coming up with, and a lot of industry help, and a lot of

professional help, then I don't think people have a need to try to work and game the system. I think, from the lab's point of view, there's nothing wrong with us saying this is this use and this is a different use and they have different characteristics.

So hopefully we won't set up a system people feel they have to game and we won't have that problem.

Wylie, you may want to comment. You sort of led us in that direction for a long time.

DR. BURKE: I actually think that Tony's comments and the discussion that we had earlier about the template do seem to say two things. We're getting warmer, and also at the same time there's work to be done. I actually think on both those issues -- that is, on the issue of whether we need to separate out or whether some template information could be shared -- it would be a very important discussion for our proposed August meeting, and the other piece is how much direction we should give and what expectations we should have in premarket review for clinical utility.

DR. McCABE: And the other thing I'd like to point out also in terms of barriers to implementation has to do with payment for these tests, and I would urge that we continue to have ongoing discussions about how -- and I know this is going to sound terribly naive, but how FDA and HCFA review could be somehow brought together and not be independent barriers to implementation.

Thank you very much, Tony.

I let this discussion go a little bit longer than we frequently do in the public comment because I thought it was a continuation of the discussion before the fire drill. In keeping with that, recognizing that our lunch hour is

growing shorter as we discuss, I'd like to invite Dr. Solomon, Dr. Spear, and Dr. Gutman just to comment on anything that you may have heard in the public comment that you wish to follow up on and give you the chance to do that in terms of the template. Any additional comments? I see a nod of no from Drs. Solomon and Spear.

Dr. Gutman?

DR. GUTMAN: Well, I think the issues that Dr. Leonard and Dr. Noll put on the table are real, that there's a dark side to all of this. We at the agency have constructed something that is as light a touch as we think we can get by with. I actually don't know if we can deliver. I'm a truthful person, so I'll tell you that we certainly would try to deliver this program. I honestly don't know. We have a long history of review that people are referring to here that is pretty data-intense and pretty labeling-intense. So I'm frankly open to alternatives.

I did put the issue of leveraging on, and I can't speak for the agency, but there actually isn't an intent -- and I apologize if somehow I've miscommunicated. There actually isn't an intent to have the usual review process applied here. I tried to make that distinction, particularly with the QSRs or the good manufacturing practices, which would, in a single fell swoop, close all genetics labs in this country. I'm not sure that's a message I heard SACGT say.

But even for whatever role we might have in premarket review, it is not the intent to do business quite as usual, and it certainly isn't whatever burden we would put on. Again, I'm receptive to whatever fantastic ideas come out. Whatever burden we put on wouldn't be all at once. We aren't prepared to do hundreds or dozens of PMAs. If anyone here believes that's the case, I have a good psychiatrist I can refer you to.

DR. McCABE: I'd like to also remind everyone that in our recommendations to the Secretary, we looked at existing tests which were already being utilized and suggested that those needed a very different level of review, because there were extant data on those tests, and we recommended what we have seen very nicely with Dr. Leonard today, and that is that there be involvement of the professional organizations and other individuals who could bring that expertise to bear and facilitate review of extant tests. So that is in the document, and we're really talking about new tests as we move on to some of the kinds of templates that we've been discussing today.

Judy, I'll give you the last word before lunch.

DR. LEWIS: It's a general comment on the template and on some of the language that is rather minor but I think is critically important, and this builds on a point that Ann made earlier.

At one point in the document you talk about registered geneticists, and I'm not sure what a registered geneticist is. And then under 13 on the guidelines, when it talks about clinical utility and "the section should contain a brief discussion of the potential clinical benefit for both the physician and the patient using the test," I'd like to make sure that we use language that's broader, because if we talk about health care professional or we talk about health care professional with expertise in genetics, then we don't get into some of the intra-professional issues around certification and licensure that are being dealt with at the level of the states in terms of practice acts.

My ability to practice as an advanced practice nurse in Virginia is very different than it was in Massachusetts, for example. In terms of who the providers are, I'm not sure they're always physicians. At some level we could be

talking about general health care providers doing some of this, and sometimes we're talking about people with specific expertise. So if we focus on that rather than use the term "physician registered geneticist," I think we broaden the net, and I think it's a small point but I think it's a critical point to make sure we get in the record.

DR. McCABE: Thank you, Dr. Lewis.

I just would draw everyone's attention to the fact that there is a revised meeting agenda. The original one that came out in our briefing books had us taking lunch at 12:30, but with the revised agenda we will take lunch now until 12:30. We will resume sharply at 12:30, and at that point we'll begin the discussion of exploring approaches to the development of clinical guidelines, with Dr. Burke leading that discussion. So, please, I know it's going to be a short lunch break, but please be back at 12:30.

(Whereupon, at 11:47 a.m., the meeting was recessed for lunch, to reconvene at 12:30 p.m.)

DR. McCABE: While we're getting our technology going, why don't we begin. This is a session exploring approaches to the development of clinical guidelines. The discussion will be led by Dr. Wylie Burke. Along with premarket review and postmarket data collection, we see the development of clinical guidelines as another important component in ensuring the appropriate use of genetic tests. Dr. Burke will introduce the session and will take the lead in the session that follows.

Wylie?

DR. BURKE: Thanks very much, Ed.

The idea of talking about clinical practice guidelines here in the committee came out of conversation around premarket review and some of the comments that came back from premarket review. It seemed pretty clear that some people commenting on our premarket review process, particularly those concerned about off-label use and how we might control off-label use, were really raising the question of how do you create good recommendations or good guidelines for the use of genetic testing. In other words, they were talking about clinical practice guidelines.

In approaching the topic of clinical practice guidelines in our discussion today, what we're taking into account I think as we go into this discussion is that the premarket review process that we've been discussing with FDA is one that probably would not include a detailed evaluation of data around clinical utility. There has to be an intended use, but there really isn't an expectation that there would be a detailed review of outcomes data.

In part, that's because often the data is not going to be there when the test is available. Some of it can only be acquired over time. And also because it's really not part of what now exists in premarket review.

If we take that issue and the lack of jurisdiction, so to speak, over off-label use together, understanding what we might accomplish with practice guidelines is important not only in and of itself, but it's important in understanding what's a reasonable expectation from premarket review. We've already said that there's something else that has to be there in addition to premarket review, and that's ongoing data collection. So there's data that comes into premarket review, but we've said that after a test becomes available, more data is collected, and there ought to be some way of pulling that data together, analyzing it, and disseminating it, and that's obviously something that Wayne is going to be talking with us about later.

But that data, then, should be used in some way to help do good practice. The question we're raising today is not should we be in the clinical practice guidelines business. I think that would be a very premature discussion to raise, and probably the preliminary answer to that is no. But it would be very helpful in our discussion to have a clear idea of what clinical practice guidelines

can accomplish, and in particular what the current thinking is about what a good clinical practice guideline would be.

Under Tab D -- or is it Tab 4? Sorry.

DR. McCABE: Tab 4.

DR. BURKE: Tab 4, there are some questions that we posed to our two speakers. We're very fortunate to have today to talk with us about what a good clinical practice guideline is and how that might inform our recommendations Dr. David Atkins and Dr. Michael Watson.

Dr. Atkins will speak first. He is the medical officer in the Center for Practice and Technology Assessment at AHRQ. Dr. Atkins received his M.D. degree from Yale, his internal medicine training was done at the University of Pittsburgh, and he completed a fellowship at the University of Washington, where he received an M.P.H. Since that time, as detailed in the biographical materials you have, he has been involved with the U.S. Preventive Service Task Force activities. He was a primary author and editor of the second edition of Guide to Clinical Preventive Services and currently is the staff director for the third U.S. Preventive Services Task Force, which was convened in 1998.

Dr. Atkins?

DR. ATKINS: Thanks. It's nice to be able to join you, although I realize I'm in part joining a conversation in mid-course. But I have over the past few years been involved, thanks to Muin and Wylie, with some of the genetic issues, although I'll really be trying to spend this time talking about an approach to developing guidelines, what we really mean by evidence-based guidelines, and the kinds of issues one needs to think about in deciding what you want out of a

guideline.

The Preventive Services Task Force has a specific approach which works very well for what it's trying to do. This group may be looking for something different, and it needs to have those things on the table.

It's important in thinking about guideline development to think about a number of key questions. First of all, what's the context in which the guideline is being developed? Presumably, if one has a guideline, it's aimed to do something positive or address concerns or a problem. One needs to think about what that context is to decide whether the guideline and the way you develop it is really going to accomplish what you want.

As an example, the Preventive Services Task Force is designed to help primary care clinicians figure out where to focus their efforts in terms of primary and secondary prevention. It knows that its audience is primary care clinicians, and it knows that it's addressing a broad range of prevention. Those two central parts of its mission helps frame the process it uses and the panel that it puts together and the perspective we bring.

So thinking about what you're trying to accomplish with a guideline then helps you define what's the evidence you need to figure out how to accomplish that, what are the outcomes, what are the clinical data one needs.

A second issue is who is the target audience, and clearly guidelines developed by regulatory bodies or rules of evidence for regulatory bodies might be quite different than rules of evidence when you're aiming your information at primary care clinicians. Similarly, in genetic testing, clearly that's an important distinction, whether you're aiming guidelines at wide use by primary

care clinicians versus their use in specialized settings and specialized populations. It's important to think through these issues up front.

Related to that is the clinical setting. Again, it relates to the information one needs. Is the information you have relevant to the clinical setting that you're dealing with? So often, the task force is looking at information about how well something works in a very specialized setting and trying to decide whether that information is relevant to what would be available to the average primary care clinician in routine practice.

Clearly, with genetic testing, the issues are quite different if it's being done in specialized clinics or in specialized laboratories versus being marketed widely out to the public.

Then lastly is why even bother? What is the goal of the guideline? Clearly, guidelines have a sort of momentum of their own, and I think now that we are 15 years into the guideline movement, people are stepping back to say which of these guidelines actually did anything, and have they really had the impact that we hoped they would have, not just on practice but on health outcomes.

Just to clarify issues on that, I'll be talking about the task force perspective, which is really a screening perspective. David Eddy has defined screening as the application to a test to detect a potential disease or condition in a person who has no known signs or symptoms of that disease or condition. Now, in many cases, genetic tests are applied in that setting, although often they're applied in the context of a very specific family history or some other reason, even if the patient is asymptomatic. But sometimes it will be applied as a sort of diagnostic

test in patients presenting with symptoms that might be related to heritable diseases.

If one sort of thinks about the range of use of genetic tests as sort of a continuum, it's sort of mass screening. Basically, marketing this thing is good for everybody. It's something that you could go down and get at your pharmacy. The example of that is blood pressure screening, all the way down to a very narrow continuum as their use as a diagnostic test in very specific clinical situations predicated on a specific constellation of uses.

In between, there's a whole range of things that are sometimes called screening, sometimes called case finding, sometimes called testing. The terminology changes, but they're a range of from less to more selective use, and I think that's an important issue for this group to think about because, clearly, as the use gets less selective, the potential that these tests aren't doing what we think they can do and want them to do becomes greater.

So a fairly broad application would be universal screening but in a clinical setting, and the example being the variety of newborn testing that's currently done and is basically policy regulated at a state level, but where there is some potential for quality control in the way that it's administered. Some tests would be called case finding but are fairly routine screening, like cholesterol. From what I gathered of the conversation, we aren't yet there with any of the genetic tests, but we might be there pretty soon. That there are tests that people think ought to be done as part of a panel of blood work in the way that we might order a cholesterol level on a patient.

Clearly, when one gets into genetic testing and the ethical issues

involved, there are places where the recommendation would not be to test everybody but to discuss testing and offer it, and to consider patient values and the potential value of that test before you decide whether to do the test. Obviously, the more expensive the test or the greater the potential for unintended harms, the more important that kind of discussion is. We don't discuss cholesterol levels when we test them on our patients because we think they're fairly reliable, aren't likely to do harm, and it's not very expensive. But when we look at other preventive measures, like tamoxifen to prevent breast cancer, clearly that's a discussion that has to consider a lot of other factors. Then further on down the line there are more selective settings.

So again, I put those out just to say that genetic tests may fit into any of these categories. The ones marked in yellow are the things that fall within the purview of the U.S. Preventive Services Task Force. But depending on the setting, depending on the intended use, the questions you ask might be quite different.

The task force question is a fairly basic one. Is there reliable evidence that providing this screening test as a regular part of care in a typical practice will do more good than harm? That sounds like a simple question, but it actually turns out to be more complicated when one looks for good quality evidence to address all the things you need to make that assessment.

The evidence, then, that a task force requires, they need evidence that screening improves health outcomes. Again, the task force has defined a benefit as a benefit in a health outcome, morbidity or mortality. So they would not consider just the ability of a test to provide information as sufficient evidence to

say this ought to be a regular part of practice if that information can't be shown to lead to important health outcomes. That relates to the clinical utility issue that Wylie pointed out.

This is a reasonable standard when you're evaluating a range of tests like mammography and pap smears. It might not be a reasonable standard if you're trying to develop recommendations for laboratory practice. So not only are we looking for evidence that addresses the effect on clinical outcomes, but we're also assessing the quality of that evidence, and I'll talk a little bit in a couple of slides about what we mean by an explicit evidence-based process.

The second issue is to consider that there's always the potential to do harm, and those harms are not just wasted time or wasted resources, although those are important considerations, but there's the potential with any test to have unintended harms. The term that is commonly used is labeling, whereby identifying a patient who comes in feeling healthy as having a disorder or a trait that puts them at higher risk for a problem may actually have a negative impact on them. I think everyone recognizes that this is a potential, especially a potential concern with genetic testing, where the public might confer a greater predictive value on a genetic test than they would, say, on their cholesterol level.

Cost effectiveness is not something that has become an explicit criteria of the task force, but I think we've recognized in our third iteration that it's information that we can't ignore, that policymakers want, and so we're trying to go about looking at cost effectiveness information in a more systematic way.

In relation to screening -- and I think some of these questions have probably already come up in the discussion about the FDA's role, but some of

them relate more to the clinical utility area -- the key questions relating to screening are can the test reliably do what you think it's going to do? We benefitted from the work of Wylie and Muin in giving precise terms to these, like analytic validity and clinical validity.

But the other issue when one is trying to decide if this test is going to make people better off is trying to decide whether the information that the test provides actually leads to changes in practice and things that will actually improve the outcome.

The third, which I already mentioned, is what's the price you pay for that in terms of harms? And then what's the balance of benefits and harms? This becomes maybe a little easier to understand if you look at this analytic framework that the task force uses. Just to define the types of evidence that are available, the top arrow really would be a study that actually compares clinical outcomes directly. So a test that offers genetic testing to one group and not to another, or a prospective study that looks at people who have had genetic testing and people who haven't and tries to look at whether outcomes are improved.

I think we all recognize that that's a difficult standard to expect with genetic testing. But it's important to have that in the back of your mind as the ideal in thinking about can you get there with other types of information. In the absence of that, you have to try to sort of piece together an indirect chain of evidence to decide whether or not the testing is actually going to lead to clinical benefits.

So the first one is how well the screening can identify someone who is genetically susceptible, and that relates not just to the analytic

characteristics of the test but the information that we have as to what do we mean by genetically susceptible, how good is the data that they're really at risk.

Then the second, the critical piece is what does a clinician do with that information? So the clinician now has information that a patient is carrying a genetic trait. How are they going to intervene to actually improve the outcomes in the face of that knowledge? We have lots of examples where we have tests that provide information, but their actual impact on the clinical outcome is far less dramatic than we would like. You could apply this to any test, even cholesterol screening or things like bone density testing. They clearly can identify people at risk, we might have interventions to help them, but for a variety of reasons the effect on clinical outcomes might be less dramatic than we think.

Again, the other point that we try to emphasize in these slides is that one needs to think about the other parts of the picture. One is are there adverse effects of screening, the labeling issues, or a false-negative test. If we had a genetic test for susceptibility to lung cancer, would a smoker be less inclined to quit smoking if they found they didn't carry that genetic risk? Also, adverse effects of intervention. If we are using this test to decide who to intervene in and the test isn't as predictive as we think, we might be doing a lot of interventions, conceivably fairly aggressive interventions like bilateral mastectomies, in patients who aren't going to benefit from that.

In terms of the types of interventions in that second part of the pathway, they would include things like information and education. So a role of the test might just be to inform a patient that they are at risk and to educate them how they might modify that risk. We might have more intensive screening if we

knew someone had a genetic susceptibility to cancer, or we might have more specific interventions, whether they be medical or surgical interventions.

In that light, there are problems in the types of evidence. So for the first question, how well does the test actually identify those at risk, we need to think about not only how well they do in specialized laboratories but how well are they going to actually do out in practice, and we need to have the data that they actually are predictive not just in a selected cohort of families that have been studied but in a general population. I know those are not new issues for you.

We need to have good data on how good our treatments are in patients who have been identified as being at risk through genetic testing. Rarely do we actually have controlled comparisons where the patients have been selected on the basis of genetic testing. So we have to worry about is the data that we have really generalizable to the context in which we're discussing them.

Then, although we have an idea of these potential harms, they're very difficult to quantify and to know whether they really exist. If they exist, are they a given, or are they things that can be ameliorated by appropriate counseling? We all think that with appropriate counseling we can prevent doing harm, but in practice that might be not as simple as we thought.

Again, just to emphasize that point, it's very difficult, although the task force tries to do that, to say, on balance, is it doing more good than harm? That's a very difficult calculation because you're rarely evaluating things on a common metric. So you might have information that a test can identify people at risk, and you have an intervention that will actually prevent early death, say, from cancer, and you're trying to weigh that against the potential harm you're doing

from increased anxiety, unnecessary surgery, unnecessary other interventions, excess screening, cost, and no one has really come up with any simple way to do that calculation.

The point is not that one should try to do that, but that by being explicit and by laying these questions out on the table, you can be clear about what do we actually have answers to and what things do we not have answers to, and what are priorities for information.

Among the questions is the issue of incremental benefit. Genetic testing might identify people at risk. There might be plenty of other ways to identify people at risk. Clearly, you don't need a genetic test to decide what intervention you want to do in a smoker. So you would need to show that genetic testing had some added impact in getting people to quit smoking if you thought that was a valuable intervention.

The real world versus ideal practice I've already talked about, but clearly it's a consideration. We know primary care clinicians don't have the skills or the training to know how to do the counseling, and we probably don't have sufficient resources in terms of professionals who know how to do genetic counseling to handle the potential demand.

Then lastly is this issue of individual preferences. So clearly, a test might not be good for the general population, but there might be specific individuals in whom it's quite appropriate, and that might be the family history or the risk they bring to the issue. But it might be their own personal preferences. Patients might place a very high value on specific outcomes or on information. Other patients might have a very low tolerance for anxiety. Clearly, those are

things clinicians deal with every day.

It's very hard for a guideline to handle that kind of variation among patients, and I don't think it's necessarily appropriate for a guideline to try to address all the different clinical scenarios that might arise. Good guidelines address the most important questions in the areas where they can have the greatest impact.

I'll close with just a couple of slides just to draw the contrast in the differences between genetic tests and other screening tests that the task force has assessed. One is the issue of predictive value. Again, this is something we're rapidly getting data from, and the Huge type approach is really helping put that in a standard context. How good are these tests at actually predicting the clinical relationship that we impute to them?

The second is the variable yield of screening. So clearly, the value of screening in the general population is going to be very different than the value of screening people defined by some clinical characteristics, whether it's a family history. The yield of screening is not just how many people you find with a genetic trait but how important is it to find that they have that genetic trait. So you might not need to know that information at birth, but it might be more valuable to know that information later on when you have specific interventions to offer.

The labeling effects, as I mentioned, might be more pronounced because genetics does have this aura of inevitability for many people in the population. As I mentioned, it's hard to quantify the added benefits of genetic information compared to everything else we can do in terms of prevention.

This is just a comparison of how genetic tests compare to

cholesterol. I think I've already made these points.

I'm not going to spend time on cost effectiveness here because I want to allow time for the other speaker. But I think it's just important to note that cost effectiveness is used very loosely in the field, and often the costs that are considered are not a really complete accounting of the total costs that are involved in any program. So that is, again, something we're trying to bring a little more explicit approach to what we really mean when we're talking about cost effectiveness. But the only message I would give is to treat all cost effectiveness studies with a high degree of skepticism, especially when it relates to genetic testing.

The clinical parameters I think I've already covered, so I'll just wrap up.

I think the key point is that the evidence one requires really depends on the context in which you're thinking about developing a guideline and what is the problem that you're trying to address. The value and appropriateness of genetic testing is going to vary widely depending on the clinical setting you're addressing, the patient population you're addressing, and the indication for testing. One needs to be very specific up-front about what one is looking for from a guideline and what audience that guideline is trying to address to decide whether it's done appropriately.

Then lastly, the evidence for a guideline for primary care is going to look quite different. The evidence that the task force would require if and when we address genetic testing is going to look quite different than if you have a guideline that's addressed to a different audience.

Thanks.

DR. BURKE: Thanks very much.

Just for the record, I want to note that the very useful terms of analytic validity, clinical validity, and clinical utility derived from the task force chaired by Tony Holtzman and Mike Watson, and we're very grateful for those terms. They are very useful.

Dave, if I could have you hold for a moment. I just want to open the floor if there are one or two questions just on clarification of David's talk. Why don't we take those now before we go to the next speaker but not go into any general discussion until Mike Watson has spoken. Any specific questions for clarification?

(No response.)

DR. BURKE: Well, great. Let's then go on to Mike Watson, who has spoken before to this committee, but let me again introduce him to you.

Dr. Watson is the executive director of the American College of Medical Genetics. He received his Ph.D. degree in medical genetics from the University of Alabama at Birmingham and did postdoctoral work at Yale University. He is also an adjunct professor of pediatrics and genetics at Washington University School of Medicine. Prior to becoming the executive director just this past year of the American College of Medical Genetics, Dr. Watson was the director of the Washington University's Clinical Diagnostic and Prenatal Cytogenetics Laboratories.

Among his responsibilities as the executive director of the American College of Medical Genetics, Dr. Watson oversees the development of

clinical practice in population screening guidelines related to medical genetics, so he's going to talk with us about that process.

Dr. Watson, go ahead.

DR. WATSON: Well, thank you again for the chance to speak before you. This is actually interesting. I didn't see the slides that the prior speaker was going to use until I came, and I was somewhat gratified that they were remarkably similar. I think the difference in our views of this is that I think the last talk was very much the perspective from the top down, sort of an ideal approach to developing guidelines, whereas my perspective is obviously as a former laboratory director and deliverer of these services, from the bottom up, from the reality of writing guidelines for geneticists and for others.

I think that's one of the things that I want to try to emphasize, some of the challenges that are placed upon the genetics community in trying to develop guidelines in a productive and really a broad way, as we need them now.

The American College of Medical Genetics has probably put out over 40 guidelines in various areas, some quite extensive and substantial that are very broad, for all of laboratory genetic testing, for instance. But one thing is obvious, and I think it was reflected in the prior speaker. The approach we take to developing a guideline is very much driven by who we're aiming that guideline at.

Many of the early guidelines developed within the College were directed at our geneticist members to help them in delivering the genetic services to the patients they see routinely. Those we obviously tend to approach through our own organization and its members and their expertise in guiding one another through the services that are being provided. But as you know, genetics is

ubiquitous now, and we are often obligated to develop guidelines that apply much more broadly than just to geneticists themselves. Some of our guidelines may impact one other specialty.

When we move to developing guidelines that are much broader and not just dealing with specialties but getting down to primary care delivery levels, everything begins to change both in what we do on the front end in putting together the groups of people who draft the guidelines, and what we do at the back end in developing that consensus, because the more multidisciplinary the guideline that's developed, the more critical is that consensus development piece.

You can't tell others what to do because you're the geneticist. We can tell one another what to do and hang each other out to dry as we wish, or help each other as we wish. But as you begin to impact other care deliverers, you really have to be attentive to them at various levels of the development of the guideline itself, and at the very least have broad participation on the back end in the consensus development process.

Now, I'm going to harken back to information that we acquired during the last Task Force on Genetic Testing's deliberations, because we thought an awful lot about how we're going to go about developing guidelines and establishing validity, both analytical and clinical. I think, in fact, Dr. Holtzman had one of his fellows who actually went out and very actively assessed the various mechanisms through which this occurs in the country, and this is not an inexpensive venture. In fact, the cost of doing this is almost proportional to the last slide.

The more people you're impacting in other specialties in primary

care, the more consensus is required. The cost ratchets up significantly for each guideline you try to develop. As we looked at the various programs of technology assessment at the time, there was the Blue Cross tech program, one that was very well recognized as a technology assessment program; the Kaiser Foundation's technology assessment program. Those are both among what people think of as the foremost tech assessment programs in the country.

But they are very, very expensive processes, because you're moving away from the people with the expertise into a more general group of people developing the guideline, having to access expertise from a number of areas. So those inherently are quite expensive and, on average, ranged from probably $25,000 out to $100,000 per guideline, with the guideline being the same way you're thinking about tests here, a specific intended use of a specific test is the test. So a guideline for a genetics issue could very well be five guidelines around each intended use of that same test and becomes increasingly expensive.

When you recognize that we only have some 700 to 800 tests being routinely done out there now, most of which don't have specific guidelines available whatsoever, the magnitude of this task is going to be substantial to start doing the gap filling.

The lower costs are actually those that we recognize in professional organizations where we're developing guidelines for ourselves. We can bring the expertise together at our national meetings, keep our costs down, direct our comments to our own membership, and even those end up costing us between $5,000 and $10,000 per guideline to develop what is very much focused on our own membership.

As I said, the more necessary that consensus piece, the more expensive the guideline development becomes. Yet this is critical to its acceptance and recognition. Actually, in our very first guidelines, we paid some attention to what at the time was an Institute of Medicine report which actually made recommendations as to how guidelines should be developed. They placed significant emphasis on the consensus-building process, both at the front end when considering whether you need to have broad participation in development, and at the back end where you have to consider broad comment to make sure that you've actually touched on all those things that are important to other practitioners who are encompassed within your guideline.

Now, our guidelines, obviously, are quite variable because we have a large laboratory contingent within the American College of Medical Genetics, a large contingent of people who bridge the laboratory and the clinical service, and then another large contingent of clinical service delivery people. One of our most comprehensive guidelines is very generic and applies to the analytical technologies that we use in our laboratories. That was our first goal, to be very comprehensive in general standards for the various analytical technologies we use and how to run those effectively in your laboratory, regardless of the target disease that you were assessing.

That entire program is now moving to a much more disease-specific focus. In the last six months, we've released one on Fragile X testing that links directly back to our triplet repeat technology recommendations for the laboratories but now links those critical interpretative components of a test result. So how do you interpret that small gray zone where a result may indicate

somebody has an increased risk of myotic instability, therefore amplification of their repeat, whereas another individual with a slightly higher number of repeats has an increased risk of penetrance of the disease and is being clinically affected, and all this within a range of repeats of about 4 or 5 in this gray zone? So we've begun to try to standardize those pieces through our disease-specific laboratory guidelines.

We also have a range of guidelines that are now clinical genetics practice focused, and those have ranged in cost, as I reflected earlier. We have put out two recently that were funded through a grant from the New York State Department of Health, one on breast and ovarian cancer screening that required broad participation of a number of specialties impacted by this guideline. That cost about $200,000 to put that guideline together.

Another guideline in that same process was on the evaluation of the child with single or multiple malformations. That was similarly expensive but not as expensive because it targeted a much less broad group of people. So we were able to do it without the same breadth of expertise of other specialties that we might be able to bring to bear when we're talking largely to ourselves.

I think we can move on without getting repetitious to the last talk.

I think, as he said, evidence is the critical piece to a guideline. If you don't have good evidence and haven't assessed your evidence well, your guideline will not be accepted and it will fall down in that consensus development process if you do that appropriately.

Included in the various ways we approach these, and I think it's sort of inherent in the problems we're all having and why we have task forces and

advisory committees, is that we often don't have that information, and it's often not in the literature. As an academic laboratory director, I can tell you that I have hundreds of patients with many diseases on which I've never published a word, because after somebody publishes three or four things specific to testing for that disease, it's not academically interesting, and I don't just write for the sake of writing -- "Here's another one."

But what that tells us, though, is that that data is all over the place in the community. So we often include not just peer-reviewed literature in our assessments but also go out and collect unpublished data. When we looked at the relationship of ApoE4 and Alzheimer's disease, that was critical. We actually were able to get 49 of the top 50 investigators in the world to give us their raw data on the relationship between ApoE testing and Alzheimer's disease, which allowed us to run a meta-analysis of that entire data set to appropriately understand what that test is doing and where it might be appropriate to be applied.

That required about $50,000 to $60,000 even though we did it with ourselves and the American Academy of Neurology. Because of the statistical requirements of the meta-analysis, it became a much more expensive guideline, and that's not uncommon, because much of the data sits out in our laboratories.

Then, obviously, also in that evidence is an assessment of what is good and bad potentially in this test being delivered to people.

Now, when we work through the development of a guideline and think about how we're going to approach it, these come from all levels of our organization, and actually often come from outside of the organization. The board of directors of the College may say this is something we recognize is important and

charge a group with developing that guideline. We also have a number of committees, advisory kinds of committees and sections where these ideas may come back to the board for their decision as to whether we need something and an assignment of a work group to do that particular task.

We often try to identify the chairs ourselves, because our goal in doing these is to do them in a timely way, which we think is usually about six months to turn one of these around, and we do that by probably identifying a highly expert chair and then identifying all the sorts of people or organizations that we think need to be represented in the development of the guideline, and then work with the chair to identify people to fill those roles, hopefully people with whom they think they can work well and quickly and get the job done.

Then, depending upon the nature, how we review those guidelines can be quite variable. They can be reviewed only by the board of directors, which is most common when it's a statement that applies to our membership only. We may have an intervening committee that has developed this working group that may do an evaluation before going to the board.

But more often what's happening is that -- well, actually, this is something that's changed over time. In the past, we had the advantage of the CORN system, the Council of Regional Genetic Networks. What that enabled us to do was to develop a guideline, and we did this extensively with almost every guideline in the laboratory area that we developed. We developed them, we'd go out to the chairs of each of the 11 regions in the country and ask them to go to all the laboratories within their region, take all the comment that comes back, condense it into a single comment to come back to us. It made our job more

manageable because we got 11 comments back instead of the 70 or 80 that we'd get back initially, because we can't deal in our organizations with an enormous magnitude of public response to a guideline.

We're also now, because we don't have this CORN system available to us anymore, within the next two weeks we'll be opening our new Website, which is a far more interactive Website, and it's a place at which we plan to post guidelines that are in a draft form to solicit opinion. How I'll deal with the magnitude of response that could possibly come from such an approach to getting comment remains to be seen. It may either limit the amount of time I spend in this job, or it may limit the number of guidelines we can do at one time. I'll wait and see how that falls out.

As to disseminating our guidelines, obviously they get reasonably well disseminated during that consensus development process because we're talking actively to those who are impacted by guidelines that we develop. We publish them in our journal, largely in our journal, if we think they target our membership. But when we think a particular guideline we've developed is appropriate or would be most visible by being in another specialty's journal because they're on the front lines, then we'll actively ensure that we're publishing in the appropriate places for our target audience.

We often duplicate those. When we did ApoE, the American Academy of Neurology published it in their journal, and we published it in our journals. We also place all of our guidelines in publicly available sections of our Website. We're now in the process of identifying guidelines within those we've developed which impact more than just our membership, with the intention of

those now being submitted to the National Guidelines Clearinghouse, which is a place where guidelines are generically being collected from all areas. I think the American Academy of Pediatrics has about 13 or 14 guidelines already there, some of which are in the area of genetics, and we'll be placing many of ours which aren't just directed at our membership also in that particular Website.

We'll make them available to payers as needed, because it's often that kind of technology assessment that guides the payers as to whether or not they consider this test worth paying for or not. So we'll often be sharing very specifically with people in an educational way to help them make appropriate decisions about whether or not a service should be reimbursed.

The currency of our guidelines. Now that we've reached an age of our organization where we actually have to worry about things getting old, we've established a formal approach to this. No guideline will be current more than three years. After three years, and perhaps faster at the rate some of our technologies are developing, they are reviewed. We have a formal committee now, the Practice, Policy and Guidelines Committee, that facilitates development, facilitates making sure things are maintained in currency. Any statement that has been there for three years either is going to be retired, reaffirmed, or modified as needed.

As I said, we have over 35 of them now, a rather extensive area in the laboratory guidances, and those are ones that we will be submitting to FDA in the hopes that they can recognize some of these laboratory-based guidelines to establish a standard for one of the boxes at least within their templates, because we do think that that's going to be very important, that we develop the standards, and

that to simplify this process a laboratory can meet the standard or can explain everything it does to FDA. I think by establishing many of those standards, we'll be able to give you the option of light motif, and enhance that option I hope.

These are just a few other guidelines we've developed that apply to various areas. Factor V Leiden has just gone on the Website. These are some of the guidelines that target much broader populations of practitioners.

With that, I'll stop.

DR. BURKE: Thank you very much.

Any questions for clarification? Muin?

DR. KHOURY: No, not for clarification but for general discussion.

DR. BURKE: Okay. We're ready to go.

DR. TUCKSON: Just one clarification. Given your assessment of the cost of developing these, any thoughts on who is going to pay these costs?

DR. WATSON: My first choice would be everybody joins the American College of Medical Genetics and we have the dues to be able to work with everybody to develop these. That seems unlikely, though, doesn't it?

I think we need to develop mechanisms. I don't think we need to develop guidance about what goes in a guideline. I think there's standardization from the Institute of Medicine. We've done a number, we've had comments, and we're developing relatively standardized approaches to these. But it is really an issue of funding. As you know, the American College of Medical Genetics has 1,200 people. I can't double their dues to double our guidelines output, so we're faced with the reality of going with what we've got.

But I think to the extent that we can work with other organizations, find ways by which we can incent the development of guidelines, and not just us but all the other organizations. Anybody who has molecular or genetics in the name of their organization has limited resources, I would suspect, and has a relatively small membership. Yet they are the people with the expertise. Figuring out how to bring that expertise to bear on dermatologic genetics and neurological genetics and the whole range is the problem.

DR. BURKE: Thanks.

We're going to go into a general discussion now, and the focus of this general discussion is any ideas that are important for us that came out of these talks, but specifically the question of whether something like a points to consider document that outlines what a good guideline is is something we should have for genetic testing; and if we should have such a document, should SACGT be involved in the development of that process.

DR. ATKINS: Wylie, I don't know if Jeff wanted to comment on that question of cost of guidelines. Is that why you had your hand up? Because I was going to respond.

DR. KANG: That and one other thing. I had a question, actually, for Dr. Watson, if that's okay.

DR. BURKE: Okay, go ahead with that.

DR. KANG: Just in terms of the two presentations, there was a remarkable overlap, but there was a place where there was a difference, and I was wondering if you could help me reconcile this. Both of you talked about evidence-based decisionmaking and that it would be the ideal, but in Dr. Watson's

presentation there was a heavy emphasis on the consensus development process. I was wondering if you could reconcile that difference. In a certain sense, if the evidence is there, I'm not sure why we need consensus.

DR. WATSON: Well, consensus is actually buy-in. I mean, consensus not only includes somebody acknowledging that they should follow your guideline but accepting that you have developed it in a reasonable and fair way and that they therefore should follow it.

The literature in genetics can be quite thin. There's a significant number of very rare disease situations where there may be only five people with really strong expertise in the area. Having reflected a strong evidence-based approach despite the fact that that evidence may be thin, it may be very much expert-based kinds of evidence rather than evidence-based, and that's important I think.

So it reflects this range of guidelines that impact genetics, from being very narrow and rare disease areas, of which there are some 4,000 or so, and 10 to 20 million people in the United States affected with rare diseases, to the more common ones where we feel obligated to approach it much more broadly, not just deal with what is a very limited literature set but an enormously broad literature set in which you have a much greater problem sorting the wheat from the chaff.

DR. BURKE: Well, I think your comment has already taken us into the heart of the discussion. So again, I don't think we're going to resolve what a good guideline is here. We're talking about how much SACGT should be involved in a points to consider, but I think we have to discuss some of these issues as we try to answer that question.

Let's go with Muin and Reed next.

DR. KHOURY: I'd like to reflect on both presentations here. I really appreciate both David's and Mike Watson's presentations.

I just want to stress a few points. It is going to become more and more obvious that when it comes to genetics and guidelines around genetic testing, most of these guidelines around the use of genetic testing are going to be spilling over to all kinds of disease entities. So by the nature of things, you have cancer and heart disease and Alzheimer's, so having guidelines related to all these disease areas, be it adult or childhood conditions, will immediately put you in a multidisciplinary way of thinking, where you bring in the disease experts, the genetic experts, the statistics experts, et cetera. Whatever we do in that area is going to involve that kind of collaboration.

Now, people have commented on the lack of data, and I think that's a key issue in driving guideline development, because as we now approach this problem of genetic testing from both ends, we're approaching it from the premarket phase where we're asking developers to put together a truth in labeling or advertisement about the test where information about clinical validity and utility may be largely missing or incomplete. From the other end, where we want to develop guidelines that are not solely based on expert opinion but have some kind of a framework of thinking and organizing the data, we all need that bridge, and maybe we'll come back to it tomorrow when I make my presentation.

But I think we do need a guideline on guidelines. I say that with a little bit of trepidation because you don't want to reinvent the wheel. Mike has mentioned the Institute of Medicine. There are other situations and other groups

that have looked at what's the best way to develop guidelines. Obviously, the U.S. Preventive Services Task Force has its own way of classifying the evidence, levels of evidence from 1 to 5, things like that. But there may be some peculiarities related to genetic testing that at least might merit a look at what exists out there, and maybe that points to consider document, that's something that SACGT might sink its teeth into.

Finally, I wanted to reflect on two things. One is that Mike said there are already 750 tests on the market. When you really think about that, there probably are less than 50 of those that do merit guidelines at this point, and these might fall under the now defunct Level II classification scheme that we spent a whole year working on, and then we threw it out the window.

The others I think can wait a little bit. More data needs to be collected. There are obviously more rare conditions we're dealing with, but at least for those 20 to 50 where it impacts large segments of the population, like newborn screening or testing for adult chronic conditions, those might be worthy of consideration.

The final comment I wanted to say is that even after you have guidelines and practice guidelines, the next step is really the translation of these guidelines to action, and I wanted to make a follow-up comment to David Atkins. Maybe, David, if you'd like to comment on the Community Preventive services Task Force, which is another collaborative government-driven entity in which people look at practice guidelines in the context of community, and they're driven not only by efficacy of certain things but how effectively they could be delivered in different settings.

For example, we know that if you give penicillin prophylaxis to all kids with sickle cell disease, you prevent or reduce the morbidity from sepsis. But what's the best way of doing this in real life? Something is efficacious but may not be effective in a real-life situation. So I don't think we should forget about the implementation of these guidelines and having some follow-up discussion about the best way of delivery.

These are only a few random thoughts I wrote down, but it's a very stimulating discussion.

DR. BURKE: David, do you have a brief comment before we go to others on that?

DR. ATKINS: No. I mean, I think Muin's point is a key one, that our agency spent a lot of recent attention on that, that you can produce all the guidelines you want, but if you haven't paid any attention to their translation, you've wasted a lot of money. I think often we spend too much time trying to get the perfect guideline and lose attention to the fact that there might be some key implementation issues that are just as important.

DR. BURKE: Reed I think is next.

DR. TUCKSON: I found this to be very, very helpful to me. I've got three questions that all fit together, and I'm wondering how it all comes together. The context of what I'm struggling with here is how do we pull together through our advisory committee the notion of who pays for this genetic testing that's about to happen. We're in a world now where the costs of medical care are going through the roof, the costs of pharmaceuticals are -- you just can't afford it. Health care premiums are going up, and uninsured people are increasing every

day.

So we've got an incompatibility at this moment, which means that in the real world, real people have to make choices about what they're going to have in their benefit packages, real people have to make choices about what tests are they going to have done and how much they have to pay for it, versus themselves paying and others paying for it.

So I think the question I'm getting to is how do we pull together the notion of who pays and how with who decides and how? Both of them did a good job talking about who is the target for the guideline. Who decides? At some point, I think the target is not only the physician, the counselor, but it is also the patient, and these guidelines need to be available to people to know this is what this stuff is going to cost me, here's what I get from it, and here's why I would make a choice for the good things.

I also appreciated the presentation to hear all the harms that could happen. But putting that whole package together, that then says to me that once you have a guideline or some sense of evidence base that is organized in a decisionable way, that is a fundamental requirement for rational behavior for the future.

Secondly, then, who should do the guidelines? Whose space is it? I think Muin's last point about a guideline for guidelines -- if we cannot at least get, at this early stage, all that we want, I think the advisory committee needs to strongly recommend here is a decision tree, because we're here to help the public. The Secretary's Advisory Committee is ultimately dealing with people out there in the world. Here is what you need to have available to you to think through

whether you want this thing, what is it going to cost you, what are the benefits, what are the harms, and here's how you evaluate the guidelines.

I'm sorry to be long. The last thing very quickly is, then, how do we pay for this guideline development? I am worried. I really do see the dilemma here, that when you throw up that slide of $100,000 at the high end -- and it may be, when our recommendation gets back to the Secretary, that specific -- and I don't want to get there yet, I'm just throwing it out -- specific items in the NIH budget and the CDC budget and other budgets need to be augmented for the purpose of developing these kinds of information guidelines so that we will have something to work from.

Anyway, that's what I'm struggling with, Wylie. At the end of the day, my questions are more through enthusiasm for seeing now a vehicle for solving a fundamental problem that we have not concretized as well as I think we should have.

DR. BURKE: Thanks.

I know David has a comment, and I actually want to say that I think your comments have implications for what we need to hear both from you and Dr. Kang, perhaps as the people who can most represent the payer perspective; i.e., can we define a guideline that really helps a payer.

David, do you want to comment?

DR. ATKINS: Just briefly on the costs of guidelines. There are two components of the cost. One is the cost of finding and distilling the evidence, and that's something that our agency has tried to play a role in, helping to support that part of guidelines through our evidence-based practice centers, and we've

been successful in getting partnerships with NIH institutes and HCFA and other parts of the government. So I think we clearly can have a role in reducing the investment required to look through all the data. Now, that may not be the problem with genetic tests, where the data is thin, but it's still not an insubstantial cost.

The second point I just wanted to make is that there are sort of two components of an explicit evidence-based process. So the first one is just being explicit, and that's an important goal. It doesn't necessarily say you can't make any comments or recommendations in the absence of definitive evidence. You just have to be explicit when your recommendation is based on expert opinion and when it's based on good evidence. The task force, because it's dealing with routine preventive services in healthy people, has a pretty strict standard, and we don't make recommendations based on expert opinion.

But clearly, groups may decide that making no recommendation isn't a viable option and have to use what they can from expert opinion and other considerations. But regardless, that choice should be explicit in the process of developing guidelines.

DR. BURKE: Thanks.

Just so that everybody knows, I have Mike next, then we're going to have Judy and Ed, Barbara, Dr. Kang. That's who I have so far, so raise your hand if anybody else needs to speak.

Mike?

DR. WATSON: I think Muin sort of led me to my comment, which is that it's obvious that people aren't worried about every test that we do.

My test for a baby with Down's syndrome doesn't raise great concerns out there. The things that I think have led to the development of this advisory committee and the task force is that other group of tests which have not reached that stage where they are considered standard of care and around which one can write a guideline.

So I think what the College has done in the past is it had two independent processes. It had a standard of care guidelines-based process, but actually I think some of the greatest hits on our Website, up until about two years ago, were points to consider types of assessments of tests, and that's what we did with ApoE and Alzheimer's disease. It was not a guideline. It was actually a careful assessment of what this test does and doesn't do, and because we didn't think it had reached a point where we could claim a standard of practice, we said here are the questions that need to be resolved for us to even be able to consider whether there is a guideline or standard of care from this test.

That's a piece that's very hard to do, and that's a place where FDA's problems and your committee's problems are going to come from, those translating tests where there isn't a clear guideline. I think there might be room for approaching some of those in a more general way. What do you want to see in a cancer susceptibility type of test? What do you want to see in a psychiatric disease susceptibility test? Let individual tests fall out over time. But if we can step back, think about it a bit more generically perhaps on the front end, and find ways of ensuring that those assessments of things in translation are able to occur also, and not just guidelines as an endpoint.

DR. BURKE: Great.

Judy?

DR. LEWIS: I really support the concept of consensus development, as well as evidence-based practice, because I think if we come at it from both perspectives, then it becomes looking at the scientific evidence, looking at it from an interdisciplinary perspective. As we're doing the consensus development, I want to make sure that we don't forget the true experts, which are the people who are living with the conditions we're talking about, because many times just because the textbook says one thing, that doesn't mean that's what it translates to in terms of the lived experience. Some of the qualitative data can be just as scientific and just as credible as some of the reductionistic data.

I want to make sure that if we're starting to look at that, that we make sure that we include the public broadly defined in terms of diversity, in terms of ethnicity, in terms of gender, in terms of all of the other variables that we need to look at to make sure that as we're putting something together, it's not something that's very narrow and very specific that just affects a very small portion of the population but it's something that has broad applicability, because if we're putting all this money into developing them, you want to make sure that they have that broad applicability. I couldn't agree with Reed more.

Does that surprise you, Reed?

DR. BURKE: Thanks.

Ann?

MS. BOLDT: I think my comments too are very similar to Reed's and Wylie's in terms of who is the target population for these guidelines, and what David had said, how useful are they really. But I think to remind everyone that when we had the insurers and payers talking to us, they really did put out a plea

that they want the consensus from the different professional organizations to provide these guidelines for them, so I think that would be helpful for them. That's what they were saying to us in terms of what they would pay for or not.

But I guess the other thing I was going to ask Mike is do you have a mechanism to track who is actually going to the Website to see who is downloading your guidelines? I mean, do you know if it's insurers? I mean, do you know that information?

DR. WATSON: In fact, that's borderline verboten in the medical Website business to have that level of knowledge about who is hitting your site. We do know what's hit heavily, and those tend to be the more broadly targeted guidelines that are hit quite heavily.

DR. BURKE: Ed?

DR. McCABE: Yes, I just wanted to follow up on Reed's comment. I think that you gave a very rational approach in terms of who should be paying and a very thoughtful approach to that. On the other hand, I think it's very important that we get guidelines out that will help individuals know what they are responsible for telling their patients about. The example I would use right now is expanded newborn screening, where you can purchase an expanded newborn screening test which will supplement most states' programs. A few states, like Massachusetts, may have the complete menu without it, but other states would not.

There are a huge number of suits right now against physicians where the families argue that they were not informed and they have a child with one of those diseases. So the physician is now being sued for not having informed

the family regarding expanded newborn screening.

So in terms of having information out there about what is the efficacy of these tests, what are the responsibilities of physicians and other health professionals in terms of notification of parents regarding these tests, I think it's very important that we get that information out there because ultimately we're putting a burden -- just by the presence of these tests in the marketplace, we're putting a burden on health professionals, and we need to help educate them about what that burden is.

Whenever a health professions organization puts out information in the form of guidelines, there's always this discussion about the burden that one has placed on the health professionals within that field. But we're also learning that if we don't put that information out, the marketplace will initiate a burden on the professional as well.

DR. BURKE: Barbara?

DR. KOENIG: I have two comments. The first is on the production of guidelines and perhaps coming back to the issue of whether we need guidelines on guidelines. In a previous life I actually did a fair amount of work thinking about issues in technology assessment, and in particular the social context of technology assessment, since that's what I do. So in terms of the sociology of guideline development and consensus, even perhaps the Preventive Services Task Force has taken a step forward over traditional consensus conferences in which everyone who thought something was the best thing since sliced bread got together in a room and came to general consensus that this was the best thing since sliced bread, which is the skeptical view of it but which I think in some cases is correct.

So these consensus statements, even if you use them, the data don't always speak for themselves. So you're always going to have some degree of expertise involved. So it seems to me that it's important to keep in the equation the fact that you need to try to -- if we have a guideline on guidelines, that you have to include skeptics whenever you do these kinds of processes. That may seem an obvious point, but I think it's something that we sometimes forget.

Then the second point is to look at the big issue of the whole role of what's going to happen to guidelines in general in practice. I was part of the Hastings Center Project, which produced a book. Actually, this was funded by AHRQ in a previous acronym for the organization. But it was a book called "Getting Doctors to Listen," which I think was an unfortunate title. But it's on the issue of what happens to the guidelines If we have sort of a whole social context at the moment that is reifying ideas of choice and patients making free choice and having everything available, I think we're also not recognizing that there are some tensions between the idea of professional practice guidelines and this other choice discourse that's going on broadly in our society.

DR. BURKE: It seems to me your comments point very much to a critical evaluation of what's a good guidelines process and what's not.

Dr. Kang, I think you're next.

DR. KANG: Wylie, I'm not even sure I know where to start here. I think the issue of who is the target audience is going to be very important, and I was kind of interested in both the presentations that people have been talking about clinicians, patients, et cetera, as the target audience, but the payer actually being the target audience has been missing. I guess David's presentation got the

closest. I think when you were saying policymakers, you're also referring to payers.

I think that if access is going to be a major concern of ours, that I would actually encourage you all to consider that the main target audience may in fact be the payer here, and that without reimbursement for these tests, we're not going to have access. So that's one comment in terms of the target audience.

Let me put on my payer hat. I'm going to take off my CLIA regulatory hat. I find myself here in two roles. On guidelines here -- and I hate to gore people's oxen, and I don't know exactly where this notion that payers actually look closely towards professional guidelines. Interestingly enough, there's a recent Stanford study I have some preliminary data from where they actually interviewed some 300-odd medical directors from managed care plans and asked them what are they using to make their coverage decisions, and professional guidelines developed by professional societies was 2 percent. In fact, the overwhelming majority of coverage decisions nowadays are being made on technology assessments being developed under strict evidence-based rules.

I think the reason why is what we've learned over time, that the professionally developed guidelines based on consensus or expert opinion always overestimate the size of the benefit. The reason why, obviously -- I mean, there's a whole list of reasons, but there's a variety of biases. The biases can be one of ownership, economics, pride, whatever it is, because frequently the experts are also advocates of what they're talking about.

Second is the lack of controls, and because of the lack of controls there's this issue of bias. There's frequently loss to follow-up. In the experts' eyes,

usually they see the successes that come in, but the failures never follow up.

Related to that is the issue of we experts frequently underestimate the impact of false-negatives and false-positives because they actually don't, again, deal with those. They usually see the true positives and true negatives.

So there's a whole bunch of issues. I have yet to actually see a place where expert opinion actually underestimated the actual benefit when it came to a properly done controlled trial. All the biases are always in the direction of overestimating. I think that the payers are moving increasingly more towards strict evidence-based rules and around technology assessments, or, as David is suggesting, to be explicit when there is a lack or absence of evidence, then call it a professionally developed consensus and understand it for what it is.

The division there may be, in fact, that if there is good evidence for, then we ought to be promoting. That's a translation issue. We ought to be going out there and saying let's do it. But if it is more of a consensus because of lack of evidence, then I think there's a question about, well, maybe what we ought to do is cover it and make it available, but it shouldn't necessarily be promoted. I think we have to wrestle with that a little bit, and there's a very important distinction there.

I guess the last comment is on the issue of who pays for these technology assessments. Insurers are increasingly paying for these, largely to help guide their coverage determinations. As an example, and I think this is what David was referring to, HCFA is paying the Agency for Healthcare Research and Quality anywhere from $1 million to $1.5 million a year for the purchase of technology assessments to use for Medicare coverage decisions. We make them

freely available, and there is a technology assessment community out there.

I do think, though, that there is still not enough money. I mean, when you think about it, if it's $100,000 a pop, that's maybe 15 technology assessments. I would encourage the committee to think through a little bit about maybe who should pay for this. I know many insurers take the posture on the commercial side that they're being taxed and that this kind of information is a public good, and so the reality is that it ought to come out of the research budgets -- i.e., NIH. A lot of the commercial insurers are taking that posture, and also the business community is taking that approach, General Motors. They say, look, we pay taxes, this is a public good that should be part of the research agenda, the so-called translation research or whatever we've been talking about.

So I think that's an issue which you all have to wrestle with.

Sorry. I think I kind of got everything out.

DR. BURKE: I think that's very helpful. You've offered us an important distinction. I guess I would say, for the purpose of what we're trying to address in this committee, both that element of "guideline development" that you're calling technology assessment, basically strict adherence to certain standards of evidence, and that aspect of guidelines that we're calling a professional consensus development, I think in any points to consider we should consider both those processes and perhaps give some thought to which is more useful or appropriate for different purposes, because, for example, the professional consensus guidance might be very useful in providing information to practitioners and providers, while we recognize that a stricter standard of evidence might be used in a payer decision.

It seems to me the issue that's coming up around who pays is also an issue that Muin mentioned in passing earlier, and that is if there is substantial cost to good information, and we agree that good information is needed, it's not only who pays, it's also what makes a guideline, what does and what doesn't.

I have Michele, Muin, Judy.

Michele?

DR. LLOYD-PURYEAR: Okay. I agree with the need to keep the target audience in mind. However, I would broaden the target audience to include everyone that we've talked about, both the payer, the health care professional, and the patient, the public. I think that really needs to be kept in mind.

I do think the core of this -- I agree with Jeff -- needs to be evidence-based, but I think as far as the consensus development process, I think that's a very important part of the process of developing a guideline. Even though it is based on evidence-based criteria, I think the process is very, very important. I remember what happened with mammography and what an uproar that was, that the strict science, if you remember, gave very contradictory guidelines to what was actually happening in practice, what the public was willing to accept in practice. In fact, even though those guidelines were based on scientific evidence, they were not accepted.

So I think you do need to have a core that distills out the science, but I think you need to then also take other considerations into account when you develop your final guidelines.

DR. BURKE: It does seem to me, just to follow up on that, if

we're clear on the distinction, we can see those two processes as related and even different steps in an overall guidelines process. So I think that clarification is helpful for our conversation.

Muin?

DR. KHOURY: I'd like to revisit this guideline issue, and I'd like to thank you for wonderful comments here. It opened up a number of issues in my mind.

Think about where we are with respect to genetic tests and the parameters, from analytical validity, clinical validity, clinical utility. Whoever does those guidelines is going to be looking at each one of these components separately. I think the payers ultimately are worried about clinical utility.

DR. KANG: And more.

DR. KHOURY: And more than that. Whereas some of the professional organizations may be worried about clinical validity. A case in point -- and I don't want to be critical to the ACMG here -- is the recent Factor V Leiden recommendations that the group has come up with, which seem to be driven primarily by clinical validity-type parameters. Wayne Grody and others who put together these guidelines were driven primarily by the fact that there is an association between Factor V Leiden and increased risk of venous thrombosis, especially if you have a family history, especially if you take oral contraceptives.

Now, the people who want to adopt these guidelines in the absence of what you can do with that information -- i.e., reducing the burden of risk or putting people on lifelong oral anticoagulation to reduce the burden of disease -- of course, they're going to say so what? We know there is an association -- i.e., good

clinical validity -- but the clinical utility still needs to be defined.

So I'm not being critical of either role here. It's just that when we approach guidelines, we need to know what we're talking about. I think keeping those data elements in mind, and the spectrum, from the analytic aspects of the lab to eventually the clinical outcomes, and the ethical, legal, and social type data are very important and will be driving the wagon at the end of the day.

DR. BURKE: I have Judy, Ed, and Reed.

I just want to interject that we've said in this discussion that one of the things we want to clarify is what makes a good guideline, and it's becoming very, very clear that the first statement in a good guideline is a statement that states exactly what this guideline intended to do and who it was intended to help.

Judy?

DR. LEWIS: I want to follow up on Jeff's comments from a few minutes ago when we were talking to the insurers. When they did their presentation to us, one of the things that became clear was, whether or not something was a covered benefit, that there really needed to be some evidence of efficacy. FDA approval might be important, looking at what Medicare/Medicaid was reimbursing might be important.

But then the other thing that became eminently clear to me was that it wasn't just the insurers, it was the purchasers of health insurance, and that that's another group that we need to consider in terms of part of our audience, because an insurance company will put together many different kinds of benefit packages, and then the employer or the purchaser of insurance is the one who chooses which package or which coverage their employees get.

So General Motors, IBM, the Commonwealth of Virginia, whoever it is plays a really important part in determining what the coverage issues are. So going to them to find out what are the key things that make them determine whether or not -- and coverage for infertility drugs and infertility treatment has been a classic example, where there are some states that mandate it and some states that don't, and plans become different.

So I think we really need to pay attention to that group as well as others.

DR. BURKE: Let's see. Ed is next.

DR. McCABE: I wanted to really address this to Mike, but perhaps David would also comment as well. It has to do with what about when different groups develop conflicting guidelines. What's the process for resolving the conflicts between conflicting guideline recommendations?

DR. BURKE: Do you want to comment on that, Mike, now?

DR. WATSON: I can. It's actually mission impossible. I think it's inherent in that consensus process that if you're talking to the appropriate groups of people who have interest in the delivery or receipt of that test, that you have addressed many of those issues in the development of the guideline. Many people come from quite varied places within the delivery of the service, and that's where we end up getting these conflicts, and it's often because they didn't include another group of people who had a strong interest in that test. Once they've done it, I think you're trapped.

As there are biases within our professional community, there are also biases within the payer community. Unfortunately, health care services is a

business, and it's a budget-neutral system. If I want money for a test I think is valid, it's got to come from somebody else who may be getting that money now. So it becomes quite difficult, and I think it's caused a lot of problems in genetics to have these conflicting statements where nothing is resolved.

DR. BURKE: David?

DR. ATKINS: We get asked about that a lot, because often our guidelines are -- we call them recommendations, not guidelines -- are more conservative than others. I usually make the point that sometimes it's a debate about the evidence, that our rules for evaluating individual evidence might be more rigorous or more conservative than others. But more often it's really the difference in perspective.

I wanted to pick up Muin's point. It depends on what you think is the relevant outcome, and I think that's where the coverage decisions get very difficult. For patients, information alone may be a relevant outcome. If something can give them information, and the information is valid, they may think they deserve that, whether it's going to improve their health or not. A payer would probably worry about that, because if we pay for everything to give that patient information, we could be spending a lot of money and not necessarily improving health, and that's going to obviously lead you to a more conservative standard.

So I think up front, a guideline ought to be clear about not just what it's addressing but what they think a relevant outcome is, and then what they think adequate evidence to prove that outcome is. Often, if you understand that or the perspective that groups are bringing, the difference in the actual guidelines is pretty self-evident.

DR. McCABE: Part of my reason for asking the question was somewhat rhetorical. I mean, I know that there will be these conflicts. But also, if the SACGT is recommending the development of guidelines, is developing a guideline on guidelines, as it were, should part of that be a process for trying to resolve conflict, to the extent possible, to identify what the issues are in terms of why the conflict exists and trying to at least comment on that conflict?

DR. BURKE: Thanks.

Reed, and then Jeff.

DR. TUCKSON: Fortunately, Judy made the point. I wanted to add to Jeff's list, as he said be explicit as a target being the health care plans. But I do think the employers really, really need to be a major defined target, because the decisionmaking, again, that they have to make with their employees about benefit packages is just absolutely essential. That, then, derives this notion of cost, which needs to be very much in this equation.

I was sad that we're only now getting to some of the cost issues. I understand it's difficult, and in one of the slides that we saw, cost was just starting to be able to be gotten to. We have to be very explicit about what this stuff costs and who bears that cost. Otherwise I think we're going to be just not useful.

Finally, I think Jeff's point is very important regarding this notion of the clinical evidence. The key word that I hope we would underscore is when we don't have clear evidence that makes it clear and we have to resort to professional consensus, then that needs to be very explicit, that there is not evidence, and therefore, dear patient, in the context of a patient-physician relationship, you need to know that there is no evidence that's clear, there's only

the consensus of judgment. Thereby, here is how you should use that information in making your decisions.

I keep coming back, then, to Judy's committee, and I'm really beginning to see, Judy, that this effort, this work is really, I think, in my mind, focusing a great deal of what your committee really has to be able to do, to say to people here's what you need to know about what it costs, here's what you need to know about how to make these choices and decisions, when it's clear and when it isn't, and so forth and so on.

DR. BURKE: So your point is clarity about that distinction is as important for the consumer as it is for the payer.

DR. TUCKSON: Precisely right.

DR. LEWIS: Can I just follow up on what he said?

DR. BURKE: Sure.

DR. LEWIS: We're really in agreement today. I'll agree with everything you say as long as you change it from patient-physician to patient-provider or patient-clinician, because I think we need to keep remembering that patients are getting their care from lots of folks.

DR. TUCKSON: No question. That is a very friendly amendment.

(Laughter.)

DR. BURKE: Jeff is next.

DR. KANG: Maybe this will be more summary. This issue that Mike raised and I think people have confirmed is the issue in terms of the difference between guidelines that you may see. I frequently find that if you look

at the perspectives from which they developed, a lot of times it does explain the differences. I think in the genetic testing, there's kind of two key, crucial perspectives that we're going to have to wrestle with.

One is this, I guess -- I don't know who said it, but the issue of the value of information to the patient irrespective of any impact on health outcome, versus health outcomes, what the payer presumably might be interested in. Most payers now, in their language, their contractual language with employers, really talk about health outcomes. So that's an issue that I think is going to be very tricky for genetic testing in particular.

The second thing, really on the cost side, is whose cost? The payer is interested in their narrow cost and can you save some downstream costs, maybe one or two years. The patient is interested, or society may be interested in societal costs, and that gets you to a completely different decisionmaking framework also, and I think you need to be explicit when you develop those guidelines. You have to be very explicit about what perspective you're bringing in. One is that information is valuable, and the second is whose cost.

DR. BURKE: Okay, thanks.

I have Elliott and Muin.

MR. HILLBACK: I found this sort of interesting in the last few minutes because we seem to be going down the track of creating a rather complex process. Most of these tests are at the bottom of the food chain in the sense of the number of times they're done in a year, and yet we're now talking about practice guidelines test by test, type of test by type of test for mostly rare tests.

DR. BURKE: I think we have acknowledged that on the list of

things in the points to consider is what tests need a guideline.

MR. HILLBACK: Okay, because we're talking about a similar bottleneck to what we've always sort of picked on FDA about versus trying to figure out how we get around that bottleneck. I think we're almost adding to it right now by trying to do some overkill. I don't know the answer. It just seems like an interesting track we're heading down.

DR. BURKE: I want to actually also clarify that we are not talking about regulatory action now. We are only talking about a points to consider, but my understanding is that the points to consider or the guideline for guidelines, even the end result of that points to consider, some guidelines process, is not a regulatory process, per se.

MR. HILLBACK: No, I wasn't thinking regulatory at all. I was thinking of the payers being the non-government payers, and if we in fact create a de facto set of regulations, not government regulations but the way things are done, that until you have clinical practice guidelines for a test, no one will pay for it, we've now created a new set of barriers instead of reduced the barriers.

DR. BURKE: And it seems to me that point should be in the points to consider.

MR. HILLBACK: And we're missing both of our patient representatives right now too, so it's a difficult time. I don't think we're hearing that voice maybe as much as we need to.

DR. BURKE: Good point.

Ann?

MS. BOLDT: Just getting back to a comment Ed made in terms

of the burden that guidelines place on health professionals, I guess one thing that David just said about recommendations versus guidelines, are there different legal ramifications depending on what we call them?

DR. WATSON: Ask the judge.

DR. ATKINS: Dave is smiling at me. It's political ramifications from the standpoint of our agency. It reminds me that in "Ghostbusters," there's a scene where Sigourney Weaver is possessed and she's trying to seduce Bill Murray, and he says, "Sorry, we have very strict rules about this, not to get involved with our clients." And then she comes out anyway, and he says, "Well, actually, they're not rules. They're more guidelines."

(Laughter.)

DR. BURKE: Do you have a comment, David?

DR. LANIER: Yes. I think many people make a distinction between standards and guidelines, and I think if there's such strong evidence that everyone should be doing it and it's considered a standard, usually in a court of law that is pretty well held up. Guidelines is a much murkier territory. I think many times what happens is that if a guideline is written, that may be considered a standard in a court of law, but if it's not written, it may not. That's the way it plays out sometimes. But it can work the other way, as well. So it's very murky territory.

DR. BURKE: I have Muin and then Reed.

DR. KHOURY: I don't want to beat a dead horse, but I want to come back to this distinction between clinical validity and clinical utility and pose a question to the group. Is there valuable clinical utility information and clinical

validity information, and can it be quantifiable?

To me, if there is research to be done in that area, and probably there is tons of research being done -- I mean, think about the early days of BRCA1 testing, where women were told that you can have either a 50/50 chance of having the BRCA1 or be at zero versus 100, and if you carry that mutation you have a lifelong risk, a 50 percent risk of breast cancer and 15 to 30 percent risk of ovarian cancer.

What is the utility of that information? Can it be measured? Can it be quantified? And then eventually, can it be valued and paid for? So to me, clinical validity questions -- I mean, knowing those numbers immediately spills over into utility or lack thereof, and I just want to explore that with the group because it obviously needs exploration.

DR. BURKE: Reed, Mike, and Joann.

DR. TUCKSON: Just real briefly, Elliott's comment just really made me think. I want to make sure that -- it sort of left the impression somehow that -- and I'm not sure if I misheard it, but that by pushing very hard to give people information about how to think through the cost and other implications of these new tests as they make decisions about their benefit packages, as they make decisions about their co-pays, as they make decisions that will affect their money, I don't see that as erecting a barrier. I would not want to think that because the patient advocate's voice isn't here, that somehow or another there's a train trying to run over those interests.

I think it's just the opposite. It's saying to people that you have to respect people who have to make decisions about money, about choices, and there

are implications to all these things. I would hope that it could be perceived that the more information people have and the best guidance they have of working through where there is certainty and guidance about working through uncertainty is in the person's interest, not some barrier that is being erected. I just want to make sure we're clear on this.

MR. HILLBACK: Let me try to clarify. What I heard was if there isn't a clear clinical practice defined, then we're not going to pay for it. So until you do all this work, it's in the great unwashed of not reimbursable, and that is a little bit where we were with FDA, which is if you can't show me safety and efficacy -- i.e., clinical validity -- you can't do the test. One of the things we're trying to avoid here is either delay in having the test available or accessible.

Now, it's a problem in that we all have trouble getting a lot of these tests reimbursed today, so I don't think I have the solution. But what it sounded like anyway, and maybe I misheard it, was that in an effort to say we're going to be able to define this, until you can define it, why would I want to pay for it?

DR. BURKE: I actually want to clarify what I think the discussion said, and I'll let Jeff do it as well. I think what we heard from the payer perspective was payers are going to be much more interested in paying something when the outcome benefit is proven, not when a guideline exists, when an outcome benefit is proven. Sometimes the proof is so evident, you don't need a guideline.

Do you want to comment on that?

MR. HILLBACK: But are you back to utility?

DR. BURKE: Utility, yes, and outcome.

Do you want to comment more on that, Jeff?

DR. KANG: Yes, I think that's right, and I was just trying to explain the current reality, for lack of a better word. Now, if SACGT wants to try to engage in some rules of evidence around how to evaluate that, I think that's reasonable.

I think the point is that where we are now, Elliott, is you wouldn't want to put that in the FDA process, because if you included that in the FDA process, then you couldn't even sell to the private market. So the point is that you can get on the market, and people can pay out of pocket or whatever sort of thing. Now the question really turns to is this an insurance benefit and, if so, should it be covered, et cetera, et cetera, in the meantime?

So I don't think our intent here is to actually create this so that you can't get paid. I guess the question really is, is there some guidance around guidance technology assessments or whatever to help payers think about how to pay?

DR. BURKE: If I could just interject, and then I'll let Reed also comment. It does seem to me that what we heard and would be reasonable to incorporate into points to consider is the kinds of things that go through a payer's mind when the payer is deciding what to pay for. One of the things I'd take from that if I were a test developer is, guidelines or no guidelines, if I had evidence on utility, I'd want to really put that front and center, which I think is a somewhat separate issue.

DR. TUCKSON: Just a very small point also. I want the committee to understand that where the world is moving, and I know that at least

where we are, at least in terms of my view of the world, it is much more towards people making the choices about the kinds of things they want covered. If you want to know whether your baby has blue eyes, that's important to you and you want your health plan to do that up front, then that's a decision that you can make, and you can make a choice to pay for that as part of what you want to do.

At the end of the day, it's increasingly employers and people making choices about what ought to be in and what ought not be in, and how you keep it in. So please keep in mind how important it is for the next coming years to give this information to people so that they make rational choices. Don't think of it only as the health plan standing as the blocker for whether something gets in or not.

DR. BURKE: I've got Mike, Joann, and Judy.

DR. LEWIS: I just wanted to respond to Elliott's point, if I could.

DR. BURKE: Okay, go ahead.

DR. LEWIS: Just in terms of the fact that the patient advocates aren't here, I'd argue that all of us are here because, in the long run, we're patient advocates. So I wouldn't necessarily just say because Mary and Pat aren't here that we don't have patient advocate voices at the table.

But I think the issue is of looking at pretty much what Reed was saying, the people who are paying for insurance, looking at what the value is. To me, some of the issues are short-term and long-term issues, and part of the issues that we hear from the payers are that people change insurance plans so often that if it's a downstream benefit, for them to cover it when the client is under a

different insurance plan five years from now or 20 years from now, when the payoff comes -- so I think looking at infrastructure issues in the insurance and in the payer system, I don't know that we can take that on here and that we're going to get universal health coverage.

But the issue to me is one of employers are with people for the longer haul, perhaps, and so getting purchasers at the table is going to help to get that longer-term perspective and that lifelong perspective. So paying attention to the fact that there are lots of people out there -- I just wanted to take issue with that one point.

DR. BURKE: Thanks.

David, did you have a comment or a response to this discussion?

DR. ATKINS: I'll wait my turn.

DR. BURKE: Mike?

DR. WATSON: Well, Judith said very much of what I was about to say, which is that there is this mix of sort of immediate benefit and public health benefit, and I think prevention is where we take the public health benefit, and diagnosis and sick people is where we're taking that immediate individual benefit. The payer's perspective and the system itself often isn't the same as the provider's perspective. It's clear that many insurers don't perceive them as receiving the benefit of prevention because of the pace at which people flow through the health plans, and that's a serious constraint.

I think it's also worthwhile, though, to get a better sense of what it really costs to deliver genetic services. There are some decent models out there. Kaiser has sort of a complete program in-house. It has certain things that don't

allow you to extrapolate the figures out to all other kinds of payment, but within the Kaiser system all genetic services are 40 cents per member per month. You lay that 40 cents per member per month up against the $100,000 guideline and I think it helps you get a perspective that this entire range -- because we are talking about lots of rare diseases that small proportions of the population take advantage of -- that overall cost is probably not as frightening as people had thought it might be.

DR. BURKE: Thanks.

Joann, and then David.

DR. BOUGHMAN: I'm going to change speeds here completely for just one moment. In the spirit of what Tony Holtzman said a little bit earlier, that this committee has been very successful in moving some things forward, recognizing that we are a kind of consensus group bringing many, many different perspectives to the table, and also recognizing our immediate audience is, in fact, the Secretary, and our charge is to bring together not just the ideas and comments of the folks around this table but the general public as well; Wylie, I'm going to ask you if you could re-crystallize for us where the ideas and the question beyond exploring the approaches on the page that I'm looking at in our books, exploring approaches to the development of clinical guidelines, what you actually were bringing to the table for this group to accomplish or assign by the end of the day.

DR. BURKE: This is a great segue. I'm going to let David comment, and then I will respond to Joann.

DR. ATKINS: I just wanted to comment because I'm going to have to step out and head to another commitment. But it seems that there are two components here. One is developing a framework for looking at different

guidelines and explaining how they were developed, deciding which ones might be more or less applicable, and perhaps resolving the differences. I think we already have a lot of that work in place.

We support the National Guideline Clearinghouse, which has a sort of standardized way of looking at these components, with an aim of giving people help in looking at conflicting guidelines and deciding which guidelines most fit with their needs, their practice, their patient population, or their rules for evidence. I think payers are going to choose certain features of guidelines, and those might be different from what some professionals or patients may use.

What is missing from that are some of the specific issues relevant to genetics and some of the scientific issues that go into that formula, and I think the framework of analytic validity and clinical validity and utility has been a very helpful one. So to help push that forward so that both patients and clinicians can understand what is established and what is not established about a new test in terms of what it can do, what it can't do, and what we're not sure but think it might be able to do would be helpful.

DR. BURKE: Thanks. The two comments are a perfect segue to get back to how we started this conversation. We had some questions for discussion that really had to do with asking our two expert presenters, and the group as well, what are the characteristics that clinicians and consumers should look for in a clinical practice guideline. To recap just very briefly where I think our conversation has taken us, the first place it took us was let's think about all the end users of a guideline. So a good guideline ought to state its purpose, it ought to state who the guideline is directed to and what kinds of actions it's intended to

guide; that is, what are the relevant outcomes that this particular guideline is considering.

To the extent that it discusses the composition of the guidelines group, it ought to have rationale for why a particular group was brought together. I think there's agreement that methods for identifying and evaluating evidence are important, and that there particularly needs to be clarity about what kinds of evidence thresholds were used in coming to conclusions. So as a guidelines process develops recommendations, to what extent were evidence-based thresholds required to be met before a recommendation would be made, and in addition to evidence on efficacy, to what extent was evidence on effectiveness taken into account or other kinds of parameters, such as social outcomes, such as cost, and in terms of cost, whose cost, et cetera.

So I think we've had a lot of discussion about what constitutes a good guideline. We've introduced some really key issues for genetics. One is that, indeed, there are conflicting guidelines, and in genetics there may be a very important discussion about the intrinsic value of information. So it's important that a guideline needs to be clear about whether it's looking at the outcome as having information or whether it's looking at the outcome as improving a particular health measure.

As we look at guidelines, it's very important to distinguish, it follows from all of this, the difference between an evidence-driven decision about action or an evidence-driven recommendation from a consensus-driven recommendation.

So all of this suggests to me that the answer to the first question of

the last two questions -- this is under number 6 on the page "Exploring Approaches." The first question is, is there a need for a points to consider document that would set forth general procedural and substantive content recommendations for guidelines development? I think this discussion trends toward a yes answer to that question. We should confirm that in our last half-hour of discussion.

The other question, which is really the concrete question that Joann's comment brings us to, is would this be an appropriate role for SACGT? If it is an appropriate role for SACGT, I think we need to ask ourselves very concretely how do we start accomplishing that? The first question, it would seem to me, is does it obviously belong to one of our subcommittees, or do we need to create another subcommittee to do that?

Open for discussion. Judy is the first commenter.

DR. LEWIS: One of the things I'd like to mention is that I think the issue of is it appropriate for SACGT would be not to take on the whole guideline world, because there are guidelines out there for everything, for anything from the consensus guidelines to the AHRQ guidelines to professional association guidelines. What we would need to focus on is is there anything special about genetics that would influence guideline development differently than any of the other processes that are out there.

So to me, the piece that would be specific for us would be the unique characteristics of genetic medicine, genetic health care.

DR. BURKE: David?

DR. LANIER: One of the things that occurs to me is that we do

have in the record this report that was written by the Institute of Medicine. I guess it's been maybe 10 years ago that they initially developed it. I certainly would agree that having some points to consider we might consider developing ourselves. But it seems to me that a group such as the Institute of Medicine could also take the work that they did and then see how that applies specifically to the realm of genetics, and that would be a relatively straightforward task for them given the background work that they've already accomplished.

DR. BURKE: So both of these comments are saying let's try real hard not to invent the wheel. But it does seem to me that there's been some discussion that suggests that there are some particular issues to genetics. Intrinsic value of information may be the potential for social harms from labeling being different, just to name a couple, where perhaps it's worth looking at existing comment on this, starting with IOM and then figuring out what else we should consider.

Other comments?

Ed?

DR. McCABE: Maybe I misunderstood, but if you were suggesting that the IOM take this forward, that's a fairly formal process with making a recommendation to them. Then my understanding is that the timeline on any kind of IOM recommendation is a minimum of a year from the time they accept the charge, just to put in perspective the timeframe. So while I agree it would be wonderful to have a group like the IOM do this, it could be a significant horizon before it was reached.

DR. BURKE: I think you were suggesting that we look at what

the IOM already recommended as a starting point?

DR. LANIER: I think instead of beginning completely new, that we at least look at the work that they have done, if there was a possibility of them taking this on, even as a kind of an addition to their original report, which might be a shorter timeline than what they did before. I've worked with the IOM and understand the limitations.

DR. McCABE: The other thing that Sarah points out is that, just in terms of who we are and who we report to, it would be very difficult, probably impossible within our protocol, to make recommendations to the IOM.

DR. BURKE: But we could use what's already been done by the IOM to inform our process.

Muin, and then Mike.

DR. KHOURY: I think this committee has already done a lot of work in this direction. I don't think it's a major leap to go into this next phase. It's really taking what you all have already done based on the oversight process, the data process, and the pre- and postmarket, and then put the few points that you put together. Of course, you look at what other groups have done and don't reinvent the wheel but just add the few additional tidbits that are specific to genetics, and this can be done fairly quickly.

I agree with Ed that anything that involves IOM is years away rather than months or weeks.

DR. BURKE: Mike?

DR. WATSON: I would actually add not just that which is unique about genetics but that which might be unique about what you recommend

that they do to those of us who do genetics. I think you're going to allow this translational step to move forward as a service while we acquire information. I see no linkage to ensuring any level of payment, not even a non-profit level of being reimbursed for those tests if that isn't built into the system on the payment side as well.

I sort of laughed earlier when Ed commented on FDA and HCFA doing this jointly. It sounded like the ultimate unholy alliance. But in reality, I think one is the regulatory system and the other is the de facto regulatory system. If you don't get paid nowadays, you don't deliver the service, and ensuring that we have a way to deliver these tests as they're translating in this clinical investigative stage, which may not necessarily be funded under NIH grants, there are clear mechanisms where reimbursement to those providing the services, even at a non-profit level, will support their access.

DR. BURKE: Reed?

DR. TUCKSON: As we think about our charge, and I'm trying to think about these questions here, we can decide to highlight to the Secretary the importance of his doing a review of the adequacy of the research base and its translational relationships between the NIH and CDC and AHRQ and so forth, that makes the foundation material available for good guidelines to be developed by the multiple constituencies that ought to have it, and that we would want to ensure that that is adequately funded and adequately coordinated.

Our other option, of course, would be to try to make an opinion ourselves about that adequacy. I think that may be difficult with the time and resources that we have. So we might just want to say, at least as a first minimal

step, that we would urge that that occur and that that review occur by him and his leaders, with the clear emphasis that our bias is that we're ultimately hoping that the raw material and its coordination throughout the effective translation agencies is available in adequate supply to those who need it to make the decisions.

Secondly, I hope that we would encourage -- we can either choose again to encourage the Secretary to use the vast resources that really are at his disposal to help educate patients and other constituencies about how to think through this stuff in terms of making the choices they need to make about cost and benefit and those sorts of things; or we could, in fact, attempt to provide some very specific input on what that education ought to look like and what those materials ought to be. I'm not sure what the answer is, but I at least want to get those two points out there.

DR. BURKE: Thanks.

Ed?

DR. McCABE: Just to begin to wrap this up, I'll put forward a point for discussion. It seems like we've come a long way and we have some ideas about what we ought to be doing, at least in considering guidelines. The data work group would seem to be the appropriate group to take this on, if they were willing to do so. Wylie is the chair of that work group. So perhaps we could discuss now very specifically whether or not the data work group would be willing to take this on and what kind of a timeline there might be, and inform us about the other tasks that you already have.

DR. BURKE: I won't speak for the people involved. I'll let others involved in the data group comment. I will say that to the extent that we

define the points to consider, to the extent that we've defined how the points to consider would really emphasize how people really use evidence, I think there's a natural connection. To the extent that guidelines are educational activities, I would think that there may be some room for us to work together with the education committee. But it would make sense for us to be involved.

Let me have others involved in the data committee comment on that. Muin, Elliott, anybody else.

DR. LEWIS: Could I just make a comment that I think there's also a natural interface with the access group, because it's stuff that's affecting patients, and it's affecting payers. So if it goes to the data group, I'd be happy to liaison and be involved so that we can have the perspectives.

You know, it may well be that it's cost-cutting and that it needs to have representatives from all the groups.

DR. BURKE: Thanks.

Muin?

DR. KHOURY: I don't have any bias. Obviously, this is an SACGT-wide effort, and I agree with Wylie that the natural place where it falls, because this is data driven or data dependent -- I mean, we can take a crack at it and then share it with the whole group. That would be my preference, rather than reconstitute another group that's cross-cutting and dismantle the existing groups.

DR. BURKE: It sounds pretty clear that any work done by the data committee with liaison should be sort of preliminary and brought back to the committee.

Ann?

MS. BOLDT: I would also include representatives from different professional organizations for this group, because we don't want to reinvent the wheel and there are groups that have already established these guidelines, this process.

DR. BURKE: And I think we heard that we really need to make an effort to get material from IOM and perhaps other sources to be really clear about what's already out there in terms of guidelines for guidelines.

Barbara, did you have a comment?

DR. KOENIG: Yes. I just want to generally endorse the idea of doing this for the reason that I think implicit in the way that we have developed our ideas about what the role of FDA should be and what the role of CLIA should be has always been this notion that the guidelines are an important piece of that picture, and the use of data. So I think if we want this to be an integrated system, then we do have the responsibility to at least think through how it interacts with those other things.

DR. BURKE: Ed?

DR. McCABE: I just wanted to ask NHGRI, I know there's been ELSI funding, and whether there had been any projects -- I'm not sure if you know or have that portfolio memorized, but whether there have been any projects that would have come out of the ELSI grant funding that would bear on this.

DR. GUTTMACHER: Ed, I don't think there are any that are going to have a huge impact on this. I think there are some that might be good background information, but I don't think there are any that are really going to drive the discussion.

DR. McCABE: Thank you.

One other point of clarification, and that was Reed's point about a letter to the Secretary. Perhaps you could clarify this, Reed, in terms of when in the process you thought that would be appropriate.

DR. TUCKSON: I don't know, and I think we ought to roll it into the work that's ongoing and then decide.

DR. McCABE: So you were not recommending it precipitously.

DR. TUCKSON: No, no. Thank you for clarifying that. No.

DR. BURKE: I know that later today we'll be bringing a discussion about a possible meeting of the data group in August, and it might be that we should think about whether we can continue this discussion at that meeting.

Any other comments?

DR. McCABE: Would you see that as the data work group, or perhaps, as we've done before, drawing on some resources outside of this committee? That was certainly helpful in the past.

DR. BURKE: Yes. I know we'll get into discussion later, but one of the reasons why I think it might be reasonable to at least have some ongoing discussion at that meeting is that that meeting, which is intended to discuss the template and ongoing data collection, very much wants to include all the interested parties. So I think we should think it through, but I think we're going to find that the interested parties are pretty similar for these two tasks.

DR. McCABE: Okay. With that, I think we have some direction here. I want to thank everyone for your presentations today that have helped us.

Thank you, Wylie.

What I'm going to do now is take our 15-minute break 15 minutes early, but it will still be a 15-minute break. So we will reconvene at 3:00. I'm hoping that we will have some time left at the end of the day by doing this that we can then address the letter that we were instructed to send to Secretary Thompson regarding recommendations against genetic discrimination. So that's my goal in doing this. We will reconvene at 3:00.

(Recess.)

DR. McCABE: Why don't we begin to reconvene, please. We probably are not going to take up the discrimination letter this afternoon because of some key people who are not here, just so that you know that. We may have some discussion of that at the end of the afternoon. We will probably not make any decisions today regarding the letter to Secretary Thompson.

Next we're going to have an update on the development of a provider summary template by Dr. Wylie Burke. Another effort we've made as a committee to ensure the appropriate use of genetic tests is to articulate what we consider to be the basic information that health professionals should have about a genetic test. For our last meeting we reviewed public comments we received about the content, feasibility, and value of a proposed framework for presenting summary information on genetic tests. Overall, the comments were supportive of the goal of educating health professionals on genetic tests and their appropriate uses and agreed that the data elements outlined in the framework were key information items that health professionals should have knowledge of when ordering a genetic test.

Some commenters raised concerns regarding the burden on laboratories as the source of information for the majority of data elements. We agreed to continue discussions of what we are now calling provider test summaries. Since our last meeting, the data work group has continued to work out the format for the summaries, and to some degree their thinking has evolved. For this discussion, please refer to the document at Tab 5 in your briefing book.

I will now again turn to Dr. Burke for an update on the data work group's efforts regarding the provider summaries.

Dr. Burke.

DR. BURKE: Thank you. I want to mention that I'm going to talk about the provider summary template concept and report what the data team has done on that process, but my conversation will lead very quickly to what we need to do next, and it's very possible that we may want to include in this same discussion something that's scheduled for tomorrow, which is our proposal for a stakeholder meeting tomorrow. The conversation will happen tomorrow, and the proposal for the meeting is in August.

The reason why these issues are connected is that I think we can think about three things that the data team has been involved in, all of which are strongly interrelated. The first is the template, what we're now calling the template, which is the guide for premarket review. The data team worked on it first, and now the work is being taken over by FDA and other participants, and it's obviously going along very well.

Another piece is what we're referring to as postmarket data collection, and that picks right up from the premarket template review, because

what happens is a test has to have a certain amount of information in order to be reviewed and approved as a test, but we know that that information is almost always incomplete. So we have a tremendous interest in ongoing data collection which will help to refine what we know and support potential additional uses of a test. So that's a very important concern.

One of the conclusions we've come to is that there isn't a simple different list for premarket and postmarket data. That is, there might be additional data elements or additional clarity of the data that emerges in postmarket, but the thinking is all the same.

Parallel to that process and getting to the focus of this discussion is the fact that in addition to information for premarket review and some concept of what information you want to keep gathering on a test, there is the concept of disseminating that information to test users, to health care providers who order tests, and to patients who would be considering the test and then ultimately getting the results of the test.

As you know, we originally talked about a template for that purpose. Now we're reserving the term "template" for premarket review. The data team has discussed what we're now calling the provider summary and has come to two notable conclusions or two pieces of information to tell you about that are different from our last discussion.

The first was that we've tentatively come to the conclusion that it's useful to present the provider summary in a question and answer format. If we, as a committee, agree that that's the right way to go, that has the advantage that we can create basically a list of questions that we would expect always to have

an answer to for providers considering to use the test. So the draft that you have that Ed mentioned is the first effort for us to come up with a Q&A document, and what we're trying to do is identify the questions at this point.

After we're clear on what the set of questions are, then we would anticipate doing an experiment very similar to what's being done with the template, which is to then try to answer the questions for a variety of examples.

Now, when you look at this question and answer document, you'll notice, just as expected, that it has a lot of parallels with the premarket template review, and that's intended. But there are two questions at the end, Question 7 and Question 8, that we've identified as being extremely important for provider/consumer information but are not part of premarket review, the cost reimbursement of the test, and we understand that often the answer to this, or at least part of the answer to this will be test cost may vary, check with your lab, coverage may vary, check with your insurance company, but this is a question that docs and patients want to know the answer to. I think it very much fits with some comments that Reed made earlier about the importance of these issues.

Question 8, informed consent/counseling, I think we're going to have to really work with examples to get to perhaps the final form of these questions, but we're acknowledging that providing information to providers and patients about minimum options and perhaps recommendations will be very important. Clearly, what goes into the answer to that question is not going to be determined probably by our committee but rather by the informed consent committee. We just are capturing that this is an important piece of information.

So to summarize, you've got a draft here. What's new is that it's

in question and answer format and it has added a couple of elements that you didn't see in the template. We are planning an August meeting, or we're going to propose an August meeting I should say, to this group. It's going to be a proposal to this group for the group's approval, and we see the August meeting as, first of all, addressing the premarket template and perhaps getting sign-off. Steve has already referred to that. But because these tasks are so closely related, we would see that another product of that August meeting would be a further refinement of this Q&A document.

After the August meeting, what we'd hope is that they'd go out for broad public comment.

I'll stop there and open it for conversation.

DR. McCABE: Before we move on to some other questions, just clarify the August meeting that you're proposing. It sounds like there's quite a bit to do in that meeting. Are you talking about a one-day meeting, a day and a half, two days? What do you think is realistic?

DR. BURKE: Well, we had planned a one-day meeting. I'll let the conversation help to inform us whether that's realistic.

DR. McCABE: Okay.

Judy?

DR. LEWIS: I think this format is very helpful. One of the things that I can envision is this being Web-based. But also, I look at Hippocrates, which is something I can download to my Palm Pilot and take into the clinical arena when I'm caring for patients and I'm prescribing a drug. I can just put my stylus on the drug and come up with the cost and the drug interactions.

It would be really nice to have something like this that was Web-based and downloadable to some kind of a hand-held device so that clinicians who would need this information would be able to access it at the point where they're caring for patients. I can see this kind of document leading to the kind of template that would fit in a database that could be easily updatable and downloadable every time you sink your Palm.

DR. McCABE: Sarah, is that the kind of thing that we could contract for if we felt that was important?

MS. CARR: I would say we could recommend to the Secretary that that should be accomplished.

DR. McCABE: I think it is important, and as someone who is surrounded by residents most of the time in my day job, if you don't have it on a Palm Pilot these days, it really doesn't exist, because the reality is that's how they access the universe.

DR. LEWIS: And I'm not saying it's something we can do, but if we can get it into the kind of template that that would work with, I'm sure that there's somebody out there who would want to do it. It might not even take a recommendation but it might be something that gets picked up by some group other than us. But I agree with you. I mean, our med school is now -- all the students are now walking in and being handed hand-held devices of some kind or another, and it's becoming just a whole new way of accessing the world. They have their books on it, and if it's not there, they don't read it.

DR. BURKE: And I think your comment also illustrates what the data is and why it's an issue that is inseparable from how we disseminate it.

DR. McCABE: And Sarah points out, and I guess I would ask Alan maybe to look into this, but GeneTests, which we've already heard the value of GeneTests. Is that downloadable to Palms yet?

DR. GUTTMACHER: Not yet, but there's been discussion of it.

DR. McCABE: Yes, because again, I think to really make information available to people in the front lines, it really does have to be compatible with the Palms. It is amazing what is being done with them, from note writing to literature access.

DR. LEWIS: To downloading driving directions on how to get somewhere.

DR. McCABE: Other comments for Wylie about the tasks that they have set, and discussion about the format, the specific questions on the provider summaries?

Yes, Muin?

DR. KHOURY: Wylie, I'm looking at the various pieces here, including the one that I'll be presenting tomorrow morning. There's obviously quite a bit of overlap between all these pieces, what the FDA has done, what the data committee has done, what the Foundation for Blood Research has done with respect to this evaluation of what exists out there. Obviously, this piece is targeted for physicians, so not all the questions are pertinent to each audience.

So, for example, I'm struggling with that. I don't know whether we're looking for a grand unified scheme here, where we have all the data elements and then we can pick and choose, where the physicians might pick questions 1 through 15 and the consumers questions 16 to 19, or are we looking to reinvent the

wheel every time? I mean, what's your view of this?

DR. BURKE: Obviously, at least reinventing the wheel is possible. If you look at the page entitled "Draft Proposal for a Pre/Postmarket Data Collection Meeting," which is the idea behind this August data work group meeting, you can see that under the objectives, the goal would be to develop consensus drafts. It's in your blue folder. I'll give people a minute to find it.

DR. LEWIS: While we're doing that, can I just change "physicians" to "clinicians"?

DR. BURKE: Yes, you may.

DR. LEWIS: Please, Muin?

DR. KHOURY: I'm sorry. I live in that world. I apologize. Can we say "health care providers"?

DR. LEWIS: Thank you.

DR. BURKE: I do want to note that we use the term "health providers" in our working group proposal.

DR. LEWIS: Thank you.

DR. BURKE: So this is one page entitled "Draft Proposal for Pre/Postmarket Data Collection Meeting, SACGT Data Working Group," and on this page the idea is to pull together a group, and that group would come up with consensus drafts. That is, around the table we'd have an agreement that we're happy with the draft, and most of the drafts that we hope to reach consensus on have already had a substantial amount of work put into them, and we'll continue to get input between now and August, which is why we're hoping that it's reasonable to come to the final consensus in one day.

So the first is a premarket review template with definitions for each data template. At this point, FDA has done a lot of work on that. The second is the model Q&A document for health providers, which you're just seeing for the first time today, but it's clearly related to that document. The third is elements of a model genetic test report, and we are gathering examples of lab test reports. We would see that as part of what the FDA would want to see. The fourth, which is the least well-defined at this point, is a postmarket data template with definitions for each data template. But Muin's group has obviously done a lot of work on that, and the idea is that that work would be brought to the August meeting.

I'm not directly answering Muin's question, but that was the background for it. The answer to Muin's question is all of these tasks, each one helps to inform the other, which is why we see it as most efficient to approach them together.

DR. KHOURY: I guess the question I have here is whether or not you want to expand this discussion to involve other than health providers. I don't want to repeat what I'll say tomorrow, but if you look at Attachment 12 in my presentation tomorrow, there are Q's and A's for different kinds of people. One is professionals, one other is policymakers. If we are talking about the grand scheme here of regulators, policymakers, professionals, et cetera, why not include all of these groups that need to know about genetic tests, not only be geared towards health providers?

I know you have to start somewhere, and I think the menu is really the same, but you just pick and choose whatever you want to emphasize with respect to what kind of data they need to know at a given point in time. If people

want to take a look at Attachment 12 of my presentation overnight, we can go over it tomorrow.

DR. BURKE: Yes, and it may be that in the time we have set aside for discussing the August meeting tomorrow, we can pick up some of this conversation again. But I think Muin's point really speaks to why we have in mind four products of the August meeting instead of one, which is that when you really start talking about organizing information, you do start talking about multiple different users.

I guess my first answer to Muin's question, my own thought but I'd welcome the comments of others, is that we have to start somewhere, and maybe it's reasonable to start with the Q&A for the health care provider that we think is going to order the test, but sort of almost immediately reaching a comfort zone with that, begin to ask whether that's the same set of questions for the other users or whether there are additional questions.

DR. McCABE: Just so everybody can take a look at this tonight, what Muin is talking about is the last item under Tab 6. So it's Attachment 12, which is the last attachment right before Tab 7.

Barbara?

DR. KOENIG: Just to follow up on Wylie's comment that the Informed Consent Working Group would ultimately also have something to say about your number 8, the only thing I would say at this point is that where I think we do have some consensus at this point is that we're beginning on the assumption that informed consent is always something that happens. So it shouldn't ever be talked about as optional. What you might want to do is think of that as the nature

of informed consent documentation.

DR. BURKE: I think we say what type of informed consent is recommended. I think that's consistent.

DR. KOENIG: Do you think it's okay?

DR. BURKE: Well, let me just say that when we say what type of informed consent is recommended, we intended to capture the thought you just described, but your language may be better. Maybe we should start with informed consent is always part of the process.

DR. KOENIG: Yes, but at what level? What type and level of documentation is necessary, if any?

DR. BURKE: Okay.

DR. McCABE: Other questions or comments?

DR. LANIER: Wylie, when we were doing the premarketing template, we indicated that there would be a different set of information provided for each intended use. Is the sense of this Q&A that there would be a separate Q&A for each intended use as well?

DR. BURKE: Very much so.

DR. LANIER: Okay.

DR. McCABE: There's some of the discussion we've already had earlier today that will, I think, provide some embellishment of what you've done here. For instance, under number 6, "Clinical Utility," there are certainly some additional measures of the quality of the data that one needs to probably annotate to help individuals understand just what kind of interventions are available and what's the knowledge about the benefits of those interventions.

DR. BURKE: And again, this speaks to how coordinate or parallel the processes are. Another thing that came out of our discussion of practice guidelines that I think really helps to clarify what needs to be here is that it should be pretty clear in this kind of Q&A document what the outcome of a test is. That is, is the outcome information, or is the outcome indications for intervention? If the outcome is indications for intervention, at that point you spell out the interventions and you spell out their efficacy.

But just as an example, there's a lot of interest in using genetic testing to identify people at increased risk who might benefit from a variety of behavioral modifications. That certainly gets a lot of play. So you could say that's an example where you're getting risk information, and that's the hard endpoint. But the soft endpoint is that you can then perhaps emphasize the importance to that individual of exercising regularly or not smoking, whatever the behavioral intervention might be.

In our blue folder, one of the things that we have is a packet of articles that just came out of a special issue in BMJ on genetics, and one of the articles in that packet is an article by Marteau and Lerman talking on this issue about how little we know about the use of genetic information to motivate behavioral intervention. So I think that speaks to being crystal clear about what it is that you get from this test.

DR. McCABE: The other comment I would make would be under number 5, where it's talking about how does a person's ethnicity, age, family history, and other factors affect the validity, specifically the predictive value of the test. I'd just like to take this opportunity to again put on the record the need

as we go forward to think about resources to actually inform that question. I'm very concerned that we not be faced 20 years from now with just saying, well, for the three ethnocultural groups in this country where we have the largest population bases, we can provide very good data in response to that question, but as we get into the smaller ethnocultural groups, we just can't afford to try to inform.

I really think we have to be very cautious that we don't disenfranchise huge segments of our diverse population from the technology that's coming out of the Genome Project.

Barbara?

DR. KOENIG: I hadn't actually read that, and just to follow up on what you said, perhaps you might want to use the language that we had adopted in terms of the ethnocultural as opposed to other, trying to sort of take a new term.

DR. BURKE: Yes. I think we'd really appreciate help on getting the language just right.

DR. McCABE: And I think my point is that we shouldn't just plead ignorance forever, that one of the things that we have talked about before and need to continue to discuss and eventually to recommend is that there be some resources put behind the acquisition of these sorts of data.

DR. LEWIS: I just want to comment just in general on the utility of this format. If you're looking at a computer, people are always doing frequently asked questions, and I think it's a format that's very user-friendly, and I like that a lot. In addition to the specific questions, I think the format is one people are used

to, it's one that's going to be searchable, it's one that is going to find your question, here's an answer, as opposed to reading through pages and pages and pages of stuff looking for the answer to the question. So I think it's just a very user-friendly way to do it. It's a real breakthrough and a very brilliant way of doing it.

DR. BURKE: You know, I appreciate the comment, and certainly user-friendly was part of the thinking here.

I do want to comment that we haven't figured out yet who is going to create the answers for each test, and that's a very non-trivial issue. I mean, to some extent, the data team was given the task of figuring out what the important information is. When you're talking about a premarket template, you know who has to come up with the information. It's the test offerer. When you're talking about a good quality question and answer document, one of the things that we got to early in our conversation was that we didn't think the answers to these questions should come exclusively from test developers.

This is where this kind of process may interact in a productive way with guidelines development. If you've got a good guidelines development process, you're getting good quality answers to these questions, but it's also a resource issue per Ed's comment.

DR. McCABE: Michele, and then Reed.

DR. LLOYD-PURYEAR: But it is also, I think, a part of the process of guidelines development. In educating providers, I think you begin to form the relationships that you can begin to fill in the blanks in a large way. I mean, I think your health care providers are going to provide the clinical information that we need and that's generally not part of the process that we

currently have at all.

DR. McCABE: Reed?

DR. TUCKSON: On the cost reimbursement, what is the cost of the test, also we might want to consider also making sure that the clinician is asking who pays for it. I mean, again, how much of this does the person have to pay versus what's covered, and they need to be thinking about that before they make people pay a lot of money, patients, unnecessarily.

DR. McCABE: Is that an easy answer, though, Reed? Because for a lot of tests, it may depend on the specific health plan.

DR. TUCKSON: Yes, they may want to ask. Because what I'm getting at is that we asked the earlier question, what are the alternatives, and I think one of the things you sort of want to know is what are the alternatives for the person. It's terrible if you have a person who has to pay out of pocket for that sort of thing, or is not reimbursed, and then what are the alternatives and what do those cost, so you don't wind up having a poor person not getting a diagnostic work-up because, in fact, the recommended thing is unaffordable, and then we haven't looked at what the alternatives were.

Again, I'm not looking at this as a barrier. I'm looking at it to make sure that we're thinking through what these choices are that people have. So I just want you to consider connecting the alternatives and cost.

DR. BURKE: And I think alternatives is a very important comment. It's very likely that any centralized, federally-supported process will be unable to provide answers for all the different localities where the test is taken, but I think if one provided a Q&A document, one might provide some guidance,

saying to a health care system that wants to use this Q&A document, "Here it is, fill in the blank here." And I could imagine, if it's a good quality document, that a place like Group Health of Puget Sound, a big HMO in my organization, might want to take such a document and put in a group health-specific answer to that question. I think we've created a format where, hopefully, that would be easy for them to do.

DR. McCABE: On the other hand, once one offers this up for editing, what would be the other editing that would be permissible to the documents? Have you thought about that, Wylie?

DR. BURKE: That's a very good point. No. I think that's a very good point, because it might be that we want to be very careful about letting people edit what we think are well-crafted answers on clinical validity and clinical utility. But again, what has not been resolved here -- our task was to identify what's the important information, not to figure out how this document is going to be created and who is going to be responsible for it. The reason why we don't have an answer to that is the obvious one, there's not a simple answer to that, and there's definitely no answer to that without identification of resources.

DR. McCABE: What are members of the committee's thoughts on who should be responsible for this?

DR. BURKE: We haven't had a detailed conversation about that. I don't think there's a committee answer.

DR. McCABE: Well, I was thinking more of the general committee here, what people's thoughts were, not your data group.

DR. BURKE: Sorry.

DR. McCABE: We almost had a volunteer from one of the agencies.

Yes, Elliott?

MR. HILLBACK: I think we have two fundamental questions, which I thought, when we originally started working on this, the idea was on the pre side that the laboratory put this together, and that means that there are some boxes the laboratory just can't do, so you don't get them done if you go to some central repository and try to make this a description of a generic version of the test, because they're not all the same. There's a CF test, there's a CF test, and there are 100 different CF tests. So I thought this was lab-specific, not a generic piece that covered CF testing in general. If it's lab-specific, then there are certain things you can't suggest a lab do, go out and find out what all the costs are of other versions of a CF test and put them all in this document.

So I hadn't thought of the question the way you were just talking about it. I was back to where we were the last time we said anything, which was that this was a lab-based document. The pre and the post we still had a struggle with because we don't know where the phenotype data is going to come from. Maybe we'll find out tomorrow.

DR. McCABE: But I think here we're talking about the provider summary as different than the premarket information. While there is some overlap between the two, my understanding was that these were really separate documents. Is that accurate?

DR. BURKE: Correct. Yes, I think the discussion that we had at our most recent --

MR. HILLBACK: Which I wasn't on.

DR. BURKE: Yes, and I apologize for that. I'm well aware of that. We're going beyond the premarket review template to create a document that is a more general document about this kind of test. Now, it would certainly have to include, for example, for CF carrier testing, that the clinical validity is variable depending upon the number of mutations tested for, and that that's information you need to look at in the test label.

MR. HILLBACK: And ethno groups and everything else.

DR. BURKE: Right, absolutely.

DR. McCABE: Muin?

DR. KHOURY: A specific answer to your question, Wylie, it's obvious to me that what goes into the answers to these questions is multidisciplinary -- public, private, academic, NIH, CDC, HRSA. Everyone has a piece of this, and maybe we can postpone this discussion until tomorrow morning, when we're sort of charged with the task of coming up with this multidisciplinary way of pulling that information together. It's not easy, and it's very challenging. I don't want to get into that discussion. It's obvious that no single place will really have all the data on this one.

DR. BURKE: But I guess a key question there is, is it the same public-private partnership that does post-data collection? It would make sense to me that it would be.

DR. KHOURY: Maybe, with an educational arm to it that would take the data and translate it into Q's and A's, perhaps.

DR. McCABE: Michele?

DR. LLOYD-PURYEAR: Then I don't understand. I think I'm back where Elliott was, a little confused now about what the provider Q&A for genetic testing is. I thought this was being developed now for every specific test, per se, where you're going to fill in the blanks, but to provide a framework for providers of how they view the information that's in the label, that's in the template, that's in other sources; that when they go to do a genetic test, what kinds of information should they know, what kinds of questions should they be asking and making sure the answers are there.

It seems like an immense thing, a huge amount of resources to develop a template, to develop a Q&A answer for every single genetic test, for every possible use. It's really highly duplicative in a lot of ways of what the regulatory agencies are doing. Since I can't even conceive of a centralized process -- I mean, I agree, if I understand what Muin is saying, that it's going to have a lot of data from a lot of different sources that needs to be pooled, but I really doubt that it will be done in a centralized way.

DR. BURKE: So I think you're proposing something that hadn't been explicitly discussed, but that one version of this Q&A document is that we have all the questions laid out and that we have generic answers that are sort of guides to people interpreting other sources of data. Is that --

DR. LLOYD-PURYEAR: Yes, that's what I thought this, the provider part, was for, and that was how it was different from the template.

DR. McCABE: Barbara?

DR. KOENIG: I think I'm sharing this confusion, because I had also thought of it as something that was going to be specific. The reason that I

raised my hand was actually -- now it's becoming more clear -- was to raise the issue that we're having the same set of issues with the consumer side of this in terms of how useful is something that's generic as opposed to things that are specific. But when I was imagining that this was going to be specific, it seemed to me that that made a logical link with something for consumers that could be specific as opposed to generic.

DR. BURKE: I don't think there's any question that what providers will need is specific documents. I think the question is how those get done. It may well be that the most SACGT could take on is giving good guidance about what the questions are and what the document should look like.

DR. McCABE: David?

DR. LANIER: I'm a little confused, too. If you're thinking in terms of a more generic approach, which I'm assuming that's what the guidelines would be about, Wylie, I can't imagine there would be a guideline for every specific test but more of a general approach to it. Because if that were the case, it would make sense to me that these would be just folded into the guideline development process.

When AHRQ developed guidelines, we would usually have what was called a quick physician's -- provider's; excuse me, Judy -- reference guide, and it would be something that would distill the information that was in the guideline for quick reference for clinicians. It would seem to me that this would serve that purpose quite well if we could recommend that as a format.

DR. BURKE: I think that's a very good suggestion. The document wasn't discussed in that way by the data team because it was being

created before we had our guidelines discussion. But I think to the extent that we have a general guidance about what makes a good guideline, it would make sense that a good guideline includes a document like this that answers these questions. I think addressing it at that level is something we could see well within our capacity to do. I don't see how SACGT can actually do the more specific piece.

DR. McCABE: Muin?

DR. KHOURY: Well, I guess I don't want to field a lot of the discussion from the morning, but we've identified the major challenges that are ahead of us here. I think what SACGT has done so far is frame the questions in a way that is guideline- or evidence-based. We've identified, in a number of ways -- the FDA has done some work, the data team has done some work. There is a lot of work that has gone into the development of the questions.

It's clear in my mind that the answers to these questions will come from a variety of sources, both public and private. Some of them are analytic issues that could be obtained by the lab. Some of them are NIH-funded projects. Some of them are HRSA projects. Some of them are CDC. Some of them are just pure private sector projects. So the challenge is, then, how do you take these questions and influence the way the data are collected, and then how the data are pooled.

One of my presentations tomorrow, and Tim will obviously share in that discussion, is for the user, it really doesn't matter where the data come from. I mean, if they want to go somewhere and try to answer Question 5(a), 5(a) might come from HRSA. Maybe 4(b) can come from GeneTests. As long as we know where the question is, and as long as we know where to find the answers,

whether somebody will put together the one centralized repository, it may or may not happen. As long as the information is available, then people might go, perhaps, to an initial gateway that will point you to GeneTests or FDA, or the FDA template or HRSA's funded activities. That might be the way to go in the long run.

DR. BURKE: And that really underscores what I think has been our task, which is to define the universe of information that's important to a provider ordering a test.

MR. HILLBACK: My quick comment was or the companies, because there is a lot of material that's going to be there.

DR. McCABE: So what you're proposing is perhaps a search engine that would search a -- I mean, that's what you're suggesting, really, if you're going to go to multiple sources to answer these questions.

DR. KHOURY: How about we discuss this tomorrow in more detail, if you don't mind. We have the whole morning.

DR. McCABE: Joann?

DR. BOUGHMAN: Wylie had suggested in the opening that if or once we get to a general format, that we might test on specific disorders. I might suggest that this discussion leads me to suggest there might be an intermediate step. That intermediate step might be exemplified, for example, in the list of questions under number 2, the clinical condition for which the test is performed.

If this were a specific laboratory that is providing the test for a specific patient situation, the first question would be for what clinical condition is this test being used? That's a very different question than for what clinical conditions should or might or may this test be used. In fact, if you were talking

about the more generic or the compiled data in a centralized place, it would be the more generalized question that was being asked.

So I think it might be useful for members of the data group or for all of us to look back through this and think of these generalized groups of questions from two or three different vantage points, if you will. In fact, that might help us come to more clarification on which questions are absolutely essential, because it would be the ones, with some very slight modification, that would reappear over and over again in each one of those vantage points.

DR. BURKE: Thanks.

DR. McCABE: Amy other comments on this before we move on?

(No response.)

DR. McCABE: What I'm going to do is take an opportunity. We were interrupted this morning by the fire drill in our discussion of the FDA and the pharmacogenetics template. Dr. Solomon is still here. Dr. Spear is not here, but Dr. Gutman is here also. So maybe if you would be willing to join us at the table again, Dr. Solomon, and we can try and revisit that discussion. I know there's been a bit of a disjunction here between the discussion this morning and the current time, but if we could go back to the template, and remember that we had discussed the pharmacogenetic template.

I had cut off Elliott. I don't know if you remember what your question was, Elliott, but we cut you off so that we could exit and beat the crush out of the building at the time. But if anybody else has any comments that you would like to make regarding the pharmacogenetics template or the use of the template in general.

MR. HILLBACK: Actually, I think we got to it when we came back and we got into some of the other pieces.

DR. McCABE: Other questions or comments for Dr. Solomon or Dr. Gutman about the template that they had begun to implement?

Yes, Wylie?

DR. BURKE: I'll just ask you what your current sense is, since both of you have been involved in developing examples of the template, what your current sense is of whether we're pretty much there in terms of figuring out what types of information ought to be asked, as opposed to whether you feel like there are gaps. And secondly, this is with the thought of an August meeting coming up, whose critical review is going to be most helpful in getting this to its final form?

DR. GUTMAN: I actually think we have a very credible start. I'm certain that you could fine-tune the template, and I'm also certain that you can never perfect it because you can't possibly anticipate all of the possible variations that might take place. There have been some suggestions perhaps, actually for people at this table -- well, not for people at this table -- a suggestion that we might strengthen some insight to pre and post analytical issues. We might take a look at those most closely.

I put on the table my cards, and they relate actually to issues that appeared in the Pharmacogenomics Roundtable and that have been here. I don't know that they need to be resolved in the context of the template, but they do need to be resolved, frankly, in either the informational and/or any future regulatory use of the template, which is actually how to make the right connections between existing analytical data and the summary, because what appears in the template

isn't raw data. It isn't even a broad exposition of data. In fact, if you put raw data or a broad exposition of data into the template, you sink it, so you make it non-useable.

So the question in my mind is how do you validate or verify or establish the link between what exists in the lab or exists in the literature analytically and what appears in the template? Then the second issue -- and, actually, Pharmacogenomics, one of the work products that group was willing to foster and one which might deserve perhaps moving over into Debra's group, for example, or to other groups, is looking at whether there is a mechanism -- literature doesn't just exist with a life of its own. It has to be selected in some way, it has to be weighed in some way. It doesn't necessarily have to undergo an intense and formal meta-analysis. If we were to do that again, we might grind to a halt. But it does require something more than just a cursory evaluation, and then you put the two together.

I'm particularly beguiled by it, because we actually practice this right now. I think I may have alluded to it, if not this morning, I surely alluded to it in the past, which is that for an established test, for glucose for the diagnosis of diabetes or for hemoglobin for the diagnosis of anemia or for amylase for the diagnosis of pancreatitis, it would be unthinkable for us to ask for clinical data. It would be just whacko to start asking people to bring in a hemoglobin device and prove that it's associated with anemia.

There may be some genetic tests where it would also be whacko to ask for very much clinical information. There might be other genetics tests where it would be whacko not to ask for information. So there are a lot of challenges in

how to deal with this template from a regulatory perspective. It would be very nice if either in the August meeting or if the Pharmacogenomics group or the Professional Roundtable genetics group would help look at it in a totally non-regulatory context in terms of what kind of scientific guidelines could be developed for whoever was stuck with that template in terms of making those key boxes mean something.

So I would see that not as a modification in the template but an appendix to the template, or an addition to the points to consider, or an expansion of the points to consider. So there are lots of problematic areas. The template is its strength and its weakness and its simplicity.

DR. McCABE: We discussed at one point in the past that if this is electronic, then these links become a lot easier. We're used to a hard copy printed version which gives references that you have to look up. But now, if one were able to just click from the template to a URL if one wanted additional information, then it seems like the information becomes much more readily available to those who wish to utilize the raw data. You had talked about some other situations where you were actually exploring these kinds of links.

DR. GUTMAN: Absolutely, and I think it's appropriate. I must say that I'm trying to remain impartial here, since I'm clearly a tainted party. But during the previous discussion, when you were talking about the questions and answers, I happened to be involved in the subgroup that was working on it, and actually my view, which was different than the view of several people here, was that the notion was that it wasn't a monograph, an approach towards answering multiple questions about broad categories. I had actually, either correctly or

incorrectly, viewed it as tied to a particular device, exactly what Elliott said.

Maybe Steve Gutman's lab and Debra Leonard's lab might offer the same test with different methodologies, and frankly with different limitations and with different results, and my vision of this was that Wylie's group had done some work that might be linked if you could ever put this in either a public voluntary database from the University of Washington or a public but not-so-voluntary database on the FDA homepage that you would actually link the professional version with these questions and answers.

So, frankly, there might actually be some health care providers of whatever nature who might not be sophisticated enough to really appreciate the nuances of the template itself and might really like a very friendly question and answer, and maybe you could combine it in a way that -- I'm not sure you have to write it in 7th grade language, but write it in a way that you could meet the needs of even educated consumers as well.

So I had actually seen that as linked to the template. I'm obviously not wedded to that. So if you could develop a monograph that produced some more general insight in asking questions about the template, that's also good.

DR. BURKE: Well, I think that's entirely within the spirit of the Q&A document, and not only that, probably more doable in the short term.

DR. McCABE: Barbara, and then Elliott.

DR. KOENIG: I just have two questions about the template format in general, not so much specific to the pharmacogenomics, although perhaps. One is, and maybe it is relevant to pharmacogenomics, the issue of multiplex testing. Have we thought about that? Is that something that's in our

thinking about the whole template mechanism? That's the first part.

Then the second part, a similar sort of question, and that is, is it clear that there will be a separate template required for each intended use, or is that something that's still on the table for discussion? Because it's not totally clear to me. It seems to me that maybe, in terms of off-label use, the off-label use language isn't really even the right language, because using a test for carrier screening versus preimplantation genetic diagnosis, it's almost as if they're not even the same thing, even though they might use the same test of DNA.

DR. BURKE: I'll just briefly comment. I know Elliott has comments, but I'll just quickly say that all the discussion in the data committee has been that a different use of a test is a different test. Some of the examples that we have seen for the templates have done some bundling, and I think it probably ought to be on our August agenda to address that, at least in terms of whether there's any bundling that actually saves time and effort and increases clarity rather than decreases clarity.

DR. McCABE: Elliott?

MR. HILLBACK: That was the comment I was going to make right before the fire drill, and I think we got to it in another way later, which is that I agree, from a lab point of view, if you're going to write a report, you have to be able to write a report based on what the intended use is. So we think there's a separate template, although there may be families of tests that are together. So that was one point.

I do like the idea of the electronic for several reasons. One, I think it does get at where we were before, which is that the Q&A becomes a

relatively generic document but allows you to go back to the templates that are filed with FDA, for example, assuming FDA lets us through their firewall, or allows you to go lots of other places, and I think that's very powerful. Just anecdotally, the most recent filing we did of a drug we filed electronically, and it's made a huge difference in our ability to respond to questions from FDA, basically reformatting data as we go along with them when they want to see data in a different way, for example.

So we are now very committed to doing that on the therapeutic side of our business, and I think that kind of thinking out of the box might find that it cuts through a lot of the "who will do this and how will we get it all done." So it's a great idea. I think we ought to keep going with that, figure out how to bring that along.

DR. McCABE: Dr. Solomon, do you have any comments?

DR. SOLOMON: Yes, I'd like to make a couple of comments.

DR. McCABE: Could you get a little closer to the mike, please?

DR. SOLOMON: I'd like to make a couple of comments based on the question that you originally put to us as far as are there any holes in the template. I'd like to expand a little bit on the area of literature and exactly what needs to get put in in order to support the particular utility that you're trying to support: how much, how broad, what are the limitations of the data. Those types of issues are not really spelled out, exactly how long the section needs to be, could be, et cetera, and what needs to go in. Who is going to judge the literature that you choose for what goes in, whether it's valid literature or whether it has some flaws in it?

So those kinds of issues I think are really some things that we want more clarification, more discussion on.

The other thing that I wanted to mention is the purpose or uses of the test. What we have in here is that we listed some drugs, for instance, that have in their labelling that they are metabolized by this pathway, but we discussed this issue quite a bit. Once you get a test out and new drugs come along that are then going to use the same pathway, you would not like to have to go back and re-do a new submission for that drug or for that application. So how is it going to be kept up to date without having a new submission every time a drug for an accepted pathway comes out?

DR. McCABE: One of the things we've talked about is the postmarket data collection and review. That's off in the future, so we haven't really addressed that, but I think those are important things that we would need to focus on as we go into that discussion.

DR. BURKE: And you've raised an interesting example of a modification of intended use that's quite different, in spirit at least, from what we call off-label use, because in that case there would be a modification but it's still the same intended purpose, as opposed to bringing a test in for diagnosis and then using it for screening.

DR. McCABE: Are there any other comments from the public regarding any of these issues?

Yes, please. If you would just identify yourself when you go to the mike, please.

DR. BATENHORST: Randy Batenhorst with GlaxoSmithKline,

who is also involved with developing the template and trying to formulate it. Our original attempt we actually tried to do based upon either looking at changes in efficacy of a drug or changes in safety of a drug, and we found that the template led to a lot of different issues around nomenclature in the way pharma companies think of safety and efficacy and the way device manufacturers think of safety and efficacy. I think it raised some issues around things that we commonly think about terminology-wise when you start going across. Different areas are looked at in different ways.

So if we bring drugs together to the market with a pharmacogenetic test, there is some inherent confusion potentially that goes along with that. That needs to be looked at. There were some discussions, and I think part of what Steve presented with the glossary is starting to go down those lines to clarify those difficulties.

Another thing I think that was raised, I think more from the pharma side and from the device connections that go into some of the pharma companies, is just around a level playing field. Where is the template going? How is it going to be applied? Will it be applied differently for clinical laboratories versus reference laboratories versus IVD manufacturers?

I guess for us, when developing a drug that may be linked to a test that we're going to deliver at the same time with the new medication to the marketplace, we need to have a clearer view of what that looks like so that we can assure that we don't get the drug developed and then figure out how we're going to deliver this test, because we don't know what the rules are as far as delivering that test, either through a reference lab or through an IVD test kit. So I think those are

some sensitive issues that I think need to get resolved with time as this goes forward.

DR. McCABE: Thank you.

Other comments from anyone?

Yes, Barbara?

DR. KOENIG: Can we move to another topic?

DR. McCABE: I just want to see if there are any other comments from anyone here who would like to put something into the record before we move on.

Yes, Sarah?

MS. CARR: At the February meeting, I think Dr. Collins especially wanted to withhold judgment about no longer needing the classification methodology. With the benefit of the additional test examples and so forth, can the committee say for sure now that it doesn't think the methodology is needed? And if so, then perhaps we should notify or sort of augment our oversight report with that addendum, then, because that's sort of still in there, that we were going to develop the methodology and so forth.

DR. McCABE: What I heard this morning was that with the template, it was fitting more into the traditional Class II, Class III classification of FDA.

Do you want to comment on this, Steve?

DR. GUTMAN: Yes. Again, you have to realize I'm trying to contain work, so I'm taking a minimalist rather than a maximalist view. So the notion would be to develop enough special controls to make us comfortable in

processing many, if not most, of these as Class II products.

I will remind you, I realize that you have had multiple occasions to be introduced to our wonderful review process, that the Class II product for us is a surprisingly diverse beast in that it can range from actually quite plebeian data sets for well-established -- I would call a Coulter counter, for example, or an equivalent hematology analyzer a fairly well-established analyzer that doesn't require very sophisticated data sets, to a very novel item. When troponin first came in with the notion that it was going to replace as a standard of care CKMB -- now nobody thinks anything about troponin. I can assure you, in 1993, we were absolutely freaked out by troponin and wondering what the hell we were dealing with.

So having a Class II product should not frighten you because it allows a fair amount of latitude. There is less control with a Class II product than with a Class III product. A Class III product has more enforcement over modifications, requires an annual report, has more manufacturing requirements. But frankly, it would be our notion that if we were to apply Class III to this new arena, as I said this morning, we are very cautious. It's not our intent to close down genetics labs. I think that would be a disaster. So a lot of the traditional concepts, for example of acquiring design controls and good manufacturing practices, needs to be tempered in light of the fact that those labs are producing work right now under CLIA.

So I actually think that allowing us to classify using a traditional classification panel, allowing us the opportunity to make most of them Class II's, a Class II is very flexible. So if we decide there is a subset of products we don't want

to look at at all, you may all fall out of your chair, but we could make them all Class I-exempt. On the other hand, if we had products that really were scary or new or worrisome or problematic, they could be made Class III by establishing that there are new issues of safety and effectiveness.

So from my perspective, I welcome your continued wrestling with that enterprise. But frankly, for our purposes, it's not needed.

DR. McCABE: Sarah, then Muin and Joann.

MS. CARR: But as far as the committee is concerned, then, you're comfortable with not providing any further guidance to FDA about what kind of test would rise to the Class III? That's all I'm trying to make sure the committee is saying.

DR. BURKE: Yes, I'll just comment. I would support that view, and I think two things, two elements go into it. The first is that we found it very difficult to come up with any test classification system that was simple and gave us what we wanted. But the second and probably more important point is that we were talking about creating a test classification system for sorting things before they got to FDA review, and then they get to FDA review.

Not only does the template, it looks to us, enable a review to go forward and sort tests, as it should, but we have an overarching goal of a streamlined process. So if you have a first step that's hard to figure out how to implement before you get to review, it's the opposite of a streamlined process. So I think what happened was that FDA showed us how it could work without pre-review classification, and I support that.

DR. McCABE: Muin, then Joann, and then Ann.

DR. KHOURY: Actually, that's very helpful. I don't think the work of SACGT has been lost throughout all the discussions about classification, because even though the FDA came up with a more conventional way of dealing with classification, on the postmarket side you're going to have to zero in on tests that affect larger segments of the population. You can't do postmarket surveillance on everything fairly quickly, so that work will still be very useful to all the agencies and the public-private consortia and groups working together; and also ultimately for things like guideline development. I mean, things like Factor V Leiden, ApoE4 and Alzheimer's hemochromatosis will probably take more precedent than the more rare genetic diseases.

So that work still holds. It may not be applicable to the oversight regulatory function, but everything else I think might be very useful.

DR. BURKE: I agree with everything you're saying, but let me just amend it by saying I think what the template does is it pulls into the body of the review process precisely those parameters we were concerned about in test classification.

DR. McCABE: Joann?

DR. BOUGHMAN: I would suggest that I think the committee is ready to dismiss with the point where we left the discussion last time in light of the work of the data committee, the responsiveness of the FDA, and the fact that they have pulled in in this process many of the stakeholders. I think we have addressed those issues between February and now in the presentation of what has been brought forward, and I would suggest that we would be ready to make such a change or an addendum statement to where we were in February. I think we've

come a long way.

DR. McCABE: Ann?

MS. BOLDT: I think the addendum is important too, in terms of how we've tied recommendations for genetic counseling, education and informed consent with scrutiny levels. So at least we need to make sure that's consistent in our language now so they understand what we're associating that with.

DR. McCABE: Barbara?

DR. KOENIG: The classification scheme may be resurrected to some extent in terms of the issues of thinking through the documentation of informed consent, so that may be useful. But on the broader issue of the template and the role of the FDA, which is what I was going to bring up before, I still have some concerns about the abandonment of the whole premarket in terms of whether the template can adequately address the larger social issues, and it's tied to the issue of how the FDA is going to be able to deal with those issues at all.

Increasingly I've been seeing -- unfortunately, I can't remember the exact discussion. It was about another product in which it seems the discourse from the FDA actually seems to be, well, this isn't our job, we only do these technical things, which is an important issue, and then the specific concern I had this morning in the discussion, which I would have raised except it was during the fire drill, was the issue of is it even beyond the bounds of the FDA to put something about informed consent and counseling, to require something like that to be in a label.

DR. BURKE: If I could comment? Probably Steve needs to comment too, but I want to comment on something that I think is a concern of

yours and certainly is a very important concern of mine, and that is that there are some genetic tests that may trigger more social risk than others because they have more stigmatizing potential. So I think the obvious example would be a predictive test, or let's say a predispositional test. I think that's the language that we want to use now. So a predispositional test has very different implications if it's a predispositional test for gum disease, for heart disease, for Alzheimer's disease. The social stigma attached with those is quite variable, or the potential for social stigma.

When we said we wanted to incorporate potential for social risk into our test classification system, what we had in mind was that if there was some threshold that got triggered and it was a stigmatizing test, it would get a more careful review. But we couldn't operationalize that. I mean, I think we have to be very honest with ourselves, that a sorting mechanism only works if it's very simple to implement.

But that issue can be seen in the template, because the template will clearly identify who is the intended testee, what information the test is intended to produce, what condition it's associated with. So all of the elements that might be there to the extent that we can define how social harm is defined are going to be in the template. We don't really gain anything by trying to have a two-step process where we classify first and then review, as opposed to a review process that captures that information.

Therefore, the much more crucial issue is whether it is possible for FDA to make different decisions about the release of a test if the test is for presymptomatic diagnosis of a potentially stigmatizing condition and where the

clinical validity data is somewhat uncertain, because I think that would characterize the kind of test that we're uneasy about. So I don't think we've abandoned this issue. I think it's really important to say all of the discussion we had about test classification is still right here in this process. Nothing has gone away.

But I think there is a very serious question we need an answer from FDA about, and that is can FDA address those issues, or do they have to become clinical practice guidelines issues?

DR. KOENIG: Just a point of clarification, Wylie. I'm not suggesting that we go back with having a pre-sorting classification on our own. I just don't want to have that one element of what we had discussed get lost.

DR. BURKE: I agree, and that's why I think the question is so important. I think we need to be up-front about the fact that that's one of the reasons we lay out data the way we do in a template, is we want to be sure this kind of information is there. We've said all along there might be a points to consider, and the points to consider might include limited clinical validity, certain kinds of conditions, used in asymptomatic people being a red flag goes up. But I guess we still are left with the question of what would FDA do with that information.

DR. GUTMAN: Well, it would certainly be our intent for a new test where there are enough questions, there is still a marketing opportunity for that test, it just has a different name. It's called an investigational device. So when you're dealing at the roughest edge, it may still be very valuable to make the test available. It's just disingenuous to make it available as a clinical test. Frankly, an

investigational device can even be charged for it. It does require some data collection, and it certainly would require informed consent.

Where I'm more uncertain and it's hard for me to answer, and I can try and query our lawyers, although I think part of the challenge of fleshing out this template or actually putting it into practice will be proof of the pudding is, frankly, how far FDA's review purview might go in terms of issues like recommending informed consent or counseling. I actually think, in terms of soft recommendations, it probably is pretty safe.

The stronger you make the recommendations, the closer you get to our regulatory edge since social issues have clearly, in the last four or five years in the context of, for example, drugs of abuse testing, which was actually discussed by Congress on more than one occasion -- we're really a scientific technical agency looking at those issues. We don't look at cost and we don't look at social issues.

That's not entirely true. If there's a product where the social issues have some impact on the effectiveness or some impact on the safety, we frankly will try to factor it in. It's not clear to me, since we haven't tested as wild an array of tests as the ones that sit at this table, I honestly can't tell you quite how that pans out.

What my recommendation would be is that you either now or in the context of the August meeting make as concrete recommendations to us as you can and we will do the best that we can within the law to carry out our mission, and we'll also promote any reasonable thing you're putting forth in whatever role we play in voluntary disclosure and data collection. But I can't make you a promise because I don't know exactly how it will sort out.

DR. McCABE: Steve, I just want to press this a little bit further. Is it possible for a test to be released for one use and have it investigational for another use?

DR. GUTMAN: Oh, absolutely. Of course. Yes.

DR. McCABE: So that you can have it in such a way that it's released for one purpose and not simply used off-label for another purpose?

DR. GUTMAN: Yes. I mean, both are possible, of course, but one of the things we do when we're charged with being least burdensome, we actually will suggest to a manufacturer that they start narrow, that they start with reasonable studies, and then as they get marketing experience or as they get revenue, that they then do expanded studies. Frankly, sometimes the literature itself will expand the studies and they never need to come back in to us. Their reason to come back in to us often is driven by the marketing desire to be able to actually put in their labeling that they have expanded uses.

DR. McCABE: Thank you.

Alan, do you wish to comment? Because this discussion started out as --

DR. GUTMAN: I think Dr. Leonard might want to comment.

DR. McCABE: Oh, I'm sorry. Dr. Leonard, would you --

DR. LEONARD: I have a comment.

DR. McCABE: Sure, sure. That's fine. You can just come to the closest microphone.

DR. LEONARD: It's very interesting to sit and listen to these discussions, because I've been sort of on the periphery working with the FDA. I

guess one of the concerns from a laboratory standpoint is how is this all going to be implemented, and I think this is where the laboratories start getting very, very nervous. So when you talk about FDA review, is this for new tests only that we're just implementing? What about all the old existing tests? And do we have to wait for an answer or approval to come back before we implement a test that we would otherwise have implemented without the FDA review?

What are the consequences for a laboratory if they don't submit information to the FDA? Are there reimbursement issues that are linked to not participating in this? Is it mandatory? And the other question is could professional organizations make test-specific templates that then could be widely distributed to all their members or anyone doing testing that could be simply gently modified by a laboratory to meet the needs to simplify this process, so that every single laboratory isn't recreating the wheel and decrease the administrative burden on laboratories?

DR. McCABE: Let me respond to some of those, but I'll respond from the position of the SACGT and may ask FDA to respond, because ultimately it will be their response that will be more important to your daily activities than mine.

In our recommendations we actually recommended that existing tests have a very different type of review than new tests. So tests that were already out on the market would have a very different review, and we recommended that professional organizations be utilized for that review, that the volume of tests would be such that the FDA would not be able to deal with this in-house, and we thought that the expertise lay with people who had been performing those tests.

So I think, the way I remember the recommendations, it was review but a different level of review.

DR. LEONARD: But will someone support the professional organizations if we're being asked to do all this review?

DR. McCABE: Well, we had suggested that the FDA utilize the professional organizations, but this is a resource issue, and we're talking about new activities and therefore the need for new resources.

Steve, do you want to comment?

DR. GUTMAN: No, that's a fair answer, and those are questions that, frankly, don't just trouble Debra. They actually trouble me. The distinction between new and old is one that she and I have actually had dialogue on before.

One of the tensions from the perspective of the agency is that it actually does account for the risk base that we've just abandoned, which is that there may be unestablished old tests that might be more worrisome than new tests that are either lower risk or well established. Frankly, even defining an old versus a new test -- is Factor V Leiden that's introduced at a new site a new test or an old test? Again, we probably would try to interpret it in a way that was as gentle as possible to minimize our workload.

The issue of leveraging, whether Walter comes up with some fantastic idea, or Debra or her co-workers come up with some fantastic idea, the issue of leveraging or developing templates, or whether Mike comes up with some fantastic idea, the issue of leveraging and developing templates that we can conform to, so a lab can say we're following this fabulous protocol but we modified this buffer and we can now plug into the literature, and making the review is,

frankly, pedestrian and plebeian and user-friendly as possible, whether we end up doing it or whether it's some -- the second recommendation, with all due respect, isn't well formed. It says that some group should do this. It doesn't name FDA, but it doesn't name anyone else either.

So it seems to me that the more collaboration, the easier we make it, the better off it is for you. But, frankly, the better off it is for us. It's the whole reason for developing templates off of which you can piggyback, so that there isn't a lot of work for anybody.

DR. McCABE: And I would certainly encourage the professional organizations to develop the template. I would encourage the organizations to do this in collaboration with the FDA so that the format fits the format that the FDA would find acceptable. But again, I may be naive by saying this, but the goal is communication, and the goal is improved communication with --

DR. LEONARD: But there are issues that turn Steve Gutman green, like talking about using RUO test kits for clinical diagnostics, and what does he do with that, and that's widely done in molecular --

PARTICIPANT: Can you explain what that is? I'm sorry, I don't know what that is.

MR. HILLBACK: What's RUO?

DR. LEONARD: Research use only, that are then adapted under CLIA regulations to be used for clinical diagnostic testing, and Steve just doesn't quite know what --

DR. GUTMAN: It's a colorful market. I haven't brought it to the table before.

DR. McCABE: But I think that, again, what we have to recognize is that the American public is concerned about some of these issues also. What you don't want to do is have issues begin to develop in the popular press regarding these types of tests such that there is a reactive response from the public.

DR. LEONARD: But these are developed under appropriate regulatory guidelines that the laboratories operate under.

DR. McCABE: No, no. All I'm saying --

DR. LEONARD: So I'm not saying that there's something illegal about what we're doing.

DR. McCABE: No, and I'm very familiar with this. All I'm saying is that the goal is to improve communication and assure the public that the testing that they're basing their medical decisionmaking upon, that they have confidence in that testing.

MR. HILLBACK: I think the basis of this regulatory program that we've been working on for a year, a year and a half, was to get away from the problem of whether there are research use only kits. The ASRs still exist, et cetera. But the point is that a laboratory, on its own, is going to put together a template that says this is what we're doing, and FDA is going to review that in about five minutes and send us back an okay. But we're going to be documenting what we know and what we don't know. We're documenting the procedures we use, whether we use a research use only set of reagents or some other set of reagents.

But what's very clear is what we do and that there's a transparency there, and I think that's basically where we are.

On the five minutes I was a little off.

DR. GUTMAN: Give us 10 minutes.

MR. HILLBACK: Okay.

(Laughter.)

DR. McCABE: Well, but I think also maybe it could be delegated to a group that could do it in 2.

DR. GUTMAN: Well, you know, Walter actually put it on the table. It will be fun to see when he comes back what he offers. I'm looking for something minimalist and gentle, but I'm also looking for something that's credible. I don't want to take a product to the public and say it's not credible.

DR. McCABE: Sure.

Wylie, and then Alan.

DR. BURKE: It seems to me wholly within the spirit of all discussion about this process that's happened in this committee that it is intended to be developed as a collaborative process where the professional organizations, labs, private partners, anybody who is interested is part of the process of developing this new process, and I think the development of the template so far has fit that model.

Just to follow up on a really crucial point that both Steve and Elliott made, it seems to me that if you put a lot of hard work into the template and defining what the template is, then it ought to work quickly. I mean, that is the whole point of putting work into defining as carefully as we can what the data elements are that have to be there and what we really mean by each of those data elements.

Therefore, the idea that a professional organization might help its

members by creating 90 percent of the template and the rest of it the individual lab --

DR. McCABE: Or even 50.

DR. BURKE: Whatever percent it is, whatever percent is doable, it's not only okay, it's strongly encouraged.

DR. McCABE: Alan?

DR. GUTTMACHER: I wanted to respond to the chair's question about how comfortable the NHGRI is with the present situation. I think we're very comforted by the FDA approach in the use of the template, which seems quite promising. I think there are still two caveats. One of them is that, as others have spoken about, we need to continue to recognize that feature of genetic testing which may indeed be unique, and that is the social construct and the social implications; i.e., informed consent, stigmatization, et cetera. So as long as those continue to be part of the process, I think it looks very promising.

The other caveat is one we're all taking, which is, of course, we're crafting something that we don't know what it's really going to look like in the end, and so that's going to take an act of faith on all of our parts, I think. But I'm willing to extend some faith right now.

DR. McCABE: Would you be willing to speak for Francis?

DR. GUTTMACHER: I'd like to probably confer with him on that.

(Laughter.)

DR. GUTTMACHER: I think the pseudo-Francis would say yes. But I think we should talk to him. We can do that overnight.

DR. McCABE: One of the things that I'm hearing from the discussion, just before I recognize Judy, is that we might be willing to put forth an addendum that says we have moved forward and we have increasing confidence in using a traditional scale that the FDA is comfortable with and knowledgeable in, that the industry also has experience with, and we might be able to do that without withdrawing what we had done before necessarily, that we're really building upon it.

MS. CARR: Well, we can try to incorporate, but we did sort of withdraw it, we did pull it back.

DR. McCABE: We did pull it back, but I think there's been discussion that all of our proceedings have informed us to where we are, and we may rely on some of that information for some other issues that we might take up in the future.

MS. CARR: It seems to me that what the committee said in response to Question 1, how do you evaluate the risks and benefits, still applies. I think what Wylie said is that those things are reflected in the template. So we haven't really changed what the issues and concerns are, but more the level of comfort the committee has in FDA's developing process.

DR. McCABE: Judy?

DR. LEWIS: I was just going to remind us that what we have to pay attention to is what is unique about genetics. The potential for things like stigmatization, while they're different with genetics, that's not a new problem. I remember when tuberculosis was a stigmatizing illness, and certainly what we've learned from HIV testing and counseling and the informed consent piece around

HIV testing I think we can build on other places. We're at a point where this is now very new, but 20 years from now there's going to be something else that's going to be the latest and greatest and this is going to become standard of care.

So I think we have to pay attention to the fact that as we're growing and developing, we need to pay attention and learn from -- there are other models out there that we can learn from.

DR. McCABE: Barbara?

DR. KOENIG: I'm sorry. I'm in some agony about this. I'm just imagining -- I'm not convinced that we're not missing a big component of what our job should be and what our task should be. I'm sitting here imagining a test targeted to particular ethnocultural groups, let's say, that says it's going to predict certain forms of violent behavior or psychiatric behavior with a violent component. Are we honestly going to say that as long as someone can find some data to support the fact that that's accurate, whether it goes in first as an investigational test or not, are we honestly going to say that there might not be some test that we simply decide ought not to be available?

DR. McCABE: Elliott?

MR. HILLBACK: Which "we" is we?

DR. KOENIG: We, the SACGT. We representing our society.

MR. HILLBACK: I don't think we're here forever, and I don't think we can write a predictive statement of what predictive tests we're going to try to say should or shouldn't be in. I don't know how you enforce what you're envisioning over time.

DR. BURKE: But, Elliott, I think we should ask Steve how they

would handle that.

MR. HILLBACK: The huggy guys at FDA?

(Laughter.)

MR. HILLBACK: Can we take that out of the record?

(Laughter.)

DR. GUTMAN: You're posing a question, actually, that has never -- I wish, and unfortunately, Barry is not here. I'm trying to understand. I thought what Judy just said about TB and HIV was interesting, and I do know that there was a lot of information related to HIV with both informed consent and counseling, and I actually don't know how far CBER was able to push the issue.

Even under the IDE, you have to realize that if it's reprehensible, and that might include socially reprehensible -- but if there are unsafe or unethical or potentially harmful products, they actually can't be studied investigationally. There may be some latitude as you're moving from IRB to IRB.

So there are some limits. But I'll be honest with you, I've been working there almost a decade and we've just never run into review questions like these before. You can make recommendations, and I can bounce them off of both policy and legal staff, but I believe in truth in labeling for manufacturers, so I have the same obligation. We'll do the best we can. We'll strive for good labeling, we'll strive for common sense, and we'll strive for safe and effective products.

But at the social edge -- and Debra didn't raise the issue, but she might -- if you do put in requirements for informed consent -- that was a CLIA question when it was put into the CLIA rules -- who has the burden for that? Do you check it? I mean, this is a very treacherous part of the journey, and I

appreciate the sensitivity, and we'll try to use what authority we have. But you're challenging me. I haven't had experience with these questions before.

DR. BURKE: Could I do a follow-up question on this same point? If SACGT were able to come up with some examples -- the one that Barbara just gave, I think, is a picture-perfect example -- of a test that's extremely worrisome for its social implications --

DR. GUTMAN: We'd run it through our template and also run it through a proposed process and see what happens. So if Barbara and anyone else wants to throw a problem case or two at me between now and our next meeting, I'm happy to see what we can do with it.

DR. BURKE: But I think part of my question is not just how it would look in the template and what you think might happen with existing procedures, but whether this points to consider document, not the one about clinical guidelines but this one that's been out there as an idea for the template, whether SACGT or some comparable body could create an advisory document that says to FDA that tests with this combination of characteristics are very worrisome, they need to go by some special committee.

DR. GUTMAN: Maybe they need to be Class III products, or maybe we need to create a new Class IV or Class V. Who knows? Sure, of course.

DR. BURKE: So it seems to me that that's the procedural question for us.

DR. McCABE: Sarah?

MS. CARR: I think the committee anticipated this very thing in your oversight report, because you actually, for a certain -- I think the way it's

worded is that for tests that raise particularly concerning social and ethical implications, that the Secretary should establish something that would go beyond, perhaps, FDA's --

DR. GUTMAN: You're at the edge, and if you go over the edge and you still think it's important, it's not impossible to attain. It might require a reg. We're actually talking about writing a reg for registration anyway. We hadn't quite thought of a reg like this. It would be a reg that would really be a charge; and possibly, depending on how far you push it, you might actually be talking about a new statute. I'm just not a lawyer, so I'm not prepared to answer that. I'm sorry.

MS. CARR: But, Steve, if a test came in to FDA that, just on the face of it, you were just not sure what to do with, you could go through channels and get to the Secretary and say, gee, we don't know what to do with this.

DR. GUTMAN: Oh, sure. Oh, sure.

MS. CARR: And the Secretary, if this committee were around, might come to this committee and say what do we do with this?

DR. GUTMAN: Oh, sure. We don't go straight to the Secretary. I go to my boss.

MS. CARR: Yes, through channels. I said that.

DR. GUTMAN: It might be fairly early in the process when we had -- again, we've never had a scenario quite this interesting, but I can assure you we've had lots of colorful scenarios, and our first response, frankly, is to take it to our advisory committee, because our advisory committee tends to have people who have expert knowledge. We have the capacity on the advisory committee to

deputize people from NIH or CDC or the VA or other government agencies. We can bring in discussants. It's not unusual for us to get a problem for which we don't have answers. That's not unusual at all.

DR. McCABE: Elliott?

MR. HILLBACK: It just concerns me, I guess. If you follow the assumption that we all have genetic defects, then every test puts somebody at risk, and I don't know where you draw a line when you start to go this way. I mean, I can dream up a disease or a situation that would make me scared to death, and I would go to FDA right away and say, my God, don't let them do that test. Every one of you in the room has something you know about yourselves that you would dream up that scenario.

I don't know how it works. I don't know how it works in a practical sense. It is the risk of genetics, and I don't think FDA, and I don't think the federal government is in a position to have any way to manage that.

So I don't know what other ways we could do it, but I'm not sure asking a bunch of people at the federal government level at FDA to do that is going to work. So if we need to regulate that some other way, we ought to think of what it is. I don't think this is it.

DR. McCABE: Joann, do you want to comment from the review group?

DR. BOUGHMAN: I would just suggest that, beyond the internal workings of FDA with the advisory panel and the larger advisory committee and processes, there are a number of people that would be involved in this process, and I would also remind you that the panel meetings are indeed open meetings, and

these issues can be brought forward and are clearly brought forward.

A very different situation but a former panel that I was a member of, when we were dealing with moving from prescribed to over-the-counter situations and the testing as it relates to drugs of misuse and abuse, in fact we moved from what we thought was an individual situation to getting to the much larger issues very quickly and kicked it into a different process outside an individual review.

Now, I don't know that that had a formal structural step-by-step manual, but there was a safety net kind of process, and because it was open, had broad representation on the panel, and because it was discussed in open meetings and in a points to consider process prior to an actual review, I think there were the capabilities to catch these unique situations.

MR. HILLBACK: But we're not talking about panel reviews for all these things.

DR. BOUGHMAN: No.

MR. HILLBACK: And if we were in this situation at the time the BRCA1 test came out, we would have had a group of people going to the federal government saying, "Don't let them do this BRCA1 test, it's too risky for people." I don't know where you draw the line. I'm sorry. Maybe I'm just trying to be too practical with this, but I just don't see it.

DR. BURKE: Well, I think you have to be careful about where you draw the line. You have to be careful about what gets kicked to an advisory committee review. But I think the test that Barbara just described is one that would.

DR. McCABE: Alan, do you wish to comment?

DR. GUTTMACHER: I can go on the record now. I'm actually really playing the role of Francis. I'm not just a pseudo-Francis. He agrees with what I said earlier.

DR. McCABE: So, with that, we can ask staff to begin to craft an addendum to inform the Secretary regarding the progress that we've made in the interval since our last communication. Anybody object to us proceeding with that?

(No response.)

DR. McCABE: Okay. If not, then for those of you who are planning dinner, members of the committee who are planning the dinner, we will meet in the hotel lobby at 6:50 p.m., 10 of 7:00 tonight, to move immediately next door to dinner at Guapo's at 7:00, and the shuttle will be at the hotel tomorrow morning at 8:00 a.m. So remember, we're starting at 8:30 tomorrow morning, and the shuttle will be there at 8:00 a.m.

Have a good evening, everyone.

(Whereupon, at 4:45 p.m., the meeting was recessed, to reconvene at 8:30 a.m. on Thursday, May 3, 2001.)