SECRETARY'S ADVISORY COMMITTEE ON GENETIC TESTING

Monday,
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Regency Ballroom
Doubletree Hotel
1750 Rockville Pike
Rockville, Maryland

Prepared by:
Friedman & Associates Court Reporters
11923 Parklawn Drive
Suite 203
Rockville, MD 20852

IN ATTENDANCE:

Chair

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

Members

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

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

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

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

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

IN ATTENDANCE:

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

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

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

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

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

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

IN ATTENDANCE:

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

Ex Officio Members

Agency for Health Care Policy and Research

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

Centers for Disease Control and Prevention

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

Food and Drug Administration

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

Health Care Financing Administration

JEFFREY L. KANG, M.D., M.P.H.
(Alternate for NANCY-ANN MIN DePARLE, J.D., M.P.H.)
Director
Office of Clinical Standards and Quality

Health Resources and Services Administration

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

IN ATTENDANCE:

National Institutes of Health

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

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

CONTENTS

Public Comment (Continued)

Judith L. Benkendorf, M.S., C.G.C.
Human Genome Education Model Project

Joseph L. Graves, Ph.D.
Arizona State University West

Michael Watson, M.D., Ph.D.
Washington University School of Medicine
St. Louis

Discrete Risk Categories of Genetic Tests:
Possible Approaches to Oversight Issue 2

Wylie Burke, M.D., Ph.D.

Discussion of Oversight Issue 2

Report of the SACGT Working Group on Outreach

Judith A. Lewis, Ph.D., R.N.

Consulting with Diverse Communities
on Issues in Genetics

Vence Bonham, J.D.
Co-Investigator, Communities of Color
and Genetics Policy Project
University of Michigan School of Public Health/
Michigan State University/Tuskegee University

Discussion

Discussion of Outreach Mechanisms Proposed by
the SACGT Working Group on Outreach

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

DR. McCABE: Good morning, everyone. We're going to go ahead and get started.

I've been asked by Mr. Friedman to make sure that we talk into the microphones, so that it'll be easier to do the transcript. So if I start waving at you this morning, then that's what it's all about.

Well, I'm Ed McCabe, Chair of the Secretary's Advisory Committee on Genetic Testing, and I want to welcome all of you to the second meeting of the Secretary's Advisory Committee on Genetic Testing. The public has been notified of this meeting through a notice in the Federal Register, which was on September 20th of 1999, and also through the SACGT's Web site. To those of you from the public who are in attendance, we appreciate your interest in the work of this committee.

At our first meeting in June, Dr. David Satcher, Assistant Secretary for Health and Surgeon General, officially charged the committee with addressing the broad array of complex medical, ethical, legal, and social issues that are raised by the development and use of genetic tests. In addition to this general charge, Dr. Satcher asked the SACGT to make recommendations on the specific issue of the adequacy of federal oversight of genetic testing. Dr. Satcher's initial deadline for reporting back was December 1st, and we have requested an extension, and now our recommendations are due on March 15th of 2000.

Background information about the current extent of federal oversight of genetic tests and specific questions to be addressed by the SACGT were provided by DHHS. During the June meeting, we discussed the questions and concluded that they should be reframed in order to emphasize the central questions of whether all genetic tests merit the same level of oversight and of what oversight provisions should be in place for such tests.

We also decided that obtaining broad-based public perspectives on the questions was such an important part of the committee's task that we should go beyond using the Federal Register for public outreach. We agreed that in order to engage the public on these complex issues we would need to develop a comprehensive background for general readers. To accomplish this work, I appointed two working groups, the Working Group on Oversight, chaired by Kate Beardsley, and the Working Group on Outreach, chaired by Judy Lewis.

The Working Group on Outreach was charged with developing a plan for gathering public perspectives regarding the oversight issues. We will hear a full report of the Working Group on Outreach's activities and recommendations later today from Dr. Lewis, but I do want to point out that the SACGT members who were part of Dr. Lewis' group were Pat Barr, Ann Boldt, Mary Davidson, Barbara Koenig, and Reed Tuckson.

Ms. Beardsley's Working Group on Oversight was composed of Joann Boughman, Wylie Burke, Pat Charache, Elliott Hillback, and Victor Penchaszadeh. The ex officio members or their representatives also participated in the Oversight Working Group, and I served as an ex officio member as well as the other representatives from their agencies.

The Oversight Working Group was to draft a comprehensive background document to serve as a forum for gathering public comments on oversight issues and to formulate possible approaches to the questions to be addressed. The starting point for the Oversight Working Group was to frame specific issues on oversight. The ex officio members played an important role in this process and helped to ensure that the focus and structure of our recommendations would address the central issues of importance to the Department.

Out of this came four issues. One, criteria for assessing the benefits and risks of genetic tests. Two, discrete risk categories of genetic tests. Three, options for oversight and the pros and cons of each option. Four, the appropriate level of oversight by category and a process for ensuring up-to-date data on genetic tests.

Once the four specific issues were defined, the Oversight Working Group proceeded to develop possible approaches and options for addressing these issues. These possible approaches and options should not be interpreted as current positions of the committee. Rather, they are meant to help foster public discussion and deliberation. While these approaches were developed principally by members of the Oversight Working Group, the members of the Outreach Working Group also reviewed them and provided important input.

The product of the Working Group on Oversight's efforts is the draft consultation document that appears at Tab 2 in the briefing materials. The document provides basic background information about genetic tests, including a discussion of their current limitations, benefits, and risks. The provisions for oversight that currently are in place are outlined. Then the paper presents the specific issues that the Secretary's Advisory Committee and the public have been asked to consider, along with the possible approaches or options for addressing them. We will be discussing each of these four issues and the possible approaches and options throughout today and tomorrow.

In addition to discussing the issues and furthering our own understanding of them, our central goal for this meeting is to finalize the draft consultation document and propose mechanisms for consulting with the public.

During the course of this meeting, we will have the benefit of insights from a number of experts on these issues. This morning, we will be hearing from Professor Allen Buchanan, who has done a great deal of research and thinking about ethical and policy issues around the regulation of genetic testing. This afternoon, Professor Vence Bonham will share some of his insights about the opportunities and challenges for engaging the public on issues of genetics.

Tomorrow, we will learn more about the oversight role of the states and private sector organizations and how they complement the federal role. We will have a presentation from Dr. Khoury at the CDC about some initial steps that have been taken to develop a public-private partnership to address the need for genetic testing.

The other major issue that we will be discussing at this meeting is genetic discrimination in health insurance and employment. One of the principal fears about genetic testing is the risk of socioeconomic harms that could result from the misuse of genetic test results by health insurers and employers. This issue is a high priority for the SACGT and it relates in very important ways to the issue of oversight of genetic testing.

We're very pleased that Christopher Jennings, the President's health policy advisor, will be here this afternoon to brief us about the Administration's effort to address genetic discrimination in health insurance and employment. We will also be receiving comments later today on a variety of topics from members of the public.

Before we move on, I want to acknowledge the hard work and leadership of Judy Lewis, who chaired the Outreach Working Group, and of Kate Beardsley, who chaired the Oversight Working Group.

I understand, Kate, you have a few comments to make about the working group's activities. Is that right?

MS. BEARDSLEY: No. Actually, I think you've covered the waterfront very nicely, and I don't want to get into the merits, because I know we're going to be doing that issue by issue.

I guess the one thing I would like to do is thank everybody on the committee for going through endless conference calls on this, and also especially the ex officios for helping us out of a jam in reframing the questions at a time when we really needed help, and finally, Sarah Carr and her group for putting together what I think is a really good background document that ought to serve a lot of purposes as well as this one.

DR. McCABE: And Judy, did you have any comments?

DR. LEWIS: Not particularly, but again, I'd like to thank the members of the group, and also acknowledge the hard work of Sarah Carr in terms of organizing us and helping with our work.

DR. McCABE: Thank you.

Sarah has a couple of administrative matters to deal with.

MS. CARR: It's actually just to point out that in your green folder is a reminder about the rules of conduct and conflict of interest that you should follow as special government employees. That's all I need to say.

DR. McCABE: Thank you.

Our first item on our agenda this morning is then to discuss "Criteria for Assessing Risks and Benefits of Genetic Tests: Possible Approaches to Oversight Issue 1," and this consultation document is at Tab 2. The discussion of Issue 1 begins on page 25 under Tab 2.

Dr. Burke?

DR. BURKE: As Dr. McCabe said, the first issue of the Oversight Working Group was to consider and propose criteria to be used to assess the benefits and risks of genetic tests.

As we began to approach this question, we felt it was important to clarify in our minds that test evaluation -- any genetic test or, really, any laboratory test -- occurs in stages, with the first stage being assurance of laboratory accuracy. So we just want to note that there's a stage at which one is assuring that there is adequate analytic validity accuracy at the laboratory stage, and that it's only subsequent to that that we look at the clinical performance of the test. As we talk about criteria to be used in addressing Issue 1, we're talking about the clinical performance of the test.

As we considered the criteria that could be used, it seemed to us that there were two general categories of criteria or two criteria that should be used. The first is clinical validity. That is, the accuracy with which the test measures either the disease state or the susceptibility state in question. Clinical validity is measured in terms of certain parameters: sensitivity -- that is, the proportion of people who have the disease who have a positive test; specificity -- the proportion of people who do not have the condition who will have a negative test; and the positive and negative predictive value, the likelihood that the condition will occur with a positive test or not occur with a negative test.

The other general criterian is that of clinical utility, which we define as the outcomes associated with positive and negative tests.

I'm going to talk in some detail about the issues to be considered for each of those criteria. That is, issues to be considered with clinical validity and clinical utility, but first it's important to note that these two criteria need to be assessed separately for each different purpose of the test and for each different population in which a test may be used, because the assessment of clinical validity and clinical utility may well differ under those differing circumstances. That's a particularly important issue with genetic tests because we often do see genetic tests that may be used for different purposes or have very different clinical validity or clinical utility in different populations.

Well, first, in considering clinical validity, factors to be considered in assessing clinical validity include, first of all, the purpose of the test, and we note in particular the differences between using a test for diagnostic or predictive purposes -- that is, there may be different implications when a test is being used to confirm a diagnosis in a symptomatic individual. For example, using a genetic test to confirm the presence of cystic fibrosis in a child that has symptoms suggesting that, versus using the test in an asymptomatic individual to predict either future disease or future risk of disease.

In addition, we note that prevalence is a very important factor in assessing the clinical validity of a test. That is, the prevalence of the genetic trait in question within a population will influence calculations of predictive value in particular.

Most importantly, when we think about clinical validity and in general when we think about what we know about a genetic test, there's a pervasive theme of needing to be aware of how much we know and how much we don't know. That is, as we assess the clinical validity of a test and, indeed, the clinical utility of a test, what we often discover is that there are things we simply don't know. There are blank boxes. There are gaps in our knowledge. As there are gaps in our knowledge, that introduces uncertainty about risks and benefits of the test, and so it's very important to acknowledge what uncertainties exist in our knowledge of clinical validity.

There are a number of factors to be assessed in clinical utility. This is the most complex aspect of what we discussed, and I'm going to try and go through these systematically.

But first, I want to say that as we talked about clinical utility -- that is, the outcomes associated with a positive and negative genetic test -- what we noted first of all was the need to look comprehensively at the outcomes of testing, and that means taking into account the social and economic consequences of testing, as well as the health outcomes of testing. As we think about the health outcomes of testing, we have all the different potential risks and benefits that may occur with the medical follow-up that will follow a positive test, for example, and again the uncertainties, the possibility that as we follow down a pathway in which a positive genetic test is obtained and certain follow-up tests are developed in order to evaluate that positive test, we may, as an end result, be left with uncertainty.

In thinking about factors of clinical utility, we also thought that it was useful to think separately about the positive and negative outcomes of both positive and negative test results. This is really just an ordering scheme that we're presenting here, but I'll say at the outset that obviously we need to consider both true and false positives and true and false negatives.

Now, obviously the proportion of true and false positives and the proportion of true and false negatives will be determined by the accuracy of the test. That is, as we measure the clinical validity of a test, we have some knowledge about likelihood of false or true positive and true or false negative, and those will influence the effects of the test, the clinical utility of the test.

When we think about the possible benefits of a positive test result, they involve, first of all, the knowledge of a diagnosis or a risk status, the confirmation of a particular health condition, and they lead,

in the ideal circumstance, to prevention and management opportunities. That is, a positive test leads to a diagnosis, which leads to treatment, which ideally improves health outcome.

Also, a positive test may provide information about family risk status. That is, the likelihood that other family members will also be affected with a certain condition and obviously then potentially have the same opportunities for health benefits from treatment. You'll note as we go through this that this very issue, the identification of risk status of families, is also a negative or a potential risk of a test.

If we look at the potential risks of a positive test, something important to consider, and it has to do with this whole area of uncertainty that we're often dealing with in rapidly accumulating knowledge, is the possibility of exposure to unproven treatment. That is, as a positive genetic test identifies someone in particular with an increased susceptibility to future disease, what we do as a result of that process is create a tremendous motivation to intervene to provide preventive treatment in order to improve health outcome, and that often leads to the consideration of treatments or interventions that haven't been fully assessed, because they're likely to provide benefit, and it's only over time that we'll know what interventions have helped and have not.

Social, psychologic, and economic harms are clearly potential risks of a positive genetic test, and as Dr. McCabe mentioned, we'll hear more about some of the concerns about uses of positive tests later, and as I mentioned, information about family risk status can be a risk of a genetic test as well as a benefit of a genetic test.

Of particular note, if a test is false positive, these exposures are in a sense unnecessary exposures, and we want to particularly note that a false positive test will lead to the exposure to unnecessary treatment in an individual who has been identified as likely to have a particular genetic problem, but in fact doesn't.

Then if we could go to potential benefits of a negative test, obviously, the potential benefits of a negative test are that if we can rule out a genetic diagnosis or risk state, we therefore eliminate the need for preventive treatment that we might otherwise be considering. I would note particularly that if we have someone who has a positive family history and the issue of potential interventions because of genetic risk has been raised because of the positive family history, a genetic test that provides a definitive negative result may relieve the need for pursuing intervention, and that can be an important benefit.

If we look at the potential risks of a negative test result, we have, first of all, the possibility of false reassurance. If a negative result has occurred in a person who in fact has a particular genetic trait or a genetic risk, if in fact it's a false negative test, there may be false reassurance or, as is often a concern in common diseases that do have genetic susceptibilities, we may have a circumstance where a negative test has removed the possibility of a genetic or a specific genetic predisposition to disease, but many other factors contributing to the possibility of disease are still present.

So, for example, in a family with a known BRCA1 mutation, a negative test tells us that the person who had that test result doesn't have the mutation that we know to be in the family, but that person clearly still has a population risk of breast cancer, and it's important that that person not be falsely reassured as a result of that negative test.

There are also potential psychologic effects of a negative test within the setting, particularly, of familial risk, and anecdotally we have certainly heard reports of survivor guilt, of people within a family who didn't inherit the genetic susceptibility and who have psychologic consequences as a result of that, and again, if it's a false negative, there is the potential of delay in diagnosis and treatment.

When we think about factors to be considered in assessing clinical utility, in addition to these generic approaches to the potential risks and benefits of tests, we have to think about some things that are very particular to a given test, and one of the most important is the nature of the health condition and of the health outcomes that occur once that condition is diagnosed. So in particular, we would note that severity of the condition is important, degree of associated disability, and the presence of potentially stigmatizing characteristics are very important in considering the implications of a genetic test.

Some of the examples that we discussed in our working group conference calls, for example, were that a genetic test for susceptibility to periodontal disease has different implications than a genetic test for susceptibility to cancer, and different implications yet for a genetic test for susceptibility to a mental illness or to dementia. So the nature of the condition for which we are making a diagnosis or identifying in particular a future susceptibility will really influence the potential risks and benefits of the test. In particular, the social and psychologic harms that might occur.

Clearly, another very important factor is the availability, the nature, and the efficacy of treatment. All of these different aspects of treatment are very important in determining what are the potential benefits that derive from a positive genetic test, and here again I would note that pervasive theme of uncertainty, that often we have what has been described as a therapeutic gap. That is, the ability to identify people with genetic susceptibilities before we have definitive interventions that improve the outcome of those genetic susceptibilities.gain, as with clinical validity, we want to think carefully about the purpose of the genetic test, and that the potential outcomes of a test may be different if we're talking about diagnosis in a symptomatic individual, because that person already has a defined problem, and often the purpose of genetic testing under those circumstances is to help confirm the nature of the problem, whereas if we're talking about using a test to predict future disease, we're talking about someone who doesn't have health problems at that point in time, and the test serves the purpose of determining what may happen in the future. When we're talking about the prediction of future risk, there's an additional layer of uncertainty.

So if it's a prediction of future disease and we have a highly predictive test, we have the uncertainty about when that future disease may occur. If it's a prediction of future risk, we're really saying the person has an increased risk, but may or may not develop that condition at some point in the future. Each of those has different implications for the risks and benefits of the information for the individual.

Again, uncertainties are pervasive. Often we have some information about the predictive value of the test, but not as much as we would like to have.

Provision of information about family members is a complex matter. In addition to the fact that you may identify potential risk in family members when you identify potential risk in an individual, we also have the circumstance that some genetic tests have the ability to identify both people who are affected and people who are carriers of a condition, people who are healthy carriers of a condition, and there are different implications for those different results. Often in the process of trying to find an affected individual, we do find carriers, which wasn't the purpose of the test, and we have to be prepared for that possibility.

I've already mentioned uncertainties about outcome. We need to think systematically when we think about clinical utility about the quality of the evidence that's available on outcome treatments.

Just a final word about important social considerations, the social implications of certain health conditions are very significant. As I've mentioned earlier, a genetic test that implies susceptibility to mental illness or dementia may be far more stigmatizing and have far greater potential for social or

economic consequences than a genetic test for periodontal disease, and this needs to be sort of taken into account as we think about risks and benefits of the test.

Then finally, there is a potential concern about tests that are targeted for use in particular population groups, that there may be broader social implications as a test is used in a group that include defining that group. How well can we define different ethnic or racial groups within our community? How well do those fit with our knowledge of genetic susceptibility? To what extent do we introduce additional layers of uncertainty about the predictive value of the test? And to what extent do we introduce additional stigmatizing characteristics as tests are targeted to particular population groups?

So those were the factors that we identified as important when we think about the two criteria that we think are to be considered in Issue 1, clinical validity and clinical utility, and I think we're now ready to open for discussion.

DR. McCABE: Okay. So this is the Issue 1, benefits and risks of genetic tests, and what are the criteria that should be used to assess these benefits and risks. We want to open this for discussion among the committee members.

Yes?

MS. BARR: Pat Barr. As I've been thinking about it and reading the literature in the notebook, one of the things that occurs to me is that we don't intend to, but in trying to categorize, we're trying to catch a moment in time that's static, and one of the things I think we're going to have to add to our thinking about criteria is how either the information changes over time or even how genes may interact differently over time in terms of what we're testing and what we can test and can't test. It just seemed to me one more layer of complexity that maybe we haven't included as much as we might in our analysis.

DR. McCABE: Yes, I think that is important.

DR. BURKE: I agree. I think that's why it's tremendously important to emphasize the issue of uncertainty, that in any given time we have to be clear about what we know and what we don't know about a test, and that will change over time.

DR. McCABE: I think this is part of the frustration of many people dealing with this, is the rapid change, and it can have a very important impact on the risks and the benefits from this.

Other comments? Muin?

DR. KHOURY: I guess in some of our discussion the issue came up what are the purposes or the use of genetic tests. I think Wylie tried to capture some of the discussion under prevalence. This issue has been on my mind for quite a bit. There are tests that you'd like to use for population screening, like in public health programs, and then there are tests that could be used for individual or family-based tests. I think some of the discussion about the benefits and risks will take on an added layer of complexity when we're thinking about massive population screening.

Wylie, I don't know if you want to address that.

DR. BURKE: Actually, I'm glad you emphasized that point, Muin, and that really comes under considerations of the purpose of a test. There may be very different implications if a test is used in universal screening versus if it's used in one-on-one clinical delivery of care, and in particular, if it's a relatively prevalent genetic trait used in universal screening, you have a large number of people potentially exposed to any false positive or false negative test results.

DR. McCABE: Yes, and I think the nature of the population, even to say, you know, diagnostic testing versus population-based testing, then the nature of the population and the ethnicity of that population can certainly influence the validity of the genetic test.

DR. TUCKSON: On that last point, do we intend to use that last point as one of the criteria explicitly or not?

DR. BURKE: We had a lot of discussion that I think probably boils down to splitting and lumping in terms of how we laid out the issues, and the working group's conclusions were that it's probably most useful to think in terms of clinical validity and clinical utility as those core criteria, and all of these other factors as factors that go into evaluating clinical utility.

That said, there's obviously a very long list for clinical utility, that being a very important one. In other words, it's not enough to say clinical utility. We have to say clinical utility which means all these other nuances.

MR. HILLBACK: I'm not a geneticist, but I think to get Wylie or some of the others to get into this issue, we spent a lot of time trying to debate could we create a list of factors that would in every case be the appropriate factors? And the more we talked about it, the more difficult, it seems to me, that that became. It almost came down to tell me what you're going to use this test for this time, and then we can tell you what the utility is. I think that's where we ended up having a lot of difficulty in trying to define this set of factors means exactly this in this case.

Maybe someone else can expand on that, but I think we spent a lot of conference call time on that topic.

DR. BURKE: And I think that's why the point about different use of tests, different populations in which test is used, is right up front as a factor that needs to be considered. Each different use, each different population, leads to a different recalculation of issues of clinical validity and clinical utility.

DR. TUCKSON: Help me, then. One of the things, if I understand our task, is to appreciate how these criteria should be used to assess, because they'll be related to Issue 2 later, which is then we apply these criteria to assessing and in assigning categories.

So I guess the question would be, and obviously you've struggled with it and it's a hard job, is to figure out how to give us a list whether you lump or split, but really that's applicable to how we're going to apply it in Area 2. I'm not sure if Area 2 already knows and understands what they want from you. Are all the wheels turning together here?

DR. BURKE: Well, I think, as you'll see when we discuss Issue 2, there is a lot of need for discussion about process, and we'll get into that more, but there's no question that even though we're saying there are two criteria, nice and simple, clinical validity and clinical utility, it's not simple at all, because those are both very complex characteristics.

DR. McCABE: Yes, Pat?

MS. BARR: Conceptually, I imagined a kind of grid, but I was struck by the article on lexicon in the way we're thinking about tests and how we name them and what we call them, and I would just encourage us at some point to be able, and maybe this is part of the lumping and splitting, to be able to talk about the language we want to use for these different kinds of endeavors, because I think it would be

helpful to us and helpful for the public.

DR. McCABE: Do you want to give any specific examples?

MS. BARR: It's the Juengst paper, and he came up with six categories. I think there were subtleties in them that may not be the best way of dividing it, but I found it helpful to go beyond predictive test, diagnostic test. It would maybe simplify our concept of use if we were trying to distinguish the tests at the first end, rather than the second one.

DR. McCABE: Yes?

MS. BOLDT: In regards to the factors for the clinical utility as well, with the nature of health conditions, we talk about severity and the degree of associated disability and potentially stigmatizing characteristic. I would also want to be very sensitive to knowing that these are so subjective, and I don't know if there are any plans that we want to try to figure out some objective criteria in terms of figuring out what's severity versus a degree of disability as well.

DR. BURKE: I actually think that's a tremendously difficult problem, and as we'll get into when we discuss Issue 2, I don't think there's any way at this point to anticipate dealing with that that doesn't really talk about process. Meaning, what kind of input do you need to add to the discussion so that all potential stakeholders feel confident that that process has been acceptable?

DR. McCABE: Yes, Francis?

DR. COLLINS: I think it's important that you have emphasized that in some categories of tests, there may be differences in the prevalence of a particular mutation, depending on the population you're studying, but I wouldn't want that to be overemphasized in a way that would tend to endorse the commonly held perception that population groups are different for biological reasons. Most of what we're talking about are social and cultural differences, and while, of course, there are founder mutations, such as sickle cell in African Americans or cystic fibrosis in Northern Europeans, that have risen to a high enough prevalence that they change the equation a bit as far as clinical utility and validity, for most of the predictive tests that we are talking about in the near future for common illnesses, the expectation is that those variants are going to be ancient and therefore shared amongst all groups.

I would just hope that that flavor came through, and that we didn't unwittingly endorse concepts of the biological differences between ethnic groups which really don't exist. It is mentioned in a couple of sentences on page 29, but maybe it could be even a little more clearly stated that this group in general decries the use of genetics in this particular way to try to draw precise boundaries around groups which biologically really don't exist.

MR. HILLBACK: I think there was a lot of discussion, and I forget who brought it up -- maybe it was Barbara -- that we really had to be very careful in that regard. So if that's not strong enough, I agree, Francis, we should strengthen it, because we did talk about it at some length.

DR. KOENIG: Could I just follow up on that? I think the problem is that it really is a double-edged sword in a way, because you want to pay attention to potential sources of discrimination, but in a way, while doing that, you're also reinforcing this idea of biological difference. So again, as with many of these distinctions and the lumping and splitting, it's not an easy task. It's not a simple task.

DR. McCABE: Yes, Pat?

DR. CHARACHE: I think this concept is also moving over towards Question 2, but I think one thing that didn't come out just now is the continuum of the utility of the test based on who receives the information and the knowledge base of the person who is ordering the test. I think we're talking now as a group of highly educated individuals on genetics information, but this will go out into the world, and we do have to worry about how the person who receives it is going to know what to do with it.

DR. McCABE: We talked quite a bit about the need for education, the need for education of the public, the need for education of health care providers, both generalists and subspecialists. That's going to be a major task to improve that basic, fundamental knowledge base, so that this information can be used effectively.

I don't know if you wanted to talk about that, Wylie.

DR. BURKE: Yes, I actually would like to comment that to me that has particular significance to the importance of defining clinical validity of a test, and in two senses. One is that I think we are recognizing the importance of making clear that a given test does have a certain potential for a false positive or a false negative test, and to the extent that we can, we define what that potential is, so people going into a testing situation are very clear on those possibilities and their implications for interpreting the test result.

As I think we discussed a fair amount in our conference calls, that's an accumulating piece of information about a given test. Often, in the early stages we know very little about clinical validity, and we need to be clear about what we don't know about that significant area of uncertainty that a person may enter into when they decide to take a test or use a test that has an unknown degree of clinical validity.

DR. LEWIS: To follow up on that point, I think one of the other things that's important is that as knowledge develops, the whole ability to play catch up in terms of the people that you've already tested and the people who have already told state of the knowledge today as state of the knowledge tomorrow is different, how do we go ahead and make sure that people have accurate information, because the whole idea of being able to do post-test follow-up with people for years as our knowledge develops and the information they've given has to be updated.

DR. BURKE: There's another nuance that we discussed a little bit, but it's probably worth mentioning, and I think cancer susceptibility offers a good example of that, and that is that there may be a significant difference between the accuracy with which you can say you've identified a risk state and your knowledge of what that risk is.

So you can be very certain, for example, with a particular positive genetic test that you've identified someone who has a susceptibility, an increased susceptibility, to cancer in the future, but you may have great difficulty in assigning the lifetime risk of cancer that that person has as a result of that positive test, and that's part, I think, of defining clinical validity.

DR. McCABE: Yes?

MS. BARR: I think that raises the question of gene/gene interaction and the question of using the first gene we find as a predictor when we know there will be other genes that will modify that, and that that information is going to increase, and whether there is going to be some kind of effort to encourage paneling when we get to those interactions or a tremendous respect for the fact that even as we find those, there will be variations. There are just too many unknowns in the human system to be able to predict with complete accuracy, and yet people use the prediction as a statement of fact, rather than as just a risk.

DR. BURKE: I think you're raising a very important point, and it leads me to a consideration of

how important it is to think about clinical validity and clinical utility together. I mean, to some extent what we really want to know is if you have a positive test, what do you do next and what benefit can you have as a result of what you do?

This is a discussion, I suspect, that we will probably have to have, and that is to what extent does a genetic test have value when it has a well-defined clinical validity, but no known clinical utility? To what extent does risk information itself represent a benefit of -- and maybe I should say no known clinical utility in terms of the ability to improve health outcome.

One of the reasons I think it's important to keep clinical validity and clinical utility separate is because we have to consider that question, but on the other hand, one of the reasons to keep those as paired concepts is that in general we will look at a test in terms of what does it lead to in terms of better outcomes?

DR. KHOURY: Can I just elaborate a little bit on what Wylie and Pat said? I think that the trigger for me was gene/gene interaction, and I want to challenge us all by thinking about gene/environment interaction, and then seeing how clinical validity and clinical utility might meld together, because as you find your clinical validity of a genetic test in the presence or absence of environmental factors, that would spill over into clinical utility.

Let me give you an example. Factor 5 Leiden mutation, which is prevalent in about 5 percent of people, is a risk factor for venous thrombosis, and it seems to be even a more significant risk factor for venous thrombosis in women who take oral contraceptives. So your clinical validity parameter of Factor 5 Leiden in relation to venous thrombosis is very different if the person is on oral contraceptives than if they're not.

That spills over to clinical utility because that begs the question should all women be screened for Factor 5 Leiden before they take oral contraceptives or not? That's more of a utility question that's driven by your clinical validity parameters, which vary by the environmental specification.

DR. McCABE: Yes?

DR. KANG: I'm Jeff Kang from the Health Care Financing Administration. I'm sorry. This is my first day, so I'm catching up here.

This may have been discussed already, but one argument for the separation of clinical validity and clinical utility is from the payer's or insurer's perspective. I'm going to take off my regulatory CLIA hat, but put on the payer's hat. Payers or health insurers are likely to pay for tests which have clinical utility, but not likely to pay for tests which only have clinical validity.

If you carry that through, one model here is in fact to regulate a little tighter the ones with clinical utility for reimbursement standpoints, but then the ones with clinical validity by itself you could kind of take the private market approach, because they're not likely to be covered, and then the reality is the individual who's getting the test and paying for it out of pocket is really taking more of a private approach to it, and then there what you really only need to do is get the system to have the adequate information, so that people can make an informed choice.

I just wanted to comment because I didn't get that sense of the reimbursement side in this, and maybe I missed it because it's a big folder, but I think that in terms of regulation there's this kind of market-based approach versus more of a regulatory approach, and I think maybe one of the ways to split this is where the reimbursers would come out of this in terms of coverage.

DR. McCABE: Yes. Going back to some comments that have been made before about the public's understanding, there was information in the packet about direct marketing, for example, and one of the issues that I think one would have to be very concerned about and very cautious about would be the public's understanding of clinical validity versus clinical utility, because depending on how you pitch the concept, someone might feel that a clinically valid test of unproven utility did have utility for them, and then they might wish to pay for that test privately even before there was reimbursement. So maybe we could have some discussion about that point, because we don't want to confuse the public, either, about these issues.

DR. BURKE: I think that's a very important point. I think we have some information, particularly in the area of breast cancer genetics, which suggests that if the test is offered it has utility. That's basically an assumption that patients bring to the health care setting. So I think that to the extent that tests may become available that have clinical validity, but no proven clinical utility, I think that's a crucial factor to inform the public about.

MS. BARR: I think the other problem with the private use -- I mean, it will show up in both situations, but it seems to me one of the major things we have to tackle is ongoing data collection, because where we go is we start with a small population, then we expand to a larger population, and our goal is to help the individual. So really, as we do that, we need to think very carefully about how we're going to gather the data irrespective of how people get the test.

DR. BURKE: Elliott and I were just discussing the fact that you could have somewhat ambiguous circumstances where you have clinical validity, no proven utility for a positive test, but yet the negative test might be predictive. You might have adequate negative predictive value in order to rule something out even if you didn't know what to do when you rule something in.

So there are a lot of nuances here, but I think they all lead to sort of a truth in offering tests. You know, as clear information as we can provide about those two characteristics.

DR. McCABE: Yes, please?

DR. FEIGAL: Just a comment, because I don't think it's discussed very much in the document, is that most of device advertising, and particularly direct to consumer advertising, is regulated by the Federal Trade Commission, which has different rules and different standards of evidence than either HCFA or FDA, and there's the particularly difficult to control setting of direct to consumer Internet advertising now that is really changing the whole landscape and the way that people self-test, self-medicate, and do other kinds of things.

DR. McCABE: Yes, Judy?

DR. LEWIS: The other thing that I worry about when we start talking about the difference between reimbursement is access issues, and if we get to the point where certain tests are available to those who can pay in addition to what their insurance will cover, we get into a system where some people are systematically denied availability to tests that other people are able to access, and some people overtest. Two sides of the same issue, yes.

DR. McCABE: Yes, Pat?

DR. CHARACHE: I think we also have to recognize that as we are now discussing those two terms, it's a continuum. There's nothing that says this is where one starts and one stops.

I think also, in consideration of some of the reimbursement issues, it strengthens my interest in combining those two. If you can't say what a test is going to do, you shouldn't do the test.

DR. McCABE: Reed?

DR. TUCKSON: As the conversation proceeds, I want to come back to a couple of points that have been made. I still think, under the purpose of the genetic test, the question raised earlier about whether it will be used for individuals or populations, unless that's too much of a splitting -- and I don't want to wreck havoc to the committee's work, but it just seems to me that as I review what we're using as our criteria, that issue doesn't come up explicitly enough, and given the public health implications, it just seems to me that that ought to be -- I'm just thinking out loud, but I think that ought to be one.

I think this point that Ms. Barr makes I think is also useful about perhaps, given the nature of uncertainly, maybe we ought to consider at the end of the day a recommendation about the data collection and the ability to assess and reassess our assessments as more is known. It seems to me that one of the first comments made this morning was this is a moment in time, and I think somehow or another we're going to have to have a certain humility about what we do at this moment and recommend ongoing kind of ways.

Finally, on this last point about the FDA and how they actually operationalize this recommendation, in terms of how they make decisions in terms of public advertising, which I think is going to be one of the most critical real-life implementations of anything that occurs, I hope that we will have a chance to go back after we finalize what we think and compare it with what FDA currently is using, and see whether or not explicit recommendations need to be made once we think we have certainty about our understanding of comparing it with what's going on in real life and make recommendations back to the FDA or whoever very explicitly.

MR. HILLBACK: Reed, I think one of the things that you really pointed out well is one of the things that's caused us a lot of difficulty. It led to a lot of conversation on the Task Force on Genetic Testing, it led to a lot of conversation in our group, and as you see, when we start to talk about the different approaches for oversight, it goes back to a point Pat made and several other people made that this is -- I hate this word, because I've used it so much -- it’s an iterative process.
Unfortunately, it's running from us faster than we can run almost. New information's available every week or every month on each of the tests we do. Whether it's a test that we've done for many years, like cystic fibrosis, we still have more information and new information all the time.

I think we'll hear from Muin on some of the things that CDC and this consortium of government agencies is doing to try to find ways to deal with this iterative process, because that's led to a lot of difficulty in thinking how do you regulate, how do you provide oversight, how do you keep up to date? If it was a static situation, it's relatively easy, but isn't.

Pat introduced the topic and I think you expanded on it well. That's one of the toughest problems we have when we get to some of the things we'll talk about tomorrow in terms of the proposals that we ought to make.

DR. BURKE: And I think where that goes is it's what triggers a reevaluation. I think that's going to become a very crucial question.

If you have a test like ApoE4 polymorphism to predict risk of Alzheimer's disease and the decision is that that's got poor predictive value and no treatment implications and we're not particularly

happy with a test of that sort being used, at what point do you have treatment intervention data that's of sufficient quality that you want to relook at that question? When do you have an intervention that makes a difference? What kind of data, what kind of quality of data, triggers a reevaluation?

I think it's that trigger of reevaluation that we want to try and create a process for and a way of defining.

DR. KHOURY: I'd like to emphasize the point that Reed made about the individual versus population use and the importance there of differentiating between clinical validity and utility, and while I agree with Pat that there's a continuum from clinical validity to clinical utility, when it comes to populations or mass screening, that clinical utility component has to be very carefully defined.

I'll give you a couple of examples. If we know that testing for PKU in newborns can predict the disease 100 percent, we're not going to do a mass screening of all newborns unless there is a low phenylalanine diet that would reduce the risk of mental retardation down to zero.

Same thing with hemochromatosis. We're not going to offer a mass screening without the knowledge that perhaps phlebotomy will lower the risk of iron overload in the liver.

So while there is a continuum and some people might think that having the information may be clinically useful per se to plan the individual or reproductive or family situation, when it comes to public health utilization, the utility has to be clearly defined among a constellation of factors like acceptance of the population and the ethical issues and the quality of the test, that there is a clear reduction in morbidity, mortality, and disability.

So that's perhaps one of the issues for discussion in Issue 2.

DR. McCABE: I think one of the issues, though, will be when is it clear? For PKU, I've lived my career through PKU, and know how long it took people to address those issues and the amount of funding that was invested in a single disease to address whether the diet was beneficial and to what extent it was beneficial, and when the intervention needed to be made.

We're talking about many more diseases with delays in onset that are much more extreme, and one of the issues I have is just how we're going to be able to track all of these and collect these data that we feel are important.

Yes?

MS. BARR: Well, and I think much of the data has come from academic research up until now, and as you said, there will be so many diseases and now so many gene/environment and gene/gene interactions, what are the incentives going to be to see that both the orphan diseases continue to be examined, but also that the large impact, low penetrance diseases will also be adequately investigated? Whose responsibility is that going to be?

I think in some sense that's beyond our charge, but it's a background to our charge, for sure.

DR. McCABE: Well, I think that the incentives are an important issue, because we can say that it's important to do these things, but without identifying how we might incentivize those who will be responsible, I think it may be hard to really accomplish what we've set forward.

There was the issue about the public advertising that was brought up and that Reed mentioned. Maybe you could go into a little bit more detail on that and some issues that come up in more traditional

device environments.

DR. FEIGAL: One of the things that actually makes diagnostic tests interesting to think about is that in more than half the states, any consumer can walk into a clinical laboratory and order a test on themselves. So in fact, when the test is available, you don't need a health professional in the loop in more than half the states. This is not an FDA determination. This is a state by state. So when you actually look at the complexity of how health products are regulated, you have all of the issues that we're already aware of between CLIA and FDA, the reimbursement issues with HCFA, but you also have the things that are regulated by the states.

Over-the-counter products and over-the-counter devices, or direct consumer testing, I think is probably something that we would see or anticipate would be down the road, but I guess I wouldn't necessarily assume that that would be the case.

One of the areas, for example, that is also very controversial that's been very hotly debated is simply the right of the public to be able to do its own drug testing for substance abuse, an area that has just as many social kinds of ramifications and implications and employer issues, and many of the kinds of parallels that there are with genetic testing. The answer to that question has come down very firmly that such tests should be available. It's instructive to actually kind of look at how some of the dilemmas of that have been dealt with and how they might parallel this issue.

For example, how accurate should the tests be? When the first tests were offered, they were offered as a battery, and one of the concerns was that they were not of equal accuracy, and that you really needed to have a confirmatory test for any one that wasn't positive. The negatives were of value. If you were negative on all of the drug screens, you didn't need a confirmatory test to say that you hadn't been using drugs of abuse, but if you were positive on any of them, you should have a confirmatory test.

In fact, that was the approach that the agency has taken, is that the cost of the confirmatory test should be included in the test that the consumer purchases, and in fact they should have incentives to send in for the confirmatory test because the current tests don't label which of the five were positive, so they mask the result, and they don't really say positive. They say negative and maybe.

As you look at the struggle with this -- and the limits of this have been pushed, because there are manufacturers that currently want to offer tests for single products. There's no way to mask a single product. Then there are the companies that feel that the -- well, we're actually not quite sure what their rationale is, but to guess, some have made the confirmatory test not paid for as part of the -- even though that currently is not in compliance with our requirements, but the rationale there perhaps being that the negative test is of sufficient value and someone should have the right to find out whether the result is accurate or not. We actually have people debating whether someone can make a decision about whether the information they get is accurate or not.

So I think you see in a microcosm all of these kinds of issues, and the fact that it's directly advertised was pointed out to me by my 13-year-old daughter, who brought me an ad from Rite Aid and said, "Hey, did you know you can get drug testing at Rite Aid and we can buy that there?" It was in yesterday's Sunday paper.

If you translate these kinds of issues and anticipate kind of a similar sort of public interest in sort of personal knowledge of something that's very private, I think we can see that this is a direction that this might move.

The rules of the Federal Trade Commission and the whole process are different than FDA, and

that's probably a topic unto itself. There is split jurisdiction in information that's provided to health practitioners and consumers between the FDA and the FTC that varies by product. There are some products where the advertising is in FDA's jurisdiction. These are the prescription products. Labeling is within FDA's jurisdiction for these products, and where that boundary is between advertising and labeling is one that even the two agencies continue to debate, and the Internet, as I mentioned before, is one area that particularly challenges some of those distinctions.

The basic philosophical underpinning of advertising is supervised by the Trade Commission, and it has a different philosophy than labeling supervised by the various parts of the Public Health Service. One agency's purpose is to promote fair competition, so part of the philosophy behind untruthful advertising is that it's unfair to the competition. It's a different kind of mindset.

Nonetheless, FTC and FDA have worked together in the past on consumer advertising. It's an issue that I think adds another wrinkle into this, but I think we are in a time where we're naive to think that we can put the genie back in the bottle and that health advice is going to come mediated through health providers who have ordered the tests, who will invite you back for a counseling session. The current framework in which tests are approved -- and by law in many states, the consumer has a lot of free access to these kinds of tests, and it's very challenging to coordinate all the different types of approaches.

MR. HILLBACK: Can I just ask a quick question? Do you know if any of the labs that are doing genetic testing have actually done testing straight for consumers? I do not.

DR. McCABE: Could the gentleman come up to a microphone, please?

DR. BUCHANAN: I know of two cases. The Human Genetics Lab at Michigan State University offers a direct to the consumer test kit for testing for hereditary hemochromatosis. It's a cheap swab, two little brushes, send it back in a ziplock bag. In the United Kingdom, until about three years ago, there was a through the mail cystic fibrosis test. That test wasn't covered by the National Health Service.

Those are the only two that I know of. There may be more. The one at Michigan State has reportedly conducted between 2,500 and 3,000 tests in the four years since they've been doing it, and they do the test on children, by the way, also.

MR. HILLBACK: Thanks.

DR. McCABE: Reed?

DR. TUCKSON: So with that last, do we know or have we had a chance yet to assess the way in which the FDA currently views validity and utility in making its assessments in this area now, or are they just not making these assessments today? And if they are using an assumption of utility and validity, how does it compare with the recommendations that have come from the subcommittee? Is that anything that we know quite yet?

DR. FEIGAL: Well, I think this is a complex topic that we're getting into in more detail tomorrow. I think the answer differs whether or not it's a laboratory home brew-type testing or commercialized test in terms of the approach, but I think this is a whole topic tomorrow, so maybe we could defer it until then.

DR. TUCKSON: Okay. I'll wait.

DR. McCABE: Are there any other specific issues that people want to address about the

document regarding Issue 1? Yes, Barbara?

DR. KOENIG: I guess I'd like to go back to the lumping and splitting questions from the beginning. One point, and I was not on the group that wrote this particular document, but in reviewing it, I'm somewhat concerned about the issue of putting all of the social consequences of testing -- sort of subsuming them under the notions of clinical utility and clinical validity, because it seems to me there may be an important argument for thinking about the implications of testing not simply in terms of this sort of quantitative adding up of all of the individual tests carried out in society, but there might be situations where there are tests which we would want to consider that have impact on the entire society, rather than just individual clinical incidences.

It may be that we can leave it there, but I just think that's an important point, that there may be some kinds of tests that we might not want to do, or just in terms of the criteria, the categories that we use to think about which kinds of tests would need a higher level of scrutiny.

MS. BARR: Barbara, are you talking sort of about individual impact versus public impact, and that we might want another column?

DR. KOENIG: Exactly.

DR. BOUGHMAN: Maybe I can make a comment about that, too. We actually discussed some of these very issues in trying to approach this in an outline format or a matrix format, and in fact the social implications portion of this almost made it another dimension to the format, and we found it very difficult to crystalize that, but I think you make a good point, and maybe we could move some comments back into the general overview section in kind of reminding ourselves and others that this would add a dimension to all of these evaluations.

DR. BURKE: I'd actually certainly just agree with the comments, and I think it's probably worth noting that we were dealing with clinical evaluation, and therefore some assumptions about the fact that we are talking about tests that have health implications, and so it may be that we need to talk about the degree to which this committee does or does not talk about genetic factors that don't relate to health.

But I would have to say, other than that point -- in other words, I think the point I'm making there is that when you've already started with the assumption that you're talking about genetic testing in the context of health and health outcomes, I think you've put some constraints on the discussion in terms of how you think about clinical utility. How you think about utility, I guess.

That said, I think it would be very helpful to have some concrete examples to help flesh out some of the broader social issues and to determine the ways in which they might really separate out from the kind of issues we are already listing in clinical utility.

DR. McCABE: Yes, Victor?

DR. PENCHASZADEH: I think that when you come to speak about social implications, you deal with not only the division of whether it's health-related or not, and you are talking about enhancement and that sort of thing, but also another level of analogy, which was discussed earlier, about public health programs versus individual clinical-based services, because one could argue that any public health policy that has to do with genetic testing and the genetic health of populations will have social implications, you can analyze that within social implications.

But I certainly would support the idea that this is analyzed separately from what we've been

discussing so far this morning, which is the individual clinical-based genetic testing, because of course you have social implications of the former also, and you have social implications about individual tests done for a health-related condition, but that can bring on an individual social stigmatization or discrimination of different kinds. So I think there are several dimensions here that we'll have probably to separate and analyze.

DR. McCABE: Yes?

DR. KANG: I kind of like where this conversation is headed, because I've been struggling with the difference in clinical utility. We talked about population-based screening and then also tests for individuals, and it strikes me that to the extent that we are trying to sort out kind of a regulatory hierarchy, that the tests that we might recommend, or some experts might recommend, for mass screening really does demand in many ways a lot of the clinical utility issues to be sorted through, the ethics, et cetera. We have to be very confident that this is useful information for whatever purpose, societal purpose.

So I kind of like a construct of maybe separating, of really being specific in saying that clinical utility is going to be the individual clinical utility, and that maybe we kind of create another construct called social utility, or I don't know exactly how you want to call it, and then the degree of regulatory oversight when you get into that box is going to be in many ways even greater because you really want to be kind of damn sure in what you're recommending and what you're getting.

DR. BURKE: Yes, I think that makes a lot of sense. I think Muin's comments underscore that you need to have knowledge of clinical validity and utility to make that assessment.

In going back to how we had set up the beginning parts of Issue 1, we had said clinical validity and clinical utility, and then just what was a small note about considering those factors separately for each different health outcome and each different use of the test, and it seems to me that small piece, based on this discussion, needs to be expanded to incorporate these issues that are being clarified.

DR. McCABE: Yes, Pat?

DR. CHARACHE: I think one of the issues that's going to be a challenge is deciding when you have crossed the threshold, because it's going to be a continuum of knowledge increasing, both in terms of laboratory accuracy, predictive value, and what have you. Among the questions that have to be thought about is who's going to decide when you've crossed that threshold and what type of criteria could be applied that says that it's now ready to be offered, with the understanding that information will continue to be accumulated over time.

DR. McCABE: Yes, Judy?

DR. LEWIS: I just want to underscore the importance of what Barbara said before about this all happening in a social context, and I agree that we should be focusing on genetic tests that relate to health and illness, but that doesn't happen in a vacuum outside the social context. That really has to be an overarcher and I think that some of those issues get measured with a different set of analytic tools than do clinical utility and clinical validity, and that it's a much more value-laden, qualitative set of tools sometimes than the tests that we use in other areas, and that we just need to keep aware of the fact that we're using different kinds of measures of value and that each set of measures may be different, but one set is no less important or valid than the other.

DR. McCABE: One of the things that I'm hearing in the discussion we may want to clarify on page 29. We've talked about social considerations, and we've really now sort of separated out, and it's

mixed into this section here, but there's the social utility public health benefit of testing, and there's also mixed in here the testing for nonhealth-related or not completely health-related issues. So we probably need to address both of those separately and specifically, and to clarify the document in that way, so that we're not mixing too many things into the one section.

DR. KOENIG: Is this a good time to discuss the issue of the boundaries between health and non-health areas or is that something that's on the agenda later? Because I confess I still have some confusion on that point.

DR. McCABE: Well, I think it's addressed in this section, so that we could certainly consider it now, because I think it is important. It'll probably come in later as well.

DR. KOENIG: Well, I have on a number of occasions tried to make a point that the boundary between health and non-health-related conditions is somewhat arbitrary and fictitious and changes over time as conditions are medicalized, demedicalized, et cetera. So I think it's not a bright line that can be used realistically in the world in any way.

But I guess I still have some confusion of was our charge specifically about health-related conditions, and I'm not clear about that.

DR. McCABE: Well, I think, as I was reading through the document, it was interesting to me to look at what we had listed as nonhealth-related conditions all have health implications, and certainly even the behavioral issues, which is one of the big concerns in genetics and is addressed in here, depending on where one comes from philosophically, you may consider that health or nonhealth or whatever. So I think that to the extent that, as you say, first of all, the boundary moves, it's fairly fuzzy, than it is within our purview.

I think that one of the areas that we discussed in a conference call, and I can't remember whether it's in here or not, is one of the areas that Francis sort of touched on, and we could get away from issues that are addressed here that have some health relatedness, but as one begins to define populations by their genetic diversity and the fact that some changes are old, some changes are new, populations are evolving, there one could get into pure social issues and looking at relatedness of individuals and families and populations. We already know that there are huge controversies related to that. That probably is going beyond our purview at this point in time, but I think certainly all the examples that were shown here have some health relatedness.

DR. PENCHASZADEH: On this subject, I think that this will be a never ending discussion and things will continue to evolve forever, because, after all, health is a socially defined concept.

But I still would prefer to keep our charge or our path or our main focus on what we can call health-related conditions, acknowledging that the border is blurry, but otherwise we'll risk going to Mars.

DR. McCABE: What you're saying is that we have enough to do with a narrow charge.

DR. PENCHASZADEH: Yes.

MS. BARR: I wonder, even with the narrow charge, though, if we could do some backward thinking as we go forward. That is, as we come up with notions of regulation or oversight or consensus building, we also think about what that will do to some of the social issues people are worried about. So we do it after the fact, but we have comment on it, because I think it's our responsibility to think about that.

DR. PENCHASZADEH: I agree with that.

DR. KOENIG: And one of my questions is just jurisdictional. For example, what about a test that's been administered in -- say that there are suggestions about oversight of genetic tests. Will those then apply to tests that are used, for example, in the justice system? Those are questions about which I am just not totally clear.

DR. LEWIS: And the other thing is I'd be willing to bet if we went around the table, each of us would define health somewhat differently, and that there might be some places where some of us would rule in and some of us would rule out, because health has a very different meaning in different disciplines and for different individuals.

DR. KOENIG: But could someone clarify that point? For example, forensics is not exactly the right word, but is that a separate regulatory system?

DR. FEIGAL: There are settings, getting back to drugs of abuse, we do not regulate the forensic uses of the tests for drugs of abuse, so that is an example. The other area that's been more on the borderline where I think we have weighed in has been in the occupational setting.

DR. TUCKSON: I think specifically I know that some of us were offput a bit by the public testimony section in the first meeting with the representative from the Justice Department regarding the use of these tests in the criminal justice system. That sure got my attention. It was this very strange moment, and I think it is important to note, since they brought it to us. I think that's what you're getting at, is what the heck are we supposed to do with that?

DR. McCABE: Well, as has been commented, we need to address this as a concern, and perhaps highlight it in this section as an area of concern in terms of different settings in which testing may be carried out and the implications within those settings. Especially if we're talking about tests that have implications that we would all consider health-related, but may be used in a different setting for a different purpose, certainly I think what I'm hearing around the table is that that's a concern for many of us.

We're scheduled to take a break now, so we're going to take a 15-minute break. We will resume at 10:45. The members and presenters are invited to the Parklawn Room for coffee, which is around the corner there, and there'll be people to help you find that.

(Recess.)

DR. McCABE: I'm going to take the Chair's prerogative of reorganizing the morning just a bit, and Dr. Buchanan's information, I think, will be very helpful to us and help us in our discussion. So he was going to speak a little bit later this morning, but we're moving him up to this slot.

The title of the presentation is "Genetic Testing: Policy Considerations." Dr. Buchanan is Professor of Philosophy at the University of Arizona in Tucson. His specialty is bioethics and political philosophy. He is the author of over 100 articles and books, including "Ethics, Efficiency, and the Market," and with a fellow philosopher, Dan Brock, "Deciding for Others: The Ethics of Surrogate Decisionmaking."

Dr. Buchanan served as a staff philosopher for the President's Commission on Medical Ethics and staff consultant for the U.S. Advisory Committee on Human Radiation Experiments. He currently serves

as a member of the National Advisory Council for Human Genome Research, and his newest book, with Dan Brock, Norman Daniels, and Daniel Wikler, is on ethical issues in genetic interventions.

Dr. Buchanan?

DR. BUCHANAN: Thank you.

I have to begin with an apology. The paper that you have is a very rough draft, as I'm sure you've detected if you had a chance to look at it. I know that time has been short, and most of you probably haven't had a chance to read it, but it's very much a work-in-progress, and I was hesitant about whether to even allow it to be circulated to this group. But I hope you'll indulge me with it and give me your comments which I would value very much.

I hope everyone has a hand-out now. It's a single sheet double-sided.

DR. McCABE: It was handed out at the break. So it should be at your seats.

DR. BUCHANAN: I would like to leave a lot of time for discussion, and time is short. So I'm going to skip over some parts of this. There's a summary that includes a taxonomy of the ethical issues, and that may be helpful for your purposes because it distinguishes a number of different areas of ethical concern.

There's a very brief and skeletal survey of the current regulatory scene which you know better than I do. The most important part is the Guidelines for Policy, and this is summarized on page 18 of your briefing book, and I would just like to go through those briefly.

Let me give a little bit of background first. I wrote this paper for other purposes than your group, but I think the timing was fortunate. I think it does have some relevance to what you're doing, and I was reacting to some extent toward what I perceived to be a tendency in some quarters, not in this committee, to be ready to move toward regulation of genetic tests without having gone through a thorough discussion of the ethical issues, and as I'll emphasize a little later, one of the important ethical issues or areas of ethical concern came up this morning several times during the discussion. Namely, the distinction between medical and non-medical uses of genetic testing, and though it has a lot of virtues, the Holtzman Report, the task force report, it flags that issue briefly, but it doesn't deal with that issue at all, and it seems to me that today, there's even less reason to omit consideration of that set of issues than there was at the time the task force report was written, and in particular, in the area of predictive tests that claim to make predictions about behavioral genetics traits, that's going to be a big issue in the future, and I think even if this committee decides that it wants to restrict its main message to medical uses of genetic tests and hence to focus on clinical utility, that at least the committee should flag that issue very strongly and say that in the future, there's every reason to believe that market forces will develop a market for genetic testing that is not restricted to anything which most people would uncontroversially call "medical conditions/health conditions."

So even if you don't make that your main focus, I think you do a great service by flagging that issue very clearly.

Well, here are the guidelines, and they're mainly in the form of sort of cautions, what to avoid. First. Proceeding on the uncritical assumption that the greatest danger is that genetic tests will be overutilized, and that marketing, unless severely restricted, will play an exclusively detrimental role by contributing to overutilization.

And the way I'd like to present this is to just point out that in general in our health care system, overutilization is not the main social concern these days. People are worried about excessive limits on utilization imposed by managed care entities.

In the area of genetic testing, there's an additional reason to worry about underutilization, besides the general problem about managed care, and that is, it's fairly well documented that fear of genetic discrimination in employment or insurance may be deterring some people from getting genetic tests from which they could benefit.

So there are at least a couple of factors in the current environment which would seem to lead us to worry about underutilization of tests, in addition to whatever worries we may have about overutilization, and that's why I think at the beginning of the process, it's important to be open-minded and not assume that the major problem that we should be thinking about in terms of regulatory proposals is overutilization. Some tests may be overutilized, some may be underutilized.

And in fact, marketing, which is a bad word in the vocabularies of some people, may alleviate some of the problems of underutilization for some tests, and it could do this in a couple of ways. If there were marketing that produced some price competition among those offering the tests, then tests might become more affordable and hence access to tests might be increased.

But probably more importantly, if there's marketing of tests that gets information out to providers and potential consumers about the value of tests, this may lead them to put pressure on insurers to cover those tests, and that's a way in which in fact you could have a beneficial effect of marketing under certain conditions.

The second point. We should avoid indulging in genetic exceptionalism. I'm not sure where that term came from, whether I coined it or Bob Cook-Degan coined it or someone else coined it, but it has some value, I think.

By genetic exceptionalism, I mean the tendency to assume that the risks of genetic services or breaches of privacy or confidentiality concerning genetic information are especially grave and require special regulation.

I think it's just a matter of looking at things case-by-case or group of services-by-group of services, and that we shouldn't simply assume that because something has the modifier genetic in front of it, there are especially grave physical or ethical risks involved, and, of course, there's a lot more about that and examples of that in the paper.

Third. Failing to weigh adequately the costs of regulation, in particular the tendency of regulation to restrict access by raising the costs of genetic tests.

I think actually that the tendency toward genetic exceptionalism feeds into Number 3, into the failure to weigh the costs of regulation. Often, people tend to assume that if a test is a genetic test, there are very special and very severe risks of psychosocial harm, and therefore it's extremely important to have a very rigorous process of informed consent, to have elaborate pre-test and post-test counseling, and, of course, those are all commendable proposals because they're designed to reduce the risk of psychosocial harm, but we have to make a distinction between optimizing with regard to the reduction of risks and what's feasible once you consider the genetic test in question to be part of a whole array of health care services that have to be provided within a limited budget.

I'm afraid that sometimes, people are so concerned to reduce the risk of psychosocial harm, that

they proceed as if the goal is to reduce it to zero without consideration of the opportunity costs, and one of the most important opportunity costs is limiting access to that genetic test but also limiting access to other valuable services, genetic or otherwise, which will get short-changed if we go overboard and fail to realize that the proper goal is to reduce risks, not to eliminate them entirely.

Fourth. We should avoid the tendency to overgeneralize from two paradigms of the genetic testing encounter: the therapeutic pessimism paradigm and the reproductive choice paradigm.

It's not surprising that the history of genetics and genetic counseling should influence the way we think about the ethics of genetic testing, and in the history of genetic counseling and genetic testing, there are two very prominent kinds of testing encounters that have helped shape the way we think about these matters.

One is typified by the case of someone having either a carrier test for something like cystic fibrosis or prenatal test for Down's syndrome. That's what I call the reproductive choice paradigm, and that's a very special kind of case because it involves some of the most intimate activities that human beings engage in, reproduction, child-rearing, and also because for the most part, there's the choices that you have when you get a negative -- when you get a positive test result are very limited. Not all genetic tests are like that.

Similarly, with what I call the therapeutic pessimism paradigm, and the clearest case of that would be something like testing for the Huntington's gene or perhaps ApoE4 mutation testing, polymorphism testing, for greater risk for Alzheimer's dementia, and there, it's a very bleak situation. There's no effective treatment. The implications of a positive test are very grim, and because of that, certain kinds of practices are appropriate. Non-directiveness is extremely important in both of these paradigms, though, of course, there are debates about what the limits of non-directiveness are.

But it would be a mistake to generalize from these cases to a whole range of other cases of genetic tests which either now exist or will certainly be available in the future.

You can think of a kind of continuum stretching from the therapeutic pessimism case, say Huntington's on one side, toward a case which you've discussed in your former deliberations in this committee, a test which can detect some predisposition toward periodontal disease, okay, and in between, more toward the more optimistic end of the spectrum, you might have something like the test for hereditary hemochromatosis, and somewhere more toward the middle, you might have a test for genetic predisposition toward colon cancer, and then at this point, further toward the therapeutic pessimism paradigm into the continuum, you might have something like tests for the BRCA1/2 mutations.

All of these cases are different, and there are going to be more different cases emerging all the time, and what's appropriate from an ethical standpoint and a regulatory standpoint will vary depending upon what the test is like. So this is a plea for a particularism, for not letting our history determine the way we look at things and not putting too much attention on these two paradigms.

And the fifth item is related to this. It's on page 19. Assuming that there's a single set of appropriate regulatory standards, and in particular a single threshold of predictive value to be required for all or most genetic tests.

I think that where the level of predictive values should be set will depend upon at least a couple of things, and you've already talked about this to some extent.

One, on what the risk-benefit profile is for that test, generally speaking, but, second, it will

depend upon the context in which the test is offered, and Dr. Kang brought this up earlier, when he said that it was important to distinguish between the context of testing where the test is covered by a standard insurance benefit package versus a case where it's being purchased privately, in a discretionary way, out-of-pocket or by some special supplementary insurance policy by an individual. I would distinguish a third case, and that is the public mass screening context, and I think that some of Dr. Kang's later remarks indicated that he thought that made a difference, also, that the standards may be quite different for those three different contexts.

For a public mass screening program, the standard for clinical validity as well as clinical utility may have to be relatively quite high for a couple of reasons. One, because you're using public funds, and there are competing uses for public funds, and there has to be a rather high standard of justification for the use of public funds to do this rather than something else.

But, secondly, if it is a public health endeavor, it's going to be something which is taken by many people to be endorsed very strongly. This actually raises an issue that I only sort of flag in my paper, but the committee might want to also flag or even discuss, and that is, the distinction between social marketing and private marketing.

I don't know if you're familiar with this distinction. I used to teach in a business school, and this was a very important distinction.

We think of what we ordinarily think of as advertising as private marketing, but there's also social marketing. There's social advertising, and it occurs whenever you have public health initiatives. That is, the media are used to try to influence people's behavior to do certain things, to sign up for a screening program for hypertension or for a genetic test for cystic fibrosis or to change their diet in some way or to live in the "healthy lifestyle," and there are ethical issues about social marketing as well as about private marketing.

But my main point is that what sort of regulatory standards are appropriate may vary quite significantly, depending upon whether it's testing in the context of a public mass screening program, whether it's testing covered by a standard insurance benefit package, or whether it's a private purchase, and again this may be somewhat inflammatory. I just throw that out for stimulating discussion, but there is an argument to the effect that if the test is safe, and if clinical validity is accurately certified, that there's something to be said for a presumption in favor of people to be able to purchase that test for themselves from their own resources, if they wish to, and that's why I'm a little bit leery about the term "clinical utility" because it seems already to enforce a kind of medicalization model.

There are going to be lots of tests in the future which, according to many people's lights, are not tests for health conditions at all, either for predisposition or for detection of a disease. But people may want them, and from one standpoint, you might say, look, it's information about themselves, right?

Why don't they have the right to get it if they're willing to pay for it? At least so long as there are appropriate conditions of truthful advertising, which is very important, and so long as there's not some clear demonstration that this is going to be harmful to other people, why shouldn't people be allowed to, for example, take tests which they at least believe are going to give them some information about behavioral genetic traits of themselves or perhaps even their children?

Talking about clinical utility and disutility prevents you, I think, from even discussing the possible non-medical uses of genetic tests.

The Holtzman Report flagged that issue but did not discuss it, the task force report, and I think again, as I said earlier, it would be a mistake not to discuss that at some length.

Number 7. It's on page 19. Wrongly assuming that any legitimate application of biotechnology to human beings is a health care service, that's what I was just alluding to, where this assumption facilitates misplaced or excessive medicalization, including medical paternalistic gatekeeping.

I don't want to be misunderstood here. I think that where it's clear that a test is a health service, that it's appropriate to have medical gatekeeping within limits, but in cases where the test isn't something that's designed to reveal a health condition, then we shouldn't assume that there should be a large role here for medical gatekeeping, and we have a lot of sad history of inappropriate medicalization in this culture, particularly with reproductive technologies.

For example, cases where physicians took it on themselves to limit access to in vitro fertilization, excluding single women or lesbian women, for example. And we would be, I think, naive to think that there's not a potential for misplaced medical gatekeeping based on an unjustified assumption that because something is a genetic test, it's a medical test.

And, finally, we should avoid indulging in an unreflective hostility to the marketing of health care services based in part on an assumption that health care is a special or unique kind of good, and in part on the failure to distinguish between the moral limitations of the profit motive and the efficacy of the market as a producer and distributor of goods.

With regard to that first assumption, that health care is an especially-unique kind of good, I'm not sure if it's unique, but I think it certainly is special. I'm not questioning that, but it's when that assumption gets coupled with this kind of unreflective hostility toward people who pursue profit that I think we run into problems, and, you know, if in fact vigorous marketing of certain genetic tests resulted in equipping consumers with information that they could take to their health care insurers and pressure them to get these tests covered, then that might be a good effect of somebody operating on a profit motive. Namely, the people who did the marketing. And whether we like it or not, in this country, we've made a kind of societal choice to use the market for health care in certain ways, for the sake of greater efficiency supposedly and cost containment, and the question is whether we can utilize the market in a way that properly reflects the special importance of health care.

That's a very general question, and I don't think that there's any reason to exempt the discussion of genetic tests from that general debate. The reason that I include this last item is that I've heard from a number of people, particularly from physicians, a kind of automatic revulsion toward the idea of marketing genetic tests, and a sort of finger-pointing about the profit motive, and I just think that we have to be a little more balanced and open-minded and, of course, be watchful and wary about the negative consequences of unrestrained pursuit of profit but also to be open-minded to the possibility that marketing of genetic tests under certain conditions within an appropriate regulatory framework might have some benefits, and some of those benefits I've already alluded to and are detailed in the paper.

Let me just close by saying one thing. I wanted this paper to be provocative. I did not intend it to be offensive, and the line between being provocative and offensive is often very hard to detect until one has already crossed it in the wrong direction.

(Laughter.)

DR. BUCHANAN: So I hope it's not offensive. Again, it's a draft, and I'm looking for input, especially critical input, for improving it. So you know, with that plea for mercy, I'll subside.

DR. McCABE: Why don't we discuss Dr. Buchanan's specific proposal before we get back to our

more general discussion, a specific presentation? Yes, Pat?

MS. BARR: Well, I would just suggest a balance of the commercialism discussion because I actually agree with you that there have been clear instances in medical history where making tests available was very useful.

But we have clear instances in medical history where making tests and procedures available was very detrimental, and one of them, I think there may be a dispute about this, but one of them, for instance, is bone marrow transplants for breast cancer patients, where it's a very expensive procedure, but there was equipment around to do it, and we didn't bother to test it first.

So there, it became a situation where the public was demanding it, the courts, you know, constructed the situation where insurance had to cover it, and we've taken a long time to find out it may not be very useful for most women. So I would just caution a balance.

DR. BUCHANAN: I think that's a great example, and I take the point. You know, it's a matter sort of of rhetorical goals here. I felt that there was a tendency to go too far in the other direction, and so I may have overcompensated, but I think that's an excellent example.

There's been a lot of information coming out about it recently in the press, and the interesting thing is it's not a genetic test, and that reinforces my general point that when you look at issues about marketing and the ethics of marketing, we shouldn't assume that in fact it's a genetic service that's been marketed and makes some enormous difference.

It may make a difference in some respects because I think our culture has a kind of gene fetishism and a kind of genetic determinist presumption about things, and I mentioned that in the paper, but I think you're right. I probably haven't talked enough about the other side, about the danger.

I take the dangers of commercialization to be obvious, but I should say what they are.

MS. BARR: As well as the dangers of individual choice, particularly in the prenatal situation, and the impact on the gene pool and all kinds of things.

DR. BUCHANAN: I'd like to hear more about that. I find that very interesting. You mean like sex selection or --

MS. BARR: Well, sex selection or wait till we get the most intelligent of our embryos or let's modify our embryos to make them more intelligent.

I mean, I think that diversity is very, very valuable, and it has proved valuable to us as a species, and we should be careful about messing with it because it's not -- is it a medical service or not a medical service?

DR. BUCHANAN: And we don't know what we might inadvertently change when we select --

MS. BARR: That's right.

DR. BUCHANAN: I guess I agree with that entirely, but I tend to think that in terms of the human species as a whole, it's very unlikely for the foreseeable future that enough people are going to be able to afford to make those changes for it to become a real risk.

Sex selection is quite different. Already in Northern India, the ratio of males to females has been radically upset by the private market in ultrasound for selection of males, but for genetic engineering -- I mean, I think it's important to think about that for the future, but right now, I think it's unlikely that most human beings have the level of affluence to be able to indulge this to significantly affect the prospects of eugenics, but maybe I'm wrong.

MS. BARR: But then you're going right into eugenics. The wealthy can do it. The wealthy are doing it. The wealthy are saying it's right to do it, and we're better. You're heading into a very slippery slope, it seems to me.

DR. McCABE: Wylie, then Reed, and then Victor.

DR. BURKE: I just want to comment on the implications of both Pat's and Allen's comments on the difficulty of understanding and evaluating efficacy, whether we're talking about clinical utility or social utility, and I think the bone marrow example's a really good one.

But it's clear that in clinical medicine, where we might assume that there's a fair amount of technical sophistication, there's a great deal of difficulty distinguishing between the value of a treatment that seems like it ought to work and a treatment that has been proven to work, and we actually have a number of telling examples, the carrot trial that showed that vitamins ought to have reduced risk of lung cancer didn't reduce it. The encainide trial that showed that anti-arrhythmics that should have reduced post-infarction death didn't reduce them, to tell us that efficacy actually has to be evaluated rigorously, yet the bone marrow treatment for breast cancer example illustrates that when you have a treatment that sounds like it ought to work, it will be attractive, and I think that has tremendous implications for how we communicate what we know, how we determine what we know, whether it's a genetic test or otherwise.

I think the other comment I want to make, which is a corollary comment, is that I think the concerns to avoid genetic exceptionalism are extremely important, but that I think one of the things that may be happening around the discussion of genetic testing is that we're being forced to realize that there's a level of rigor that we should be taking toward all tests, that's coming out in the discussion of genetic tests, but really the broader application ought to be use these same principles to apply to other tests as well.

DR. BUCHANAN: I agree. That's the good thing about genetic exceptionalism, is that when you reflect on it, it forces you to call into question all sorts of things you took for granted in other areas, like the effects on equality of opportunity of people being able to send their children to Harvard rather than to the local community college.

You don't have to worry about effects on equality of opportunity by engineering embryos, but once you do start to think about that, you may reflect on other social practices that have similar impacts on opportunity that we never questioned before.

DR. McCABE: Reed?

DR. TUCKSON: Yes. Actually, I sort of came out where Dr. Burke did as well. On two areas on the introduction of our document, I've sort of gone back and tried to rethink about how we can capture this idea of the context of genetic tests within the larger context of other issues, so that we show where it is unique, because I do think that, Dr. Buchanan, there are some special considerations here. Otherwise, you know, we wouldn't be here.

The public wouldn't be as concerned, and I mean we have to speak to those special

considerations, but putting it in the context of larger issues is, I think, something that the introduction of our work is going to have to attend to, just as I think we will need to relook at how we phrase or address the issue of uncertainty.

At this moment in time, our work is a snapshot, and I went back at the break and relooked at the introduction again, and we probably have not adequately addressed that contextual issue as a fundamental challenge for everything that comes after that, and I think we're going to have to address that a little more specifically.

Dr. Buchanan, I appreciate your point that you were being provocative in some ways. I found your criteria very useful, to be quite frank, and a great way for us to think.

I am concerned as we look at some of the implications of them, particularly in the area of, as you've well defined, this not assuming the application of biotechnology to human beings is always biomedical and this misplaced medicalization.

At the end of the day, the poor doc out there is going to have to counsel that patient or other counselors are going to be involved in this, and while we are certainly not looking to be a totalitarian state, there is a legitimate challenge to the clinician, and so that as we take up your challenge on this point, I think we're going to have to have a lot of very specific conversation about what the implications then are for the legitimate exercise of the patient-physician relationship, which is a fundamental sine qua non here, and we're going to have to really look at some support for that poor folk on the front line here.

DR. BUCHANAN: I agree entirely, and there's one place in my draft that begins to address part of that set of issues, and that is I make a distinction between what physicians or other health care providers think of in terms of their self-identification as a professional as being the appropriate kind of activity to engage in versus other kinds of activities that may become available in biotechnology.

I think one of the important identity issues for health care providers, not just physicians but genetic counselors, is where do we stand on this? What are we doing? Is this what I was trained for? Was I trained to be providing tests that supposedly give information about the predisposition of somebody's child to have a sunny disposition or to be gay or to have some other behavioral characteristic or is that something that's really not health care, and though it's not my primary concern, I may have some special social obligations to have input into the public dialogue about how that's carried out, if it's carried out, how it's regulated, et cetera.

So again, I mean I think you're exactly right, that even for what you and I might agree are non-medical uses of genetic testing, that there's going to be a natural culturally-based tendency for individuals to look to their physicians or other health care providers for guidance, and before they can provide that guidance, the health care providers are going to have to settle some of their own identity issues about what they're really doing as doctor or as nurse or as genetic counselor, and I flag that issue here.

I think it's extremely important, but I think what's particularly important is to distinguish the questions of what should be provided as a matter of health care and what should be provided comfortably by health care providers versus what should be available?

Okay. There may be some uses of these biotechnologies which should be available to the public under certain conditions, which most physicians or genetic counselors would rightly not regard as health care. Okay. It's a separate question. The identity question is to some extent a separate question from the question of availability, not entirely separate, but it needs to be distinguished.

DR. McCABE: Victor?

DR. PENCHASZADEH: Well, you certainly achieved your task of being provocative here, and I think we all should appreciate that because sometimes, you know, we are on the trench lines, if you wish, of answering patients' concerns and so on and so forth. So you know, a guy like you, you know, on the philosophy of things and that makes us think about things.

Now, we really appreciate it. I'm serious about that. Now, there are a number of issues or a number of subjects I will take issue from of what you're proposing because, first of all, there is no, so far as I know, there is no -- about the marketing piece. You know, I don't have any hostility towards marketing, but I don't think there's any proof that relying on the market for health care has indeed been effective in containing costs, for one thing.

If you compare with other developed countries where the market is not that strong as it is here, you have much better cost containment than you have here. There is no proof either that prior marketing increases efficiency. So that's one point.

The other point, and it's perhaps -- I hesitate to use the word "philosophical" because we're here with someone who's a real philosopher, but I have problems with the terms and the concept of private decisions and individual choices because I don't think that they are so private and so individual, you know.

We live in a society that what people decide is really influenced by so many factors outside the individual, you know. Those guys that you say that may opt to have a test for intelligence or enhancement or whatever human characteristic, I wonder on what basis their decisions are made, you know. At least in part, you have to concede, they are made because somewhere, you know, there is this tendency to think that everything is genetic.

There's genetic determinism and redeductionism is not coming from our genes. I mean, it's not an individual choice to decide that everything is based on the genes.

It's part of a wave that we are going through, this transition phase of our biological knowledge and probably will change in the next generation or whatever. So I have also a problem in dismissing some of the issues, saying, well, there will be very few people that will do that because there will be very few people that will be able to pay for that. That's not a right argument because if you think that something is right or something is wrong, it should not depend on whether there are many or few people that will have the money to pay for the enhancement or whatever.

So once you try to find other ethical arguments to allow for these to be available to anyone or everyone. I don't have any problem about the profit motive because this is a society that was built essentially on at least in part on the basis of the pursuit of profit, but you yourself, you caution about unrestrained pursuit of profit, and I wonder what you mean by unrestrained, and how and who would restrain pursuit of profit.

About the role of physicians, I think I would subscribe what Reed Tuckson just said. I don't think we have to indulge more in that.

I really think that we will continue to see patients looking for counsel to their physicians because they see -- it is not only this culture. I think it's worldwide. Health-related issues come to physicians, and many non-health-related issues, even for something that is not particularly health, I think physicians will have to counsel and will have to be equipped to be able to counsel patients.

I think that the question of psychosocial harm of genetic testing and genetic conditions in general is not something that was invented by the medical profession or by geneticists. There is a lot of literature about that that we've seen over the past decade or so, that people really suffer and suffer probably more when the conditions are at least in part determined by their own genetic constitution than when it is due to environmental factors.

So I think, you know, I really appreciate, and I think we all should appreciate, making us think about all these issues, but that's what I had to say about this now.

DR. BUCHANAN: I'd like to just reply very quickly. With regard to the last point, of course I don't deny that there are serious psychosocial harms. I'm just against sort of a sweeping generalization that whenever something's genetic, you have to assume that you're at a sort of limiting case of seriousness in psychosocial harm.
So we don't disagree on that at all.

I don't disagree that people will continue to come to physicians, and that it's even appropriate for them to come to physicians for advice about applications of biotechnology, whether they're strictly speaking medical or not. So we're in agreement on that.

What counts as unrestrained pursuit of profit? Well, again I don't think we have to start from scratch in the genetic area here. We know something about the kinds of considerations which are relevant for regulating markets generally, and in particular markets having to do with health care services, and I think that, you know, this came up in the earlier discussion this morning, that a commitment to thinking hard about the ethics of marketing, that is the information or alleged information that's given either to providers or to consumers in the case of direct marketing, that's absolutely essential, and anything the committee can do to emphasize that point is going to be valuable.

And who should do it? Well, part of the task of the committee is to decide to what FTC, do I send it to FDA, we had some discussion of that this morning, should be leading the charge in making sure that there is accurate information given, that people don't confuse clinical validity with clinical utility, et cetera. So you know, I'm all for that right down the line.

Now, about this question of whether the numbers count, whether genetic interventions will reduce diversity to a dangerous point is a matter of the numbers. It's a matter of two numbers. How many people undertake it, and how high their reproductive rate is compared to the rest of the population, and that's all I was talking about.

There's another section of the paper where I talk about something that Dr. Koenig brought up earlier this morning, and that is the importance not just of looking at the risks and benefits for individuals of taking a certain test but the cumulative harms of large numbers of people taking those tests, and one of the possible harms that I identify in the paper is that given our society and the kind of gene fetishism that you mentioned and I mentioned earlier, the affluent may respond to and encourage market which in turn encourages them to engage in a whole range of biotechnological interventions in the genetic area that aren't really health care services, and that may drain resources away from the unfinished task in this country of providing an adequate level of health care to everybody, and that's a serious problem, and that's a clear case where a fairly small number of people in terms of the population might have a huge detrimental impact. So I'm agreeing with you. I'm not disagreeing at all.

You mentioned you wondered whether what I'm calling private decisions are really private decisions. I agree entirely. Even our private choices are very strongly influenced by our social class, our

religious affiliation, all sorts of things. But again I'm not convinced that we should just assume that it's entirely different in the genetics area than it is in other areas. That's true everywhere as far as I know, and yet we do make a distinction in this society between a private sphere and a public sphere.

It's a hard line to hold, but it's a commitment to being able to draw that line and provide some area of discretion for individual choice is essential to having a liberal society.

As to whether there's any evidence that the market for health care has reduced costs, well, the increase in the percentage of GDP devoted to health care has slowed down. It may be a one-time savings because of certain kinds of techniques in managed care. It's too early to tell.

I'm not by any means an advocate of an unrestrained health care market. That's why I said I think health care is a special good, and that means that it shouldn't be treated as other goods are in the market, but I'm really not leading the charge in favor of commercialization of genetic tests.

All I'm saying is don't assume that commercialization is all bad and has bad effects. Instead, look at the situation and see to what extent what kind of marketing, under what regulatory schemes, will have this effect or that effect, and what struck me in the literature is that people tend to be very negative about "commercialization" and never even consider the possibility that under certain circumstances, it may increase access.

I can give you an example of this. Okay. I have a hereditary hemochromatosis, so does my brother, and I have a nephew, my brother's son, who decided to take this test at Michigan State University because he didn't want to get a medical record saying that he had this genetic condition because both myself and my brother have been refused insurance when it was known that we had this condition.

Okay. Now, there's somebody making money out of providing that test. They're just about to raise the price on that test because they're adding this third alleged mutation that the French group came up with a month ago or so, and I don't care what their motives are really. I mean, they may be horrible people. They may be good people. I don't really know. But I think that my nephew found this to be a valuable service, given the imperfect situation that we have now where having a medical record, having your medical record evidence that you have a genetic condition, may in fact be very bad for you.

So I'm just saying look at it case-by-case. Don't assume commercialization's good. Don't assume it's all bad.

DR. McCABE: Kate, then Jeff, and then Muin.

MS. BEARDSLEY: I just wanted to go back to the marketing issue for a minute because I'm really intrigued by the positives that you point out that are associated with marketing and can be associated with marketing, and I also have sort of a visceral reaction any time I'm thinking about whether the government is going to be involved in prohibiting or suppressing speech just sort of as a general principle.

On the other hand, I think you've kind of assumed, I think, that the marketing we're talking about is going to be truthful and balanced, or I thought you --

DR. BUCHANAN: No, no. I mean --

MS. BEARDSLEY: But maybe one way to think about this is to think about not so much about marketing versus no marketing but correct marketing versus incorrect marketing, and I'm just intrigued by that possibility.

DR. BUCHANAN: I agree entirely, and obviously I didn't put it very well, but that's what I'm aiming at. You can't even have that discussion if you just immediately assume that marketing is bad.

MS. BEARDSLEY: Right, right.

DR. BUCHANAN: Okay? I want to have that discussion, but again I tried to say marketing can under certain circumstances or may under certain circumstances have this positive benefit. Okay. But truthfulness in advertising, which is easy to say but hard to specify --

MS. BEARDSLEY: Right.

DR. BUCHANAN: -- is obviously incredibly important, and again I agree. Given the low level of genetic knowledge among the general population and even among many providers, and given the kind of cultural bias toward genetic determinism or gene fetishism, there may be special dangers, and maybe I didn't emphasize them enough.

I mentioned at one point that there may be special dangers about manipulative advertising in this area. It may be easier to con people in this area because of our fascination with science and our gene fetishism, and so especially strong scrutiny may be necessary.

DR. McCABE: Also, I'm going to point out that as we get into our outreach discussion, there are cultures who have completely the opposite view, and one might say are genetic anti-determinist and really don't accept some of the very fundamental principles that many of us in genetics would accept.

So we have to also understand that there are people who have very different views and that are culturally determined --

DR. BUCHANAN: This is extremely important. I'm a minor consultant on a project to design a Medicaid Program for the Navajo Nation, and the difficult thing about even talking about genetic testing with many members of that group is that they have a belief that if you talk about a possible bad outcome, it increases the chance that it will occur, okay, and so there's certain things you just don't mention, you know, like predisposition to disease. So that's a barrier to even having a discussion about whether the benefit package for the Navajo Nation should include a battery of genetic tests or not.

DR. McCABE: Jeff?

DR. KANG: I want to respond to everyone. I would like to circle back at some point to the three contexts that you're proposing here because in many ways, HCFA, consciously or unconsciously, is moving in this direction there is the regulatory standards around individual choices in the private market then there are the kinds of standards that you would want for your benefit decisions.

DR. McCABE: Can you speak more into the mike?

DR. KANG: Oh, I'm sorry.

Then the third would be the kinds of standards that you would want for your publicly-sponsored programs, kind of where there's a major commitment, and I would like to come back and circle back to that and that kind of context and its implications for our work here.

But I had a question for you. In many ways, that middle one, the kind of standards that you want

for your coverage decisions or what's in the standard benefit package, really drives us to narrowing the question to not clinical utility but actually to medical utility because that's currently what we're covering. It really is medical utility, and I think what we're wrestling with, though, is that with genetic testing, there is the broader clinical utility, and I think where this is different than the other health care services that we talk about, because I think this construct works for the other health care services, is when you start broadening it to the clinical utility, you then bring in the ethical issues, the societal ethical issues, and I've kind of been wrestling with where does the broader clinical utility and/or the ethical issues in your mind, where would you see that being played out?

Would you see it being played out at the individual free market or would you really see this as a broad societal kind of publicly-sponsored where it has to be very highly regulated?

DR. BUCHANAN: I think this comes back to Pat Barr's point.

DR. KANG: And it really does come back to your issue. See, I don't think you get that dilemma with health care services per se because it's less with the ethical issues.

DR. BUCHANAN: Well, I think you do get it with other kinds of health care, but maybe you don't get it as visibly and dramatically as you might in this case.

DR. KANG: Okay. So where would you see it playing out? At the individual --

DR. BUCHANAN: Well, I can say this much. I'm not in favor of what some authors have called laissez faire genetics. That is, I don't think an unrestricted market is appropriate, and when I say unrestricted, I mean assuming already safety and efficacy of the test and that kind of thing, and just sort of let it rip after that for the reasons that Pat Barr said.

There can be cumulative effects on the gene pool in terms of reduction of diversity, depending on how many people can do this for how long, but there can also be effects on very basic societal values about what it is to be a parent, about what it is to be a child, and it's perfectly legitimate for bodies like this and for legislators and others to think about those things.

All of us as citizens should be thinking about them. So I don't think you can leave it to the market in that sense. It would be nice, you know, in this report if you could just say, well, we're just talking about the medical value or disvalue of this test for this individual who may take the test. That would make your life a lot easier, but I don't think you can do that for reasons that have become very apparent here, and I think you can clearly say that you cannot leave it to the market. I think you can say that much, and then you can draw on history and look at some of the problems that occurred in the eugenics movement where it wasn't a market in genetic services, but there's work by Troy Duster and others about the idea of back-door eugenics or laissez faire eugenics where there's reason to believe that there's a serious risk that some of the things that we abhor in the early eugenics movement might come about through the unrestricted operation of a kind of genetic supermarket.

Okay. So you can say that much, and you can base it historically in just the way that Pat was alluding to, and then you can ask what are the institutional resources of our society for identifying these kinds of risks of cumulative harm and for dealing with them, and it's always going to be a balancing act, right, because our society gives a lot of weight to parental choice regarding their decisions whether to have children, under what conditions to have how many children, et cetera, and that if you try to ward off these cumulative harms of many individual choices, you will have to at some point restrict individual choices. That's the big balancing question.

DR. KANG: So your bullet here under 6, the first bullet, when you say "under what conditions should a genetic test be offered in a publicly-sponsored screening program?" there also is where -- and/or under what conditions kind of -- is there a greater or is there a cumulative genetic issue which society --

DR. BUCHANAN: Well, I think under all the contexts, you have to ask that question, right. You have to ask whether even in the case of the private discretionary purchase of some genetic service testing or intervention or otherwise, whether it's likely that repeated instances of this are going to give rise to consequences that are very harmful.

So I think that that question is invariant to the context, but I think I'm agreeing with your earlier remark that in the case of the publicly-sponsored program, where there's the social marketing of the test in effect, right, that the regulatory standards, if anything, should be higher in those cases because you're using public funds for this rather than something else, and you need to justify it, and because you're endorsing this.

People will take it as an endorsement if you have a public program with social marketing, and you better be sure about the clinical validity of the test and about the utility, and so the standards should be even higher in that kind of case.

DR. KANG: Well, I agree with that, but I was trying to turn this now into kind of a three-tiered regulatory approach, and it struck me that if you determined that there was a particular test that there was a great potential for cumulative consequences, adverse to the genetic pool, that that actually would be the place where you would kind of up the regulatory oversight.

DR. BUCHANAN: You certainly could, and that's why I tried to sort of cover myself on that by saying other things being equal, the public screening context should have higher regulatory standards.

But if in fact for the private choice area, you found that there was some serious cumulative risk, then you might have higher standards there. Now, there's a problem about how you would restrict this kind of choice that results in or is expected to result in cumulative harms, right, because if you try to regulate it out of existence, you may create a black market or you may create a foreign market.

I live 50 miles from the Mexican border, and I can imagine that if certain kinds of tests were prohibited in the United States, very quickly, 50 miles away, there would be clinics springing up which would provide those tests, and this raises a very large set of issues, I think, for the committee as to what extent should regulation be international as opposed to national.

DR. McCABE: Muin? And as Muin is asking his question, I just want to point out the time for everyone. We've got about 10 minutes left, and then we will be moving on to Issue 2 in our deliberations this afternoon. So if there are general things that you'd like to ask about.

DR. KHOURY: As I was hearing the discussion, my mind was being taken in so many directions, but let me start off by commending Dr. Buchanan for his effort to put down these general guidelines that make a whole lot of sense individually and as a group. It's hard to argue with these guidelines because on the one hand, we don't see them in the printed literature. All we see are the arguments on the other side, and it's good to have a balance.

However, having said that, we live in the reality right now that make the applications of these guidelines a little bit more tentative. We should keep them in mind, but we shouldn't forget where we are right now.

Let me start with Item Number 4, the idea that we cannot overgeneralize from reproductive choice and therapeutic pessimism paradigm, recognize the heterogeneity of genetic tests. That's probably where we need to start because that's where we live right now in sort of conditions where there are no treatments like Huntington's disease or the prenatal diagnostic arena.

Now, as the genetic testing for susceptibility of common disease emerges, the third paradigm which you didn't mention here is the therapeutic gap, sort of where we have genetic tests. We don't know exactly the clinical validity and/or clinical utility, and maybe hemochromatosis falls somewhat under that, but we have hundreds of these that are coming up, and to me, that leads automatically to the idea that in order to bridge that gap, and in order to accomplish Items 1 through 8, not to engage in unreflective hostility to the marketing of health care services, we need a lot of data, and that data has been a major challenge. I mean, you'll hear me tomorrow.

As you sit down and try to review what exists, even for things like hemochromatosis and cystic fibrosis, where you think you know a lot, there are large gaps in our knowledge base that exist at the current time, and those kinds of data are going to be crucial, both for policymakers, both for public health programs, both for individual physicians and for patients, to know what it means to seek, let's say, a hemochromatosis test, let's say to get tested for that third mutation, and we engage in -- I mean, we live in a world that's less than ideal, and ideally, at any given point in time, consumers and government agencies and the private sector and everyone should have a finger on the pulse where they would at least recognize and be able to transmit in an unbiased way the current -- I mean, what do we know about that genetic test? What does it mean to have a positive or negative result? And whether it's done by regulation or through a public/private partnership effort, to me, we can't do all of these things without having that framework in mind, and that's very crucial.

The second quick comment I wanted to say, it seems like we're throwing public health programs into a more level of scrutiny as far as regulation, and I'd like to disassociate those two things.

You can have a public health program that is driven by consensus statements and less by regulations. So I mean I would like to disassociate the idea from a regulatory paradigm, imposing more regulation on a public health program, from the idea that maybe you can do it with higher levels of scrutiny with or without regulation. Just keep that in your mind.

DR. BUCHANAN: Yes. That last point's really important. Regulation is not the word that I should be using. I should be talking about standards, and the standards may be either achieved through regulation or through consensus and less formal practices, and what I really meant to say was that if anything, other things being equal to cover myself, the public health screening context should require higher standards. Whether the standards should be brought about by regulatory means or not is an entirely different question.

On this point about knowledge, I mean I couldn't agree with you more, and, of course, there's a huge public health role for CDC in particular in providing the knowledge on the basis of which either public programs are undertaken or insurance provides benefits or individuals make discretionary purchases, and that's extremely important, and, you know, I should have said a lot about that. I didn't. You pointed out a huge gap because it's not enough to say that you should have truthful marketing. You've got to also have some level of knowledge about which to be truthful in the marketing, and that, I was too sort of easily assuming as a qualification on my -- I wouldn't say my enthusiasm for the market, but my lack of unreflective hostility toward the market.

When I say that, we shouldn't indulge in unreflective hostility to the market. That leaves in the possibility of reflective hostility. Okay.

(Laughter.)

MR. HILLBACK: Well, it also argues very strongly, given how iterative this is, back to my favorite word, that you have to find ways to keep upgrading the information almost on a daily basis, and that is not a mechanism that's easy for everybody to do, whether that's the provider of the test, whether that's the user of the test, whether that's the regulatory or oversight bodies, and I think that's going to be the biggest challenges, one of the biggest challenges when we get around to how to provide oversight, is how to cope with that speed that we're all talking about.

So I keep making that same point, but I think it comes out of your discussion very clearly, that that's a significant issue we're going to have to deal with.

DR. McCABE: And it's a cost issue, also, as you point out, that we can't create a paradigm that prices genetics way out of the reach of everyone. So we have to provide the information, but we have to try and seek some new ways of doing this that will not be incredibly expensive.

Are there other general comments? Pat?

DR. CHARACHE: I'm enjoying being provoked and raise the issue of the need to establish some type of balance between this medical paternalism and public choice or free choice, and, of course, we have to face this in a wide range of areas.

But I'm thinking of two things. One is the down side of the public choice because inherent in every test, there's false positives, and I spend a lot of time counseling patients who've had a false positive test for HIV, and I can see similar challenges in this setting, particularly if it's anonymous screening, and there's no M.D. intervention built in.

The other area I'm busy thinking about is the insurance industry, that if there are no requirements as to when you may or may not do this screening, they can anonymously without informing someone who applies for a policy to screen for certain genetic disorders themselves if they feel this is of benefit to their particular marketing initiatives.

So I think this is a continuum that we have to think about in terms of specific tests, specific industry needs.

MS. BARR: I have one more general concern or two. You talked about physician paternalism, and I think that's a misnomer because I think doctors live in a culture, and I think there's cultural paternalism that doctors respond to, and so I would talk about medical faddism as well because there are particular times when -- ritalin is an example. Antidepressants are an example. So doctors are perhaps prescribing in response to knowledge dispersion in the society and culture rather than something you might call physician paternalism.

DR. BUCHANAN: I agree. It's very hard to know which they're responding to,right, whether they're sort of imposing their preferences on the patient or whether they're responding to these cultural signals.

MS. BARR: How they develop their preferences.

DR. BUCHANAN: Yes. Well, I've never thought that the paternalism is a one-way street. It takes two basically. It takes the expectation on the part of the patient to some extent to turn over authority

and to expect the physician to operate in this way, and I've actually written about that.

I mean, I don't think of medical paternalism as being something that's just in the power of physicians. It's culturally-supported both within their own particular culture, but by the larger culture, and you see the differences when you look at the difference between the United States and Great Britain in terms of the level of cultural support for medical paternalism. Quite striking.

DR. McCABE: Reed?

DR. TUCKSON: I'm sorry. She's following directly on that.

DR. McCABE: Okay.

DR. KOENIG: Yes, just very quick. Paternalism isn't necessarily bad, also. Most people, if you talk about the inherent basis of the caring relationship, when you're sick and vulnerable, you often want someone who knows more than you do about something to take care of you and to help you, and you want to have a say in that. So there were abuses in the past, but just to keep that in mind.

But as we move into genetics, and perhaps the person considering the test is not quite so vulnerable, then the dynamics change quite a lot, but that was another way in which I personally was provoked by your -- statement.

DR. BUCHANAN: No, but I tried to say unjustified paternalism, making it clear that not all paternalism is unjustified.

DR. KOENIG: Okay. Maybe I didn't read that. There are also disputes about whether what you describe is paternalism or not because whenever I engage an agent as a principal, whenever I engage an agent, I delegate certain areas of activity, and I don't view that as paternalism at all. I view that as an exercise of my autonomy, but that's sort of a verbal dispute.

DR. BUCHANAN: I agree entirely. I didn't mean to use the term "paternalism" as such, as anything pejorative. It's a question of when it's justified and when it's not. Even medical gatekeeping, I don't view that as a pejorative term. It's a question of when it's appropriate for physicians to be the primary controller of access and when it isn't.

My only point was that where it's not a medical service, at least you're going to have to make an argument to show that the medical person should be the gatekeeper, and you may be able to make the argument successfully, so I appreciate it. Maybe I wasn't as careful as I should be, and I'll go back.

DR. McCABE: Kate has a brief follow-up, and then Reed.

MS. BEARDSLEY: I was just going to say that while it seems to me that paternalism may sometimes be justified, sometimes it's not justified, and that whether people have a choice about paternalism or not depends to some extent on what information is available to them. So if you stop the flow of information to them, then you increase their necessity to be dependent.

DR. BUCHANAN: Yes, absolutely.

DR. McCABE: Reed?

DR. TUCKSON: Just two quick comments. One on the point that's on the table now. I do think

that we will need to be, you know, careful in our use of these words, such that we, you know, bring folks together and try to solve these problems as opposed to push us away.

I think that, you know, paternalism is in its own a pretty loaded notion. Again, you know, there are always folk who are in any world not doing what they ought be doing, but at the end of the day, most folks are out there trying to do right by their patients, and they're trying to figure their way out of this thing, and so I think we want to be very careful about being able to say to folks who are legitimately struggling to exercise their moral and ethical responsibilities to their patient to give them the kind of guidance, advice and counsel and so forth. You know, they ought not be beat up about trying to do that, especially when there is uncertainty in this brave new world.

The thing I actually wanted to ask you to do maybe later, Allen, is you sort of opened the door to an intriguing thought, and that is you sort of asked rhetorically maybe or actually maybe specifically what are the social tools that we have that deal with these kinds of ambiguous questions, and I wonder whether or not you either have now or maybe you can help us to think about after the meeting is over today analogies in other areas of social life that we can draw upon that help to look at how to find the solutions to these thorny problems.

I mean, although it's amazing to me, but all the best answers actually aren't in medicine and health care. It's a strange phenomena.

(Laughter.)

DR. TUCKSON: Whenever I discovered that there are other smart people in the world, but to the extent that we can draw from other experiences, it might be kind of fun for us to have that supply.

DR. BUCHANAN: I'll just say one brief thing in partial response to that. I think this committee and other committees like it can play an enormously important role if you're willing to be forward looking. That is, not just concentrate on current medical uses, you know, predictive tests for diseases or predisposition to diseases, but look at these larger issues about what many of us regard as non-medical uses of tests, and the special problems they may raise by way of cumulative effects.

You don't have to give all the answers, but you can do such a tremendous service by honestly identifying the problems and highlighting them and being willing to show people that it's possible to reason about them. That is, that you can look at the arguments pro and con, and it's very rare that you find an array of arguments that will give you the correct answer, but it's very easy in many cases to rule out a bunch of wrong answers, and, you know, you may not find the argument that's completely dispositive, but you can poke holes in a lot of bad arguments.

The arguments are out there. It's not just philosophers that give them. The arguments are there inchoate form in all of the public discourse. You just have to surface it and then subject it to scrutiny.

So I would be so bold as to say that I hope this committee will be an ethics committee, and that's not to disparage all of the important work on getting the information out, on talking about what the standards for CLIA should be. That all has great ethical import, but I would just urge you to go a lot further than the Holtzman Report, the task force report, went in looking at these larger social issues.

Getting them on the public agenda, helping to stimulate a scholarly debate and a public debate about them, this is an important institutional resource that you've got here, and I know you're under a tremendous time pressure, but maybe you should engage in the collective act of civil disobedience and say --

(Laughter.)

DR. BUCHANAN: -- this is the kind of job we're going to do.

MS. BARR: We did it once.

DR. McCABE: I want to thank you very much for being willing to share your draft with us and certainly has been very provocative and appreciate your input.

At this point, we're going to break for lunch. We will resume at 1:00. There are tables reserved downstairs for the members of the committee and the presenters. It's at the hotel restaurant on the lower level, and there will be individuals who will help you find your way down there, and I'm sure will help get us back on task at 1:00, too, because I find that we're having a lot of fun talking about these issues on the side as well.

Thank you very much.

(Whereupon, at 12:07 p.m., the meeting was recessed for lunch, to reconvene at 1:00 p.m.)

AFTERNOON SESSION (1:10 p.m.)

DR. McCABE: This afternoon, the first order of business is going to be public comment.

I'd also like to mention that we have a little bit more time because Christopher Jennings is unable to be here today, so we have an extra about 45 minutes in the schedule.

Now, having said that, we don't need to expand just to fill the time, and it will give us more opportunity for discussion. But some of the individuals who are prepared for public comment have told me that they might run over five minutes. So I won't bring out the hook until about 10 minutes then, and if you can keep it shorter, that's good, and you'll have more time for discussion then after your presentations.

First of all, let me refer you to Tab 5. This is the information that we were given prior to the meeting today. Our first presenter will be Dr. Penelope Manasco, who's Vice President, Worldwide Clinical Genetics Communications and Education for GlaxoWellcome.

Do you need help with overheads?

DR. MANASCO: I'm pretty multi-faceted.

DR. McCABE: Okay.

DR. MANASCO: Dr. McCabe and members of the committee, on behalf of GlaxoWellcome, I want to thank you for giving us the opportunity to share some of our thoughts with you.

I would like to echo some of the things that have happened already this morning. I think Dr. Buchanan actually put a great intro into -- really, it's like you don't have enough to think about in your remit, we want to add a few more things for you to think about in your remit.

So what we want to do is to just bring your attention to another issue that may not have come to light yet but will be something that's going to be very, very important, we believe, in the next few years, and so we would like to have you consider it as you go through your deliberations, and that is genetic testing is not genetic testing is not genetic testing, and I think we've already seen that this morning, and so far, we've really focused in this area, gene-specific tests for disease, both those tests that are sort of monogenic disorders and those that are susceptibility genes.

But over the next few years, there's going to be, I believe, an explosion in what we call pharmacogenetic applications of genetic technologies, and that is that there are going to be both gene-specific tests that will be markers for safety and efficacy of medicines as well as new forms, polymorphic marker profiles, and so because we believe it's going to be very widely used in the health profession and will really go through all parts of the health care industry, I wanted to spend a few minutes and talk about those and what we believe some of the issues are and really ask you to consider those in your deliberations.

Again, today, a lot of time has been spent, and I won't spend time on the gene-specific tests for disease. I think the committee is covering those issues very fully, but we want you to be thinking about these additional tests.

The gene-specific tests are also called candidate gene approaches, and the genes are usually genes that are important either for the target for the medication or for metabolic pathways, the p450 enzymes or things like that. These genes have already been shown in the literature to be markers for both safety and for efficacy, and I think over the next few years, there's going to be many, many more of these genes that are going to be identified.

Obviously there are pharmacoeconomic issues that are important here. Issues, such as whether medicines will be kept off a formulary if only a small percentage of patients will actually respond to the medicines. So there are a number of issues, and yet we don't presume to know all of them, and so we're eager to have you share in the deliberations and think about what some of those issues might be.

The important thing is the ELSI issues, or the ethical, legal, and social issues, we think are quite different when you're talking about markers for efficacy of a medicine or for safety of a medicine than when you're talking about either diagnosing a disease or looking at the susceptibility of getting a disease, and so our main request to you today is that you consider these different applications as you make your recommendations, realizing that there are different ethical, legal and social issues, and again we don't have all the answers. We're eager to be in the discussion so that we can discuss what they are, but as you make your recommendations, to realize this difference and take it into account and address it in your recommendations, the differences between the pharmacogenetic and the gene-specific tests for disease.

I think I have a couple minutes, and I just want to mention where we think this is going to go. In April of this year, the announcement was made that a consortium of 10 pharmaceutical companies, the Wellcome Trust, and five academic centers went together to form what's called the SNP Consortium.

The SNP Consortium is designed to develop a map of single nucleotide polymorphisms across the whole genome and to make that freely available to everyone, academics, everybody, and I think that this is actually going to be the way that we're going to be able to find markers for safety and efficacy of our medicines, and the reason that I just want to share with you what we think that'll be, because I think it's a very abstracted form, the genetic information. I didn't put that up quite high enough.

So if you think about it, in clinical trials, we would study a map of the genome, of these SNPs, and look again for common areas for patients that either respond to our medicines or common areas for

patients who have specific adverse experience.

We would then use an abstracted form of this, just the few SNPs that are important, to actually put into a test that would be used prior to a patient taking a medicine, and again, instead of having maybe a 30 to 40 percent chance of a medicine working, we're hoping to be able to give predictive power of 80 percent or so, so that we can actually tell physicians, payers, patients, that, you know, you're going to have a much higher likelihood of responding to this medicine.

So the important thing for you all to think about here is that this is very abstracted information. There's nothing that people can learn about somebody's disease from this. It will be just a group of SNPs that will be used, and so I think in the health care system, we'll have a combination of both gene-specific tests and these SNP linkage disequilibrium profiles. That's going to be a catchy one to market.

But, anyway, we believe that we'll have a combination of these two kinds of approaches, and that again they will have different kinds of issues attached to them, and so that the restrictions that you may consider, please think about how will this affect these specific markers.

So I thank you, and, Dr. McCabe, do you want to have questions?

DR. McCABE: Yes. I think there's time for some questions. First Kate, then Francis.

MS. BEARDSLEY: Can I ask if most of these pharmacogenetic tests are being developed as test kits that will fall under FDA in sort of the regular course or that won't, depending on how everyone looks at it, or are they lab-based tests?

DR. MANASCO: That's a good question. I think right now, we're still trying to find the markers.

DR. McCABE: Why don't you come over to the podium? You might want to turn that off, so we don't get feedback, as you go over there. If you don't mind coming to the podium, it might be more reliable.

DR. MANASCO: Sure. My voice is so loud.

DR. McCABE: That won't get picked up by the recorder, though.

DR. MANASCO: Okay. How are these tests going to be delivered?

MS. BEARDSLEY: Yes. Are they going to be test kits which FDA generally has jurisdiction over, assuming they're medical devices, or are they more likely to be developed by labs and delivered as services?

DR. MANASCO: I don't know that I can say. My sense is, you know, we're going to want a rapid turnaround, but I don't think I can tell you. Like I said, right now, we're really worrying about trying to find what the markers are and making sure that we have reproducible results in multiple studies, and then I think we'll look at how is the best way to deliver that.

So I don't think I can really give you the answer right yet.

DR. McCABE: Francis, and then Pat.

DR. COLLINS: This is sort of a nomenclature question, but your diagram sort of neatly separates

genes that are involved for predicting disease and those involved in pharmacogenetics.

My own sense is a lot of what we discover when we try to look at drug responsiveness in a particular illness is going to be stratification of that illness into multiple different subtypes.

So for instance, when you try to figure out why some diabetics respond to this oral agent and some others don't, much of that underlying difference in drug responsiveness probably reflects the difference in the various molecular contributions to the illness, whether they're primarily insulin-deficient or insulin-resistant.

I think that means that the tests that one uses to make predictions about which drug to use in a particular patient are also going to be tests that make predictions about the natural history of the illness, and to sort of say, well, it's a different thing here because it's pharmacogenetics, and it's not really disease prediction.

A lot of them are going to be both, and that's going to, I think, complicate things a bit. There will be some that are looking at, say, drug metabolism, where perhaps what you learn about that particular individual's genotype makes no prediction about their risks of illness. But many of them will be a mix of these two things.

DR. MANASCO: I think you're right, although I think that what we've seen is even if you were to subdivide and say you were going to use a genetic test to diagnose the subset of diabetes or the subset of asthma that a patient has, even when you get down to that level, there will be differences in how small molecules will interact with a specific receptor or target, and so you're right. There is some, but I still believe that there will be some variability based on the molecular structure of the compound and how that interacts with whatever that target molecule is.

So I still believe that there will be differences even after you've subdivided on the basis of disease, but there will be some crossover. It's clear that that's going to happen. We try to just change in how people think about the genetic tests.

DR. McCABE: Pat, and then Muin, and then we're going to move on.

MS. BARR: I have sort of a set of economic questions. One is, have you projected what kind of costs these tests will have, and what that will do to your industry in terms of looking for new drugs versus identifying people to use the drugs we have?

And then, the other piece is, do you imagine that there will be new drugs or modified drugs, and you will go through FDA, but it would be a different kind of process in terms of setting up your clinical trials?

DR. MANASCO: Absolutely, yes. I believe that right now, when patients don't respond to our medicines, we don't know why, you know. We just know that they don't respond. We don't have any systematic way to study them, to in fact design a medicine that will work in that population.

So one of the beauties of this is in fact to be able to understand why some people respond and why others don't, so that you can develop new medicines.

I think clinical trials are going to be designed differently. Clearly, we're designing ours already differently, where we're collecting genetic information and doing genetic research on our patients in clinical trials to be able to start to identify what the markers are.

So I think trials will be different. I think the way medicines will be packaged will be different, that the diagnostic or -- it's a hard term. Nobody knows really what to call it, but whatever it is will in fact be part of how you prescribe medicines, and how much will it cost? I don't know. I think right now, like I said, we're still in the very early stages, and mainly I want people to be thinking about this coming down the line.

But it's not going to be an exorbitant amount, and if we can go with things like the SNP profiles, which in fact are amenable to automation, then it should make it easier than some of the difficult kinds of genetic tests that are done now for multiple mutations in a specific gene.

DR. McCABE: Muin?

DR. KHOURY: Yes. I'd like to expand a little bit on what I think I heard Francis say and elaborate on some of my own ideas here.

The way you have the decision tree, and then each one of these splits into monogenic versus polymorphisms, and I think on the other side, too, that's the way I would like to make that at the beginning.

I think by saying non-disease at that right-hand side is very misleading because some of these SNP profiles or polymorphisms, the variations in those that will predispose you to either side effects of drugs or better therapeutic response of drugs are the same genetic variations that are involved in the natural history, and the way you interact with the environment, be it pesticides or infectious agents.

So I think we cannot think about those as separate and not related to disease because some of these same SNP profiles will have a lot to do with the pathogenesis and natural history of disease. So just keep that in your mind.

DR. MANASCO: Well, clearly, we're using the same kind of SNP profile to try to understand susceptibility genes. I think mainly if you think about how it will be delivered to the patient is where we think that you can use abstracted information and not deliver the same kind of information with all of the same kinds of ethical baggage, if you will, along with it.

So that if you are going to do your tests, and it's going to be six or eight combinations of SNPs, that's going to be very different, and what the patient, what the insurer, what everybody else gets from that.

DR. KHOURY: I guess what I'm trying to say, the ethical baggage is different for monogenic versus polymorphism, regardless of whether it's drug-related or prevention or intervention. That's where I split the ethical baggage. Monogenic, sort of high-penetrance genes, versus the rest of the world, and because the ethical components are very different, and they will have subcomponents there with treatments related to medicines versus other interventions that may have nothing to do with medicine, but could be public health intervention.

DR. MANASCO: And I would agree with you that there are different issues there, and we were trying to be more simple in our presentation, and we probably should have separated those two because clearly the issues are different, and I would agree with that. Thank you.

DR. McCABE: Francis, briefly.

DR. COLLINS: Just a quick follow-up. I guess I was a little concerned in your suggestion that

pharmacogenetic profiles could be packaged in some way that would make them less ethically-charged. If they're based upon variations that do have significance for not just drug responsiveness but actually disease natural history, I don't think it would be ethical to obscure that part.

So that part and parcel would have to be part of what the patient learned, and in that case, you have taken on the baggage, like it or not, and I suspect that other kinds of pharmacogenetic tests that come on the market in the next 10 years, at least half of them will have those overtones and will be very difficult to separate out from what we've been talking about this morning as far as disease predictions.

DR. McCABE: The other thing that you mentioned very quickly was the pharmacoeconomics, that there's a definite benefit to the drug company to identify an individual who may have an untoward event.

DR. MANASCO: Absolutely.

DR. McCABE: There may not be the same benefit to identify 30 percent of the people taking the drug that's not benefiting from the medication.

DR. MANASCO: Actually, we believe it is beneficial.

DR. McCABE: Okay. Well, that's good. That's good. I just wanted to be sure that that wasn't the pharmacokinetic issue because again it gets to what Francis was saying, that it's important to not obscure information that might come through.

DR. MANASCO: Oh, absolutely. I think that just one comment is that we want the patients who are going to get better with our medicines to take our medicines. It doesn't do anybody any good if we can identify who is not going to respond and then to have them take the medicines and have the risk of side effects and all the other things that go along with it. We clearly want to target our medicines to the right patients.

DR. McCABE: I think we're going to have to move on. Hopefully we'll have some time at the end to come back to some of the discussants, but I want to be sure that everybody has a chance.

Thank you very much.

DR. MANASCO: Thank you.

DR. McCABE: Our next speaker is Rod Howell. Dr. Howell is President of the American College of Medical Genetics.

Dr. Howell, do you want to use the podium?

DR. HOWELL: I will use the podium.

DR. McCABE: And I think your comments, if people wish to refer -- yes, they're in Tab 5.

DR. HOWELL: Dr. McCabe and members of the committee, the American College of Medical Genetics is a professional organization that is interested in both the clinical and laboratory aspect of medical genetics, and we have as part of our major mission the aspects of education and genetic policy. So we're delighted to have an opportunity to comment today.

Since Dr. McCabe has been rigid in restricting my time, what I'm going to do is depart from my usual presentation and read certain parts of my presentation that's in the book that I want to be sure that we cover today.

Two overriding perspectives drive our views of how genetic testing should develop. First, because testing is relevant to so many medical specialties, it should be incorporated into medicine as a whole and should not be segregated solely as the province of geneticists.

Second, genetic testing should not be selectively burdened with solving the problems associated with the current health care delivery system.

While we agree that issues of quality, privacy, discrimination and health insurance are significant in genetic testing, they are similarly important in other areas of health care in general. Where problems and concerns are generic, we think solutions should also be generic.

Genetic testing can be offered in a wide array of scenarios. The uses for heritable testing, either from basic genetic diagnostic testing of individuals with disease to the identification of individuals with reproductive risk related to their genetics and the identification of individuals with future genetic risk.

Genetic testing used to identify acquired changes associated with infection or cancer is little different from many other currently-used biomarkers of disease. Not all are readily amenable to government regulation, and, arguably, some should probably not be subjected to the complexities that can be associated with such controls.

In the area of oversight of test development and, where appropriate, transition from investigative testing into standard clinical service, it is important to first consider the stage of development of the test and its target population.

Much of the discussions of inappropriate use of genetic tests have involved the use of tests during the investigative stage of development, where performance characteristics are still being determined. During this stage, the main requirements are that the participants be fully informed of what the testing will and will not tell them, and then of any potential risks and benefits that should be fully disclosed.

In recent years, economic factors have significantly impacted this stage of development, and I will come back and discuss those shortly.

The great majority of disease-associated genes are identified through the study of affected individuals. When sequence variations are clearly pathological and deterministic in nature, the tests rapidly become useful in diagnosis, and standards for such determinations are in the final review by several task forces, including those of the College as well as the American College of Pathology.

Lengthy external review processes could significantly delay implementation of testing used to detect diseases, such as cystic fibrosis, the muscular dystrophies and certain forms of heart diseases. Decisions about the uses of these tests in clinical diagnosis are typically practice-of-medicine decisions and are driven by an understanding of the related medical literature.

At the opposite end of the spectrum are gene tests that predict disease development in otherwise normal individuals. Some of the more visible examples of these have been discussed today, such as breast cancer, hemochromatosis, and Alzheimer's disease.

It will be critical to ensure that any added oversight of susceptibility testing not constrain

diagnostic uses. In other words, the level of oversight may differ for different types of testing.

Genetic testing is, however, unique in that it can reveal reproductive risks to current and future generations. Individuals carrying such genetic abnormalities are typically clinically normal. The need for testing may arise in families with individuals who are affected or may be targeted at specific high-risk populations by public health programs.

Oversight and decisionmaking required for these predictive tests should be and would be very different than those used in the clinical diagnostic arena. It seems that governmental bodies might be most susceptible to political aspects of predictive testing and therefore perhaps not the best place for regulation to reside.

More appropriate, should be broadly representative bodies, such as practitioners, stakeholders, consumers, similar to the composition of this particular committee at the table. The availability of standards, however, on which decisions are based will be critical for the ability to develop these tests.

Economic issues underlie many problems related to what some consider the premature release of genetic tests. Academic medical centers have historically been the place where tests are developed and translated into health care. The academic centers have subsidized much of this clinical research activity, but shifts to managed care and excessive cuts in laboratory reimbursement have limited their ability to fund independently this work.

In genetic testing, this problem is further exacerbated by the fact that for the vast majority of disease-related genes, there's a population for whom the test is immediately useful, which results in widespread use and appropriate reimbursement.

The problem has been to identify then the appropriate individuals, families, or other populations to be tested based on a priori risks that may be ranging from high to very low.

Further complicating this fact is the genetic tests can also be used to determine carrier states that may impose reproductive risks but no direct risk to health benefits to the person being tested.

An additional economic factor has begun to impact genetic testing significantly. Patents on human genes and their mutations have allowed patent-holders to exert undue influence and impose undue costs on testing. Some have attempted to monopolize the tests by requiring that their laboratory be the only one to offer the test based on the patented sequence. Such monopolies lead to several problems.

Competition for quality assurance and pricing is lost, and the delivery of patient services negatively impacted through the inability to obtain independent second opinions on testing results. Unreasonable pricing of licensing agreements has already begun to negatively affect certain testing.

Further, the mission of academic medical centers in training the next generation of laboratory scientists is compromised by the inability to provide and expose trainees to certain tests and the local expertise in the patent tests.

The American College of Medical Genetics has determined in its recent policy statement that the very concept of patents on naturally-occurring human genes and on sequences should be revisited, and enforcements of patents on our currently highly-manual testing procedures should be curtailed, and I've enclosed in your material the statement that the College has recently prepared about this issue.

As alluded to previously, the question of whether tests are valid is much less problematic than

defining the specific indications that justify genetic testing. For the most part, state and federal agencies responsible for reimbursement decisions have disregarded genetic tests for reasons ranging from suggestions that the target disorders are too rare to decisions that all genetic tests are in the developmental stage.

Such arguments can be difficult to counter for several reasons. The regulations of the Clinical Laboratories Improvement Amendment established criteria that are very different from the FDA for whether a particular test should be considered "orphan" due to the limited population. This discrepancy occurs because genetic testing brings about a totally new paradigm to testing.

Target populations have traditionally been considered to be clinically-affected groups. However, due to the power of genetics in the prevention of disease and the identification of risk factors for disease, potential target populations are far larger than the clinically-affected populations.

In addition, most criteria by which rare diseases are assessed for orphan disease status consider the general population rather than highly-specific populations that might be the subject of genetic testing.

In 1983, the Orphan Drug Act was passed to promote the development of products for rare disease as defined by those occurring in fewer than one in a thousand persons. Examples of these would be cystic fibrosis, the leukodystrophies, Tay-Sachs and phenylketonuria.

There's probably no better example of genetic testing at the population level with associated diagnosis and treatment with improved outcome than phenylketonuria. Newborns throughout the United States are tested. Those who are diagnosed as affected are treated with the resultant intelligence that is near normal while lack of treatment results in profoundly-retarded persons.

It would certainly be unacceptable for testing related to rare disease to be overly-constrained by regulatory requirements aimed at controlling a relatively few genes for disease susceptibility. There's also the issue that genetic testing for carriers of rare genetic diseases will commonly identify as many as one in 50 people in the general population.

Knowledge and education about genetics seems to be as deficient in regulatory bodies as in many areas of medical practice, and I might say that takes a lot, because genetics brings unique paradigms to thinking about disease and disease-preventing services. Most regulatory bodies must consider their approaches in order to effectively address what's in their purview.

I'd like to close and make a few points that we think would be very important in moving forward.

One is professional organizations, such as the American College of Medical Genetics, and our colleagues, the American College of Pathology, will continue to improve and broaden quality assurance programs, and there are a lot of those currently underway in the area of medical genetics.

We are also actively working to develop standards of practice for laboratory services and the clinical parameters around which decisions about testing are made. Educational programs are evolving, and wider audiences are being offered information that promotes genetic literacy.

We must maintain the clinical investigational aspect of genetic test development and ensure that participants are aware of what is known and what is not known about a particular test without constraining the diagnosis of disease or rare disease applications.

Economic issues related to our changing health care delivery system and its financing underlie a number of problems that must be addressed. These include standards by which decisions are made about

reimbursement for genetic testing offered for both disease and disease prevention.

We must address at the highest levels of government the negative impact of patents on the provision, pricing and quality of genetic testing services, on the training programs and the availability of local expertise related to genetic tests, and on the transition from high-cost/low throughput testing to low-cost/high throughput testing systems.

Professionals involved in the particular tests and the consumers who may utilize them should be adequately represented on all regulatory bodies making such decisions, and I'd like to comment that certainly our professional groups remain prepared to work with the Secretary's Committee and others in accomplishing some of these goals.

Thank you very much.

DR. McCABE: Thank you very much.

We have time for a couple of questions to Dr. Howell. He will be part of the panel tomorrow morning, so that we'll have another opportunity then.

The other thing that I'll mention is that if you provide Sarah with testimony in electronic form or with overheads, I know that GlaxoWellcome did provide us with overheads in electronic form, then we can also have them as part of our documentation and on the Web site.

DR. TUCKSON: Could we get copies of those today? Xeroxes of the ones?

DR. McCABE: Do we have those? I don't think the figures are in here. I don't know if you have a computer with you. You could print them out or if we could get xeroxes off of the transparencies.

DR. MANASCO: We can get electronic copies printed out.

DR. PENCHASZADEH: I have a question.

DR. McCABE: Sure.

DR. PENCHASZADEH: If I understand correctly, then the position of the American College regarding regulation is basically the concern that it may delay or it may be a hurdle in terms of implementation of rules and oversight of new regulations.

Do you have any position on the type of institution that should be involved in regulation? You know, government agencies or in consultation with the professional organizations?

DR. HOWELL: Victor, I don't think we have any specific thing. Our concern, I think, would be focused considerably on the predictive testing rather than the diagnostic testing. The diagnostic testing, I think, should flow through what I would call traditional services that are currently assessed and regulated at the current time and obviously need to be greatly enhanced.

But I think that certainly as one goes ahead, as you've heard the complexity of bringing aboard, genetic tests, who should be tested and so forth, I think to have those done by an oversight panel certainly would be far more appealing than a regulatory body.

Tomorrow, I'm going to talk about some ideas I have about -- I think one of the very biggest problems that we have is the situation when a test has been devised. Cystic fibrosis is an excellent

example. We know a tremendous amount about cystic fibrosis, but the spectrum of the disease is much greater than we know, and as people are tested, the question of how do you get the new information into the system, how do you analyze all the material that's coming in, and I have some thoughts about that that I think would fit better in the context of the meeting tomorrow.

DR. McCABE: Pat, and then Reed, and then we'll move on.

DR. CHARACHE: I'm wondering, Rod, if you have thoughts on how to translate your very excellent current program into general usage, and how to monitor, through surveillance or other mechanisms, whether your standards are being applied.

DR. HOWELL: Again, I'm going to talk a little bit about what I would think would be a useful pilot-type program tomorrow, Pat, about some ideas. Whether they will work, I don't know, but I think that the whole problem of educating the whole world, the medical community, the public, et cetera, about so many things is an enormous project, but I do have some ideas about some pilot projects that probably will work.

DR. McCABE: Reed?

DR. TUCKSON: I think actually that may get to -- and maybe my question will wait till tomorrow. I really do want to understand even more about how we can feel confident that an oversight panel will accomplish the public objectives in a way that, you know, will give confidence as opposed to -- and thereby allows us to avoid the more onerous implications that you imply for the regulatory body. I mean, given that I think we're going to have to have a lot of specificity about if we were to recommend that kind of thing, how it's structured, and what the experiential base is, you know, that allows us to do it because I think you make an important point, and I think the question is how do we support that? So the more you can give us on that maybe tomorrow, the more help it will be.

DR. HOWELL: Well, I'm sure many people have good ideas on that.

DR. TUCKSON: Great. Thank you.

DR. McCABE: Thank you very much.

We'll move on to Dr. Tom Frank, Medical Director of Myriad Genetic Laboratories.

DR. FRANK: Thank you, Dr. McCabe, and members of the committee. I will keep my remarks to under five minutes. Probably about 14 seconds.

I am the Medical Director of Myriad Labs, which does BRCA1 and 2 analysis for the diagnosis of hereditary breast and ovarian cancer syndrome, and I'm thinking about Dr. Buchanan's remarks that his provocative statements were meant to be constructive. I hope to be similarly constructive.

Your committee's been charged with considering when a genetic test should be available for clinical rather than research purposes, but, in addition, there were some recent events that focused attention on the importance of accuracy in genetic testing. I'd like to comment on these briefly.

Specifically, this was an account of a false positive BRCA1 result that was performed last year by a laboratory that's no longer in business, and this account stimulated a national discussion on whether genetic tests are less accurate or less well-regulated than other tests performed in medical laboratories.

Most of the accounts about this lab error contained two erroneous statements. The first, that medical tests that are not genetic are regulated by the FDA, and, two, unlike other medical tests, genetic tests are entirely unregulated by the Federal Government, and neither of these statements, as I believe you know, are true.

The public clearly has a right to genetic tests performed according to the same hopefully high standards expected of other important medical tests, and so laboratories performing genetic tests are in fact accountable to the same federal regulations as all other medical laboratories.

We certainly agree that as technologies evolve, that it's important to reanalyze the efficacy of those regulations, but I would caution against starting from scratch.

I want to leave the issue of accuracy and now talk about clinical validity and clinical utility concepts that have been discussed extensively by this committee and will no doubt continue to be.

Now, this committee's considering whether in effect to confine genetic tests to research protocols for a defined period of time until clinical utility and validity are established.

My concern is that such a policy would likely result in more erroneous test results, not fewer, because research tests are performed in research laboratories, and research laboratories are completely exempt from federal regulations of quality control and personnel training that govern testing in clinical laboratories.

So indeed, we can see the results of restricting BRCA1 and 2 to research protocols just north of the border in Canada, where results are used by doctors for patient care decisions, but the turnaround time in the research labs is about two or three years compared to the two or three week turnaround time that we offer in our clinical laboratory in the U.S.

A recent example illustrated that the Government of Ontario has actually been willing to pay for prophylactic mastectomies for women on the basis solely of a family history of breast cancer, but until recently, they refused to authorize clinical genetic testing on the basis that they considered it experimental, and one woman's prophylactic mastectomy was in fact already scheduled before her successful appeal allowed her access to a test result from our lab.

The result demonstrated, by the way, that she did not carry the mutation in her family, allowing her to cancel the now-unnecessary surgery. I'm not revealing anything confidential. All this was written up as a front page story in the Toronto Globe and Mail.

Dr. Collins posed the following question to this committee at its previous meeting. What kind of data is needed before genetic tests become used in clinical as opposed to research activities?

Now, this committee is diverse and likely there will be several points of view and have been several points of view expressed on this issue, but I believe that from a medical standpoint, one answer prevails, and that is when it becomes undeniably unethical to withhold from a patient the results of a genetic test or any other medical test, the test can no longer really be considered to be experimental.

The recognition that test results cannot ethically be withheld from a patient, I believe, constitutes an acknowledgement of the clinical value of the information, and I want to illustrate this by an account that appeared in the national media, boy, about seven years ago.

This event actually took place before the discovery of BRCA1, and an investigator who did not

know the exact gene responsible for hereditary breast cancer in the family knew, through a linkage analysis, specific markers associated with cancer risk in that family.

According to the national publication, he had not planned to return the lab results to the members of the family, stating, and this is a quote from the account, "his sole interest was to use the marker to home in on the gene itself."

However, he discovered that a member of the kindred that he knew did not carry the marker of risk had nonetheless scheduled a prophylactic mastectomy, and the investigator responded in what I hope you will agree is the only ethical manner possible.

He and his colleagues made his laboratory test results available not only to that individual but also to all of the other adults in the family who sought the information following informed consent.

He said, and again this is a quote from the publication, "We realized we had information in our hands that could dramatically change people's lives right now, not some time in the future."

This statement was made more than three years before tests for BRCA1 and BRCA2 were clinically available, and I believe that these statements illustrate the clinical validity of being able to test for hereditary breast and ovarian cancer syndrome.

I'm not presenting this result to discuss this specific situation but really because I think it illustrates something very important, a very important principle, which is that when knowledgeable experts -- and that harkens back to Dr. Howell's recommendation of a professional body -- when knowledgeable experts are ethically compelled to provide test results to patients for their individual medical management, such test results, I believe, have clinical value.

Now, the value may have limitations, and these limitations must be clearly communicated to the health care professionals and patients, but I think the value is there nonetheless. So I caution this committee against taking an action that would inadvertently have the effect of removing genetic tests from federally-certified clinical laboratories for an extended period of time and confining them instead of research laboratories that are exempt from all such oversight.

I believe the most important responsibility of the committee is to ensure that physicians and patients seeking genetic testing have full access to accurate medical test results.

Thank you.

DR. McCABE: Thank you, Dr. Frank.

Yes?

DR. BURKE: Thank you very much. Very interesting comments.

I actually think that some of the examples you've just given us point to a very important complexity. Specifically, the ethical obligation to provide information in the example you provided stemmed from a circumstance where a test had powerful and accurate negative predictive value.

The value of the test, I think the reason why there was an ethical concern to provide information to a family in that circumstance, was because that high negative predictive value allowed members of a high-risk family to avoid unnecessary treatment, and I would certainly agree that there's a tremendous

value.

I think we already identified that that happens to be one of those circumstances where we see tremendous utility to information that has predominantly clinical validity and actually a lot of uncertainty about what to do in a positive test.

What is particularly difficult, I think, in that example and in other examples that we may come to discuss is that that occurs in a setting of great interest in testing on the part of individuals for whom the test can provide no predictive value. In particular, no negative predictive value. That is, I think there are a number of survey data have already been published that suggest that women with a positive family history who do not meet criteria for autosomal dominant inheritance nevertheless tend to be highly interested in the idea of BRCA1/2 testing perhaps because they are pleased with the idea that they have a low likelihood of carrying the mutation and may be reassured by a negative test.

The point I'm really getting to here is that we do, I think, have to think very actively about the likelihood that we will be dealing with circumstances where the genetic test has great value for a very small subset of potential customers and not much value to a much larger subset of potentially-interested customers, and how we deal with the regulatory issues that arise when there may be an ethical obligation to provide information in relatively rare circumstances but a lot of concern about broad use of the test in most circumstances.

I thank you for that example because I think it's a good one for us to talk about.

DR. FRANK: I'm sorry.

MR. HILLBACK: No. Go ahead.

DR. FRANK: The problem is you can't really have a negative -- Dr. McCabe?

DR. McCABE: That's fine. Go ahead. Why don't you respond?

DR. FRANK: You can't really have a negative test without having a positive test. The reason that a negative test with great negative predictive value could be provided was that in tandem, other individuals in that family were in fact getting positive test results, and rather than dispute the points of the predictive value of BRCA1 and 2, I would say that these are important principles not only for genetic tests but for all medical tests, that if I as the pathologist returned an endometrial biopsy with a report of papillary interstitial metaplasia, which actually is a real diagnosis, that there's a certain obligation to explain to the clinician at the other end what that means and what that may not mean.

I think that these are not principles limited to genetic tests, and that the solutions should be in concert with those used for other diagnostic tests, such as biopsies.

DR. BURKE: No. I agree with you. I certainly agree with that latter point, and I also agree that where you have high negative predictive value, generally speaking, you have high positive predictive value.

I think the utility of the positive information is less clear than the utility of the negative predictive information in those high-risk families. I was more concerned about the possibility that use of a test that has both high positive and negative predictive value for a very small subset of families is one thing, but as the test becomes commercialized, one opens it up to a much larger potentially-motivated group of testees for whom we can't provide those kinds of predictive value benefits.

DR. McCABE: Francis, then Elliott, then Pat.

DR. COLLINS: So Tom, I wanted to ask you about the scenario that you paint, which I think is a little overly-sharp edged in terms of either this test is available through a CLIA-approved federal certified laboratory or else it's being done in a research laboratory that doesn't have those constraints.

Obviously one could also argue that for a test that's still being evaluated, a much better circumstance, and there are many tests in this category right now, is that the test remains the subject of research, but the testing part of that research project is carried out in a CLIA-approved laboratory in some collaborative way between the organization that's doing the research protocol and that laboratory who has the skills and the appropriate quality assurance to be sure that they're getting the tests right.

So I don't know that it's quite fair to say, well, you know, if the test is not freely available from a commercial source, then it's forced back into a less well-overseen research arena where more mistakes will get made.

As we all know, if you're giving the results back to the patient as part of the research protocol, that result had to be done in a CLIA-approved laboratory. So that pathway still exists. You may want to respond to that.

DR. FRANK: I do think that's a fair statement. I certainly would not ever anticipate that this committee would have made a ruling recommending the black and white scenario you described, but I think in practice, if there's a regulation saying that a test is not allowed to be provided by a CLIA-certified lab on a clinical basis, that many CLIA-certified labs will not have very much incentive to actually develop the test and perform it.

Speaking from the perspective of my previous academic position as well as my current commercial position, labs generally do test, even if they're academically-based labs, when there's some kind of funding to support it.

Now, if there's a research grant to support the test in the academic setting, it will do it, but if there isn't, and if there's no possibility of reimbursement, it's an investigational test, an insurance company will not reimburse for it, then even an academic lab will hesitate before offering it.

So I think that this could be an inadvertent result of that situation.

DR. McCABE: Elliott?

MR. HILLBACK: Yes. I guess to follow along on that, the question is, should a government oversight body be the decisionmaking rule about whether this information is available or whether we're back to the medical practitioner who is caring for this patient, who now has to make an assessment along with the patient, is there utility here, and how do we take advantage of it?

Because if this is really that rapidly changing, you know, I think it's going to be back to our challenge of how does some regulatory oversight body stay active and stay up to date in providing an oversight that's not a month, a year, two years out of date, and so I think one of the questions we have to ask -- it's a system issue, not a lab issue -- is where are the users of the information, and can they be discernible experts or discernible enough to understand what to do with that information once they get it?

DR. Frank: Well, that is certainly the situation with medical tests in general. I think the question

before the committee is whether genetic tests should be separated out into a different scenario, and that's what you'll be wrestling with.

DR. McCABE: Pat, and then Barbara.

MS. BARR: This is a very brief comment, and it's not directed only to you. I am concerned that every time we have a test, that we'll identify some predictive value for a particular disease, we are creating a medical syndrome. I think the language and the lexicon is really inappropriate, and we should be thinking of another way to talk about this.

In certain very high-risk families with particular pedigrees, you might want to particularize a name, but when these tests are being used for populations as a whole, what you're going to have is a public where everybody's got syndromes, and I don't think that's really what we want to do.

DR. FRANK: Well, I would, Pat, respectfully, disagree with you, that hereditary breast and ovarian cancer syndrome does exist as does hereditary non-pyopoiesis cancer syndrome. These are actual medical situations that are not prevalent, thankfully, in the general population, but individuals do have them, and it's not simply individuals who come from large enough families to have 20 first-degree relatives with breast cancer, but they really do account for a significant proportion of breast and ovarian cancer, and those individuals warrant a separate course of medical management as was discussed by a national consensus committee that Dr. Burke can speak more expertly on than I can.

DR. McCABE: Barbara?

DR. KOENIG: Well, let me second Pat's comment about language. I also think that that's very important because we have to watch very carefully how many syndromes we create, and does everyone in those families -- what about the non-genetic family members of those families? Are they part of the syndromes?

I think we really have to watch how this spins out, but I wanted to make another comment, again back to the issue of social context, and in your testimony, I've been very interested since the beginning of the BRCA1 and 2 story about this particular narrative about the woman being saved from a prophylactic mastectomy. That's a very interesting story, and we hear it over and over again.

But just to point out that that is an interesting phenomenon in where did that recommendation come from in the first place, and if there wasn't the idea that one needed to do a procedure which may or may not be necessary, that then there's no need to save them from that by doing a test, and that there are places that don't recommend doing this particular surgery.

So just to keep in mind that it's the background recommendation of the surgery that's driving the need for the test, but that brings up my more general point, which is, as someone who works in bioethics, I'm concerned about what I see as rationalizations based on ethics ideas that will move new technologies into clinical practice prematurely on the ground that you have this obligation to disclose results prematurely, and I think in our discussions about regulation, I think we need to be very cautious about that, about oversight, because you can say about everything, well, we have an obligation to disclose this because we have this information, but if you really don't know what that information means, then what kind of an obligation do you really have to disclose the information to someone participating in research?

DR. FRANK: Barbara, I think that's a very important point about prophylactic mastectomies, and it deserves an answer. Prophylactic mastectomies were certainly not created by BRCA1 and 2 testing. The procedure's been done for decades on thousands of women solely on the basis of family history, and in fact, people have been diagnosing hereditary cancer syndromes for decades based solely on family

history. The information is there. It's in the family history. People have been acting on it in often irreversible ways, such as prophylactic mastectomy.

Now, genetic testing for hereditary cancer syndromes is not perfect. We know, for example, that BRCA1 and 2 testing probably is unable to detect a subset of clinically-significant abnormalities in these genes, but it's a whole lot better than simply taking a family history and telling everybody in the family that they're at the same increased risk, even though only half of them are and half of them aren't.

So I think that it is important to point out that people do take these interventions. They do go on medications based on the "Gail" model, which doesn't work for women with BRCA1 and 2 mutations, and they're using the best information available, knowing that in five or 10 years, we'll have better information. That's how medicine has been progressing.

DR. McCABE: If it's very brief, and then we need to move on.

DR. BURKE: Just a very brief comment, very germane to what Barbara and Tom have just said. I think your point about prophylactic mastectomy is all the more important when you look at the data that says women from high-risk families, the majority of them who are candidates don't choose this intervention, that actually on a minority choose this intervention.

It's a classic example of an intervention that probably has far less effectiveness and efficacy because it's actually unacceptable to a majority of people for whom it might be recommended. So I think thinking in those terms is extremely important.

DR. McCABE: Thank you very much.

Our next speaker is Dr. James Allen from the Association of State and Territorial Health Officials, ASTHO. Dr. Allen?

DR. ALLEN: Dr. McCabe and members of the committee, thank you for the opportunity to appear before you on behalf of the Association of State and Territorial Health Officials, otherwise known as ASTHO.

ASTHO represents the public health agencies of the United States and territories. Its members generally serve as the appointees on public health of the nation's governors, and they are the chief executive officers of the health departments or public health agencies of the U.S. states, territories and possessions.

State health officials are poised to effect change and carry out public health policy at the state and national levels through direct dialogue with governors, state legislatures, state congressional delegations, and representatives of federal agencies.

State health officials bear primary public sector responsibility for the health and well-being of the residents of their states. In this role, they have the fundamental responsibility for the public health functions of assessment, assurance and policy development.

This responsibility, and these primary functions, certainly relate to the burgeoning field of genetics and genetic testing. Examples of public health's responsibilities regarding genetics include the following: conducting epidemiological research to understand more fully the relationships between genotypic variability and complex health conditions; conducting public pilot projects in genetic services delivery; educating the public, health care providers and policymakers about genetics and its relationship

to health; assessing the use, efficacy, safety and application of genetic technologies through surveillance; developing policy and strategic plans to maximize the benefits of genetics to the population's health; and integrating genetic information into existing public health programs to capitalize on new genetic discoveries to improve health.

State health agencies, particularly state public health laboratories, have long maintained a primary role in quality assurance in genetic testing. For example, in newborn screening. These functions often include licensing or certifying the personnel and the facilities that perform genetic tests.

Current advances in medical genetics will expand and challenge these roles significantly. The introduction of new genetic technologies in public health and clinical medicine will require continuing professional education opportunities for physicians and other health professionals, as you already discussed this morning.

The need to address technologic and quality assurance challenges for genetic testing of all types, not just for large-scale testing and screening, will be an important challenge. As we are all aware, genetic testing also raises extremely important ethical, legal and social concerns.

With these considerations in mind, state health officials and ASTHO intend to take a leadership role in preparing for the opportunities and challenges presented by genetic discoveries and the resultant genetic tests and applications.

Many states already have taken a leadership role in enacting legislation to ensure the privacy and confidentiality of patient medical records, including the results of genetic tests. States have also been at the forefront in passing legislation to protect against discrimination in health insurance and employment based on the administration and/or results of genetic tests.

It is important to note that many state/public health responsibilities regarding genetics and genetic testing require resources that state health agencies simply do not have, however, either through federal or state means.

As this committee deliberates its recommendations for the oversight of genetic testing, it also should consider the resources necessary to implement them effectively.

ASTHO has recently developed the capacity to begin to address many of these issues through a project funded by the Office of Genetics and Disease Prevention at the Centers for Disease Control and Prevention, the CDC.

The purpose of the project is to provide state health officials and program directors with information about emerging genetics and public health issues. The goal is to enhance the capacity of states to assure that results from genetic research are used responsibly in public health practice.

ASTHO has worked closely with other national policymaking organizations, such as the National Conference of State Legislatures, the National Association of County and City Health Officials, and the National Association of Local Boards of Health.

To facilitate communication on current issues, ASTHO is working with a number of other partners to plan and host the Second National Conference on Genetics and Disease Prevention that will be held December 6th-8th, 1999, in Baltimore, Maryland. There is a brochure on the table outside telling you more about this conference.

The purpose of the conference is to address public health opportunities and challenges presented

by advances in human genetics research. The theme is integrating genetics into public health policy, research, and practice.

ASTHO's partners for this conference include the CDC, the National Human Genome Research Institute, the Maternal and Child Health Bureau of the Health Resources and Services Administration, the Johns Hopkins School of Hygiene and Public Health, and the Maryland Department of Health and Mental Hygiene.

We expect approximately 600 public health professionals, researchers and policymakers at the local, state and federal levels as well as others from academia and industry and consumers to attend. Dr. Francis Collins is the keynote speaker for the conference.

ASTHO has also formed a Genetics and Public Health Work Group to guide its policymaking efforts about genetics, to provide oversight for its genetics project activities and to serve as an expert resource group for state health agency feedback and representation.

Membership on the work group includes state health officials, senior deputies, state genetics coordinators, and representatives of ASTHO affiliates, such as the Association of Public Health Laboratories, the Association of Maternal and Child Health Programs, the Council of State and Territorial Epidemiologists, and the Association of State and Territorial Chronic Disease Program Directors.

ASTHO would like to offer the expertise and unique resources of this work group as well as ASTHO's broader state health official membership as a resource for the Secretary's Advisory Committee on Genetic Testing to assist you in your efforts to address the oversight of genetic testing.

Genetics is not new to state health officials and agencies. State health officials have a wealth of expertise developed over decades of operating newborn screening programs and genetic services through maternal and child health.

State public health laboratories have long been responsible for the oversight of the validity and reliability of laboratory tests, including genetic tests, and state epidemiologists have begun looking at the linkages between population genetics and susceptibility to diseases.

Some states have formed cross-programmatic task forces to prepare for the integration of genetics into new areas, such as chronic disease and environmental health. The state public health officials and their staff could be a valuable resource to this advisory committee.

On behalf of ASTHO, I extend an invitation to the committee to work with state-based public health as we move forward in this new and exciting field of genetics.

Thank you for the opportunity to speak before you.

DR. McCABE: Thank you, Dr. Allen.

Reed?

DR. TUCKSON: Thank you as well, Dr. Allen, for a great presentation.

One area that I would wonder whether you could consider taking back and consider explicitly being helpful, and that is in the notion of public health leaders develop shared visions for health and policymaking at the community level. That's one of the major expertise that you all bring.

The Outreach Committee is struggling with, successfully, but struggling with ways of how we're going to get that sense of shared vision for communities to participate in, giving up their input and feedback on these issues, and particularly given the number of times this morning we've talked about that this is a changing field. So that always, no matter what we do today, we'll have to update.

And the question really then is can we task ASTHO as a major participant in the development of a community-based vision for the kind of issues that we're struggling with in testing in general but genetic testing in specific since that's what we're here to do?

DR. ALLEN: Thank you for those comments and the suggestion. You're absolutely right, that as we change the way in which we practice medicine and public health, we really do need to become much more community-oriented. It has become an essential part of how we operate as a country, and in this regard, I think certainly state health officials, the state public health agencies, can provide a great deal of assistance and leadership, and, yes, we, ASTHO, would be willing to take on that challenge with the caveat, with the understanding that there are 50 separate states, the District of Columbia, there are county health departments and large city health departments throughout, and not all of them with, of course, make the same level of commitment that I think we as a national agency representing them will be willing to do.

I think we also ought to look at other opportunities to bring in other partners. I will just mention very specifically the Turning Point Project that the Robert Wood Johnson Foundation and the Kellogg Foundation at the local level have funded to try to build these kinds of community partnerships to enhance understanding and the application of public health principles.

I think working in concert with groups like that, that we really can develop some models and move this process forward.

DR. TUCKSON: When is the conference on genetics disease prevention?

DR. ALLEN: It's early December.

PARTICIPANT: 6th, 7th and 8th.

DR. TUCKSON: So we would have benefit of the results of that meeting in time for us to use somewhat in our work, and if that be the case, Dr. Allen, it would be, you know, again useful if you could have, you know, whatever's learned there synopsized and maybe, you know, as sort of putting it out, people, that we're asking for guidance and assistance. No need for us to reproduce the wheel.

If you're going to bring all the smart people together, would you do something about work for us? Ask the questions and give us the answers.

DR. ALLEN: I certainly think ASTHO would be willing, with CDC and others, to take on that challenge, and we'll get information back to you.

DR. TUCKSON: Thank you.

DR. McCABE: Thank you very much. That could be a big help to us. Thank you, Dr. Allen.

Our next speaker is Judith Benkendorf, who is a genetic counselor and Professor in the Department of Obstetrics and Gynecology at Georgetown University Medical Center, and Genetics

Educator for the Human Genome Education Model Project, the HuGEM Project.

Judy?

MS. BENKENDORF: Thank you, Dr. McCabe.

I know it's illegal to gamble when you're in the government, but there have been 35 identical folders passed out, and one of them doesn't have the contents of my testimony, it has our overheads. There will be a granola bar for the winner. Monetary value less than $25 or a video, a video. Otherwise, we can do this without overheads.

DR. BURKE: Here it is.

DR. McCABE: Francis had it.

MS. BENKENDORF: That was a risk assessment of three percent. Okay. Moving on.

I actually want to divert a little bit from the theme of genetic testing and go back to the theme that was on the table loud and clear at the end of the meeting in the Summer, and that was genetics education.

I don't think I need to convince this committee, you can put on the first overhead now that we have them, but rarely a day goes by in the genetics community without somebody somewhere mentioning genetics education, be it the need to reach the public more effectively, to try to procure more funding to train our existing cadre of genetics professionals, or to prepare non-genetics health professionals who meet with individuals and families on the front line for the genetics revolution.

I think we all agree that this is a critical time for these activities. We are broadening our understanding of the genetic basis of common complex adult onset disorders, and we await the clinical integration of new genetics tests and risk assessment capabilities, such as stretching the Gail model to create similar models for other diseases and cancers.

These events will all elevate health care professionals of all sorts to providing at least a minimal level of genetics care and will also include all citizens as potential consumers of genetics services.

In preparation for this, the National Coalition for Health Professional Education in Genetics is about to release genetics core competencies for all health professionals. These competencies are laudable, but how in the world are they going to move from a printed list into action?

We believe that the Human Genetics Education Model Project, which I'll refer to HuGEM, offers the perfect paradigm. This is a multi-faceted ELSI-funded collaborative initiative between the Georgetown University Child Development Center and the Alliance of Genetic Support Groups.

The ultimate aim is to provide genetics education and resources to members of six health professions, and these will be audiologists, dieticians and nutritionists, occupational therapists, physical therapists, psychologists, social workers and speech-language pathologists, working through their professional organizations. Combined, these organizations represent over 650,000 members.

At its inception, in the, I would guess, pre-embryonic stage, the goal of this grant was actually fairly simple: to develop and implement a collaborative genetics education model for these associations working through their leadership and their membership, to increase the knowledge and sensitivity of these professionals to the Human Genome Project, human genetics in general, and the ethical, legal and

psychosocial implications of genetics testing and research.

Well, 28 months have now gone by, and the relationships HuGEM has built with the seven collaborating organizations has many parallels to the parenting cycle, from preconception planning to providing mentorship and adulthood, and what I'd like to do now is walk you through the 10 steps of our adopt our association and mentor them in genetics model.

We'll start with the preconception agreement. This is when we defined our core faculty. The two PIs or co-directors are Dr.

Virginia Lapham of the Georgetown University Child Development Center and Joan Weiss, representing the Alliance of Genetic Support Groups.

We also have a medical geneticist and a genetic counselor who have lead roles in the project. A consumer representative from the Alliance of Genetic Support Groups has a vital role in identifying consumers to participate as educators.

Six health professionals, and I think this was really key to some of what we did, one per discipline. These are health professionals with active roles in the provision of genetics services to individuals and families with genetic conditions, through their affiliations with Georgetown's Child Development Centers serve as discipline liaisons and faculty role models.

So we weren't just the geneticist outsiders coming into these organizations, saying, you know, you and us, and we're going to teach you genetics, and I really think the discipline liaisons were key.

Next, we sought prenatal counseling, and this was to assure that the education that we provided would be relevant and meaningful to the health professionals. An extensive survey was mailed to 3,600 individuals. These were 600 practitioners chosen at random from each of the organizations, and we had quite a nice return rate of 57 percent.

In the next slide, you'll see a little bit of what we learned about what's going on in the clinical setting. We learned that 16 percent of respondents refer for genetic testing, 19 percent refer for genetic counseling, 30 percent report genetic counseling, report doing some genetic counseling at least about genetic concerns, and then about 70 percent say they've discussed the genetic component of a condition with clients, yet few report high confidence in carrying out these tasks, and nearly one-third have had no formal training in genetics, not a course, not a workshop, not a lecture.

So based on the survey returns, we did a needs assessment and looked at priority topics for education, and I'm going to keep those topics up as I go through how we parented these organizations.

We started with parent-infant bonding, Child Development 101. During the first year and concomitant to the survey being taken, the HuGEM II faculty and discipline liaisons met with the boards, the leadership and the national staff of the seven associations basically to describe the projects and its benefits, this was our own educational marketing, to heighten their genetic literacy and build a supportive infrastructure for fostering the genetics education agenda.

We then moved to primary education, and these were just classes or workshops, 18 of which were sponsored by HuGEM at national, regional and local conferences during the next year. In these workshops, which were anywhere from two to six hours, we reached 650 professionals. The content and faculty both smacked of our multi-disciplinary theme. We presented an overview of the Human Genome Project and ELSI issues. We updated on the genetic advances related to the disorders seen by those

professionals.

The discipline representatives talked about the role of those professionals in dealing with families, with genetic conditions, and the consumer representative gave a personal perspective. The individuals then viewed a video tape which had case histories on it or rather case studies on it, and that has been donated to the committee, several copies of that video tape, and the case studies were discussed in small groups.

Training materials were distributed to those attendees who had interest in serving as kind of genetics point people or resource people back in their work settings, and over 250 of the 650 workshop participants have volunteered to serve as trainers.

We then moved on to secondary education. So now we're somewhere between high school and college, offering a week-long course, and two of these courses were offered, one in May and one in July of this past year, to a total of 10 senior representatives from each organization, and five from each discipline were chosen to attend one of the two 30-hour faculty development programs.

Most of the attendees were actually university faculty members who will be providing pre-professional and continuing education in genetics through existing courses and by establishing new programs. They'll also have an input in policy and procedures for the organizations as they now have been tapped as their organizations' leaders.

After the core courses, the graduates left home for the first time, perhaps off to college, to test their wings on their own. They have responded that their eyes have been opened, their patients are better served, and their career paths have been influenced. They are doing a whole host of things which are listed in detail in the testimony, but it includes integrating genetics into the content of courses they are teaching.

They're being asked to lecture in other peoples' courses. They're using our own materials to develop some of their own and integrate them into courses. They are adding genetics information to the clinical services they provide. They have a better understanding of the genetics issues in the media, and many of them have already served as point people for doing that.

They're initiating programs in their states to educate their own professionals. They are writing articles and advocating for curriculum and practice guidelines in terms of genetics education for their organizations.

The HuGEM faculty are still partnering with the core course graduates in many of these endeavors, and we're also helping them to identify genetics professionals and consumers in their local areas so that they can be more independent as they move away from home and into new cities. Outreach is being extended also to make sure that there's multi-cultural participation.

The organizations now have had some free time to take on some extracurricular activities. The energy and excitement HuGEM II has really ignited within the organizations, has taken on a life of its own and far beyond anything we ever perceived.

Five of the seven organizations now have a representative on NCHPEG, and the other two are thinking about adding representatives. All are planning to publish the survey results germane to their disciplines in their journals. Many have featured genetics in their newsletters and several have already established genetics task forces internally with long-term genetics education agendas. Again, these would have never occurred without HuGEM as the catalyst.

Well, there's always a nurturing infrastructure back home. As the HuGEM II outreach initiatives wind down, we have become kind of the neutral communication clearinghouse for these organizations. E-mails go back and forth and advisory committee meetings provide opportunities for the associations to remain connected to one another's activities. So this is across disciplines.

Through HuGEM, course participants have networked within their own disciplines as well and actually solidified their intra-disciplinary presence. In one case, the 10 members of the organization banded together and felt their organization wasn't taking genetics education seriously and lobbied them and now have convinced the leadership of their professional society that this is something they need to take seriously and really develop as an agenda.

We have a few next steps before letting our offspring, shall we say, spread their wings and fly, and that is to reach the field work facilitators or those people really teaching the practicum in the undergraduate and pre-professional programs in these professions, and we are proposing to do another round of core courses aimed at the clinic supervisors, at which point we would actually work on their own clinical skills, so they could integrate them with the didactic curriculum which has been brought back by their colleagues.

So that we're actually going to help them build their own skills in taking genetic family histories, interpreting genetic family histories, making referrals and identifying resources, and then following up on the medical and psychosocial sequelae of having the families they serve see genetics professionals, and we hope through building their own skills through an interactive workshop with the consumers from the Alliance of Genetic Support Groups really as the teachers, working with the genetics faculty, this will be the last phase and bring things around full circle.

So as our organization members spread their wings and fly, the mentorship of HuGEM won't go away. We are still university-based and Alliance of Genetic Support Groups-based experts with technical support. We will offer some seed funding to these organizations and help them access genetic services as needed and genetic resources.

But we believe these six disciplines are really ready to go with their uniquely-tailored genetics education initiatives. As proud parents, we stand back, and we're really very pleased to watch them take off. We've gained insight from our experiences and observations, and we've also incorporated much feedback from the organizations, and from that, we're really convinced that adopting a discipline to mentor provides a novel paradigm for putting genetics education competencies into action.

Ultimately, a large number of health professionals and consumers will be reached, and we have seen the associations with whom we are collaborating become more confident about their ability to learn genetics. There seems to be a genetics phobia out there. I see it in the medical students that I teach as well as in the other health professionals, especially those not grounded in science, and much of the groundwork has been laid.

Working with discipline members, I think, again has been key. Those members of their disciplines with experience in genetics has allowed us, the geneticists, not to be the outsiders because we're bringing insiders with us as we teach.

The use of consumers as partners in education has brought personal meaning to the theory and practice issues in our curriculum. At a time when the clinical commitments are stretching all genetics professionals, we believe HuGEM II has found the adopt and mentor an organization model to be highly efficient, effective and rewarding, and it is a model that the HuGEM faculty would be proud to see

replicated.

We'd be both honored and delighted to assist in its application across disciplines and to university-based genetics programs and organizations across the country.

Thank you.

DR. McCABE: Thank you very much.

We have time for a brief comment or two. We do have some of the instructional books and the video tapes. So if people wish to look at them at some future time, maybe we could even -- I don't know if we have a video this time around, but maybe at a future meeting, we could set up one for a break or something like that.

MS. BENKENDORF: The case studies that go along with the video are in all of the packets. We've used those for springboards, as springboards for small group discussions and encourage the professionals to take the video, the video manual and the case studies back to their work place.

DR. McCABE: Any questions or comments? It's a very interesting way of spreading the word and getting others to be involved. Pat?

DR. CHARACHE: I was just going to say I think this is a very nice outreach concept with the gradient effect and certainly sorely needed.

DR. McCABE: Yes, I think it's needed among professionals as well, and in fact, Judy brought me a set of videos for us to look at for the College and also for our own medical students, so that it may serve as a resource for many of us for our institutions.

Thank you very much.

MS. BENKENDORF: Certainly.

DR. McCABE: Our last speaker of this group for public comment is Joseph Graves. Dr. Graves is Associate Professor of Evolutionary Biology, Department of Life Sciences, Arizona State University in Phoenix.

DR. GRAVES: It may be fortuitous that I managed to be the last person to speak today because many of the previous speakers motivate many of the portions of the comments I'm about to give.

I am also Secretary of a division of the Society of Integrative and Comparative Biologists, known as DICI, Division of Integrative and Comparative Ideas. So my talk is going to be somewhat different than the preceding talks, and it's entitled "Molecular Reductionism, Social Constructions of Race, and Allelic Polymorphism: Implications for Genetic Testing."

It has been said that those who do not learn from their history are doomed to repeat it. The history of science has been filled with individuals rushing to simplify complex scientific phenomena for the purposes of their own socially-prescribed agendas. Witness in this century the noted geneticist C.B. Davenport and the workers of the Eugenics Record Office at Cold Spring Harbor, simplified and misrepresented the state of the existing knowledge of human heredity.

To Davenport, all human characteristics could be reduced to simple unit factor Mendelian traits. This erroneous assumption was made necessary by the ERO Program, where if human characteristics

were unit factors, they could be rapidly altered by the positive and negative breeding and immigration schemes advocated by the eugenicists.

In an editorial printed in the October 15th, 1999, issue of Science, I believe that Neal Holtzman warns us that the same sorts of misrepresentation of the scientific results of the Human Genome Project are possible. For example, he suggested that early representations of the project amounted to the statement that our "destiny" was in our genes, and to the idea that new discoveries resulting from the project might minimize or prevent the appearance of disease phenotypes all together.

This optimism has already led many biotechnology firms to develop tests to diagnose or predict the risk of complex genetic disorders, such as Alzheimer's, breast or colon cancer. As an evolutionary geneticist, I must be concerned with any exaggeration of the power of the present studies to predict the onset of disease phenotypes.

These studies are problematic because they do not nor can they at present adequately control for the effects of the environment and other complex genetic phenomena on the expression of genes; e.g., gene-by-environment interaction or epistasis.

Gene-by-environment interaction is ubiquitous in nature, and it is clear that human populations do not experience the same environmental phenomena, particularly in a world where social inequality and injustice are the rule.

For example, diet is one of the most likely factors associated with cancer incidence. Thus, an allelic study of cancer incidence in Japan might not be relevant to Japanese Americans due to their different lifestyles. Alleles that supposedly predispose African Americans to hypertension might not be found in Western Africa.

Environmental factors between nations in Western Africa and North America may lead to different genetic systems being responsible or being found responsible for a given phenotype. Thus, the utility of the proposed genomics studies depends on the appreciation of the complexity of gene-by-environment effects.

The unique histories of populations that have been used to localize target alleles for specific diseases may also create additional difficulties. A recent study of the BRCA1 mutations associated with early onset of breast cancer in Ashkenazi Jews showed that these mutations did not, and I repeat did not, confer susceptibility in a larger sample of English women.

Here, it is possible that the population bottlenecking experienced by Jews of Eastern Europe may have played a role in producing a genetic background conducive to the expression of these mutations.

The simple fact is that identification of allelic variation associated with particular populations may not readily translate to others.

Now, this is directly relevant to the problem of "special populations," defined by the NIH and other research agencies as including women, minorities, and the disabled. Biologically, of course, there's nothing special about these populations. This euphemistic reference only admits that these groups have been historically left out of both the experimental designs in medicine and the community of designers themselves.

Both of these are serious problems. First, it will be difficult to produce valid information on the nature of human allelic variation if only European and Asian populations from economically wealthy

countries are studied.

Secondly, interpretation of that data will be compromised by the continued use of socially-defined "racial categories" as opposed to recognizing that human variations occurs along discordant climes. Thus, no biologically-defined races exist in the human species.

Furthermore, the history of interbreeding between populations is such that any member of a socially-defined population could be found to have any specific allele. Thus, the claim of Evens and Relling in October 15th's Science again, that pharmacogenetic polymorphisms may be "racially defined" is misleading.

The polymorphisms may have been discovered between "races" precisely because discreet racial categories were used originally motivating in the analysis. If a different set of genetic markers were used, one might be able to define different polymorphisms. We could design a pill for people with whorled fingerprints as opposed to loops, and it would be as valid as the development of a white, yellow or black drug.

Human genetic polymorphisms have always defined our social bigotry. We must cease this hang-over of the 19th Century to drive research into the new millennium.

In summary, the Human Genome Project and its potential genetic testing arising from it offers great promise. However, care must be taken at all steps of the implementation that we do not overstep our scientific analysis to foster social or financial interests.

In addition, that scientific analysis needs to be cognizant of the inherent difficulties created by genetic complexities, such as gene-by-environment interaction and epistasis and interpreting the significance of results.

Genetic polymorphisms that might be useful in genetic testing need to be elucidated based on the evolutionary forces, selection, migration, genetic drift, et cetera, that produce them as opposed to 19th Century social construction as a race.

In part, this might be facilitated by the inclusion of more of both scientists specifically trained in evolutionary genetics and those originating from the ethnic minorities historically victimized by these notions of race in the decisionmaking process concerning genetic testing at all steps towards implementation.

Thank you.

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

Are there comments, questions, for Dr. Graves? Yes, Barbara?

DR. KOENIG: I very much appreciated your comments.

DR. McCABE: Could you speak into the microphone, please, Barbara?

DR. KOENIG: I'm sorry. I forgot the mike.

I very much appreciated your comments, and I just wanted to ask if you could offer us any more specific guidance as we move forward on how to deal with the fact that the consequences of testing might fall disproportionately on categories of individuals defined by these defunct social categories, socially

defined categories of difference, and how that should be considered in the oversight process, because this gets back to some of the comments we talked about this morning, as to how to define social criteria that might lead to the need to look at certain kinds of tests more carefully.

DR. GRAVES: Well, my view is that we need sort of a Manhattan Project in the philosophy of race and medicine because physicians, clinicians, researchers believe that the social constructions of race in the 19th Century are real, even though there is more than abundant research, anthropological research, genetic research, over the last 50 years indicating that this is nonsense, and so we really need to rework our view of what human genetic variation is and how it specifically accounts for the types of disease phenotypes that the Human Genome Project and the development of genetic testing and pharmacogenetics will motivate. So this committee really needs to play a role in that.

I don't want to point fingers, but I noticed in the last presentation that they used the term "racial," and racial has so many confused connotations with it, that any publication coming out of this group needs to be very clear on the language it's using to describe genetic variation, and so there needs to be this effort taken at all levels to clarify the confusion, and I really do think that this committee needs to be diversified in ways that include scientists from underrepresented minority groups.

Now, despite the myth, there are a number of highly-qualified geneticists, physicians, et cetera, from these populations, and one of the ways that, you know, in terms of things I've been involved in, that these issues are constantly raised and the vigilance is maintained, it's by the activity of those individuals, and so those two things, I think, are crucial in helping to move this process along.

DR. KOENIG: I hope you noticed that we did not use the word "race" in any of our documents.

DR. GRAVES: Yes, I know you haven't.

DR. KOENIG: Yes.

MR. HILLBACK: We had some strong influence on that.

DR. McCABE: Yes, we discussed this quite a bit in the conference calls, and the terminology that we decided to use was "ethnocultural" groups as opposed to either ethnic groups or racial groups.

I'm wondering if you would comment on that.

DR. GRAVES: Yes. I think that that's fine because what we're really talking about is geographic variation, and the way that people are really identified have to do with their cultural identities, not their genetic background.

I mean, if you look at me, none of you would be able to tell my ancestry simply by looking at me or anyone else in this room, but, of course, the first notion you see is here's a black scientist walking to the mike. That's what most people think because we're so wedded to the 19th Century conception of race in every-day practice.

But in fact by my own genetic ancestry, known ancestors, I'm only nine-sixteenths West African in terms of my allelic variation. The other seven-sixteenths comes from Europeans and American Indians, and that's true of virtually every person. So you cannot look at them and tell what specific alleles are going to be present in that person, and therefore we need to do everything we can to get this message out and particularly coming out of this group.

It's going to have a lot more impact on people who work in this area, private corporations who do

biomedical research, and universities, physicians, conferences, et cetera. So I think there's a role for this group to play that is actually greater than might be expected simply, you know, by simple analysis.

DR. McCABE: Thank you very much.

There are no other comments. What I'm going to do is just open up for about five or 10 minutes to see if there are any comments from the members of the audience who have not had an opportunity so far to speak.

If anyone wishes to comment on any of the deliberations from the previous meeting, from the meeting so far or from what you see that we're going to be discussing over the next day and a half?

MR. HILLBACK: It's a quiet group back there.

DR. McCABE: I took people by surprise, probably. I know some of you, and I'm surprised by your not taking this opportunity. I won't mention any names.

Okay. Well, Mike, thank you. Just because I was looking at you when I said that.

DR. WATSON: Just one comment.

DR. McCABE: Please use the microphone.

DR. WATSON: Actually, it's based on some discussion earlier.

DR. McCABE: This is Mike Watson, who's from the Washington University School of Medicine in St. Louis.

DR. WATSON: It's actually terminology used earlier, which I had some difficulty with in the task force and some difficulty with this morning, especially in the context of clinical validity and utility, talking about false positives and false negatives.

I don't know that we have the right language for the kinds of genetic testing that we're going to be doing. False positive has a somewhat bad connotation to it, but I think in the terms of a predictive test, that's who I want to be. I want to be the person who has the genotype who doesn't get the disease, and if there's a treatment available or a lifestyle modification available, and I can take advantage of it, I want to be the false positive.

So the difference between false positives and positive predictive value, I think, is important, and when you're talking about the language of utility and validity, it's very different clinically than analytically, and I would try to sort those terms out, and even possibly think of new ways of discussing these sorts of issues relative to your deliberations.

DR. McCABE: You want to be a false positive, but you want a confirmatory test, right, so that you know that you're the false positive?

DR. WATSON: I want to be analytically right and the clinical false positive.

DR. McCABE: Yes?

DR. BOUGHMAN: I just have a question. It was mentioned earlier today, it was also mentioned

at our June meeting and has arisen very briefly in one conference call, but I'm not sure where the issue of patenting might or might not fall into our discussions, either now or in the future, and I don't want to lose that as a potential topic of discussion, if and when appropriate.

DR. McCABE: Further discussion of that point? It did come up in conference calls. It's come up in some of the e-mails. It's come up in presentations to us today. Well, other people's comments? Yes?

MS. BARR: I think it's a fundamental issue, and I think we have a duty to comment on it, even if we're told it is beyond our scope to make recommendations on it, and I think we have an obligation to discuss it and bring some expertise in to discuss it.

Patenting has been useful. It's very useful in certain situations. There are public arguments for it, and yet it can also be very detrimental, and it may not be something we have control of, but I think it is something we should speak about.

DR. McCABE: Is it something we need to deal with before March 15th or can it be on the agenda for after March 15th?

MS. BARR: It's practical problem. It should be on the agenda before, but I don't know how we're going to do that.

DR. McCABE: Okay. Elliott, and then Rod.

MR. HILLBACK: Coming from a commercial company, I also feel it is a big issue. We don't know that we have any patent on a particular gene. I don't think we're against patenting per se. I think there's issues around how patents are used or not used or abused.

But I do think it has a big impact on what we should be discussing because one of our issues, I think, is accessibility. Someone else raised the issue of quality and the way patenting might be abused is impacting on quality, the ability to have more than one lab doing a test. There's not much incentive to set up a whole audit system to audit one lab and be able to send samples somewhere else to test them out.

There are a lot of issues like that. So I do think that it's something we ought to talk about if we're going to take on our whole role. I think like we deferred at least the major issue of education of the M.D. community to some degree until we finish this first task for Dr. Satcher.

I think this is another one that we could end up spending so much time on, we would have to really be civilly disobedient in terms of meeting our other goal, but I do think it's something we should talk about. It is a hot issue.

DR. McCABE: I'll let Rod speak briefly, but one of the things that I want to just have everybody thinking about is patenting in the context of oversight and outreach. Those are our two very specific charges. So that those would need to be the context in which we considered them before March 15th.

Rod?

DR. HOWELL: I would urge the panel to consider the patent issue. It's very complex because it has not only to do with pricing but also has to do with licensing accessibility.

There's been considerable news in the media nationally about people who no longer can afford testing because of pricing. That's been widely discussed. The College has recently done a survey of our

members, and 25 percent of our members have discontinued doing certain genetic testing because of complexities of patent issues.

So it's an important issue, and I would urge you to consider it, although it's complex.

DR. McCABE: Thank you.

Yes, Pat?

DR. CHARACHE: I think in terms of the concept of oversight, it has a major component because of the issues that Elliott was raising in terms of the accuracy and quality of the information being produced. For proficiency testing, where there is no commercial test, the Number 1 surrogate alternative is to share the same samples between laboratories, and this removes any possibility of monitoring the quality of the test that is being done.

DR. McCABE: Thank you.

MS. BOLDT: Just a flip side of that, too. I guess the question that I would like Rod to address is in terms of reimbursement. If these labs aren't getting reimbursed, what other efforts is the College doing to hopefully get better reimbursement for not only genetic testing but also genetic counseling?

I know that the CPT, we're trying to get codes passed, but that's not been successful yet.

DR. HOWELL: I'll be brief on that. The reimbursement for genetic testing is very complicated. It's a major activity of the College. We're working very closely with the AMA that is centrally involved in decisionmaking about codes and so forth, to be sure that they're available.

Let me point out that Medicaid reimbursement for one test that I'm aware of is less than half of the fee charged by the patent-holder. So those create just extraordinary problems, and they really must be addressed.

DR. McCABE: I'm going to move us forward then. Thank you very much for the comments from the public. I'd just remind everyone that this will be a part of each of our meetings, so that we hope that we will have public comment at each of the meetings.

Reed?

DR. TUCKSON: So can I take it that we have a pretty good consensus that we are going to address patenting, and that it's just a matter of whether we try to squeeze it in before the first date?

DR. McCABE: It sounds like that was what I was hearing.

DR. TUCKSON: Great.

DR. McCABE: That we should take up the patenting, that there are certain issues that impact on oversight. It might be important to have it in the background document for the outreach so that we can get responses to it. Whether we solve it by March 15th or not, I think, will be the issue.

DR. TUCKSON: Great.

DR. McCABE: But perhaps we need to make note that we do need to add it to the background

information.

Rod, on behalf of the American College of Medical Genetics, included their recent position paper on this as an appendix to the packet.

Any other comments on that issue? If not, let's move on.

The next topic will be "Discrete Risk Categories of Genetic Tests: Possible Approaches to Oversight Issue 2," and Dr. Burke is going to present.

DR. BURKE: I'm going to report now on the discussions of the Oversight Working Group on Issue 2. That is, if we agree on criteria, and we had proposed clinical validity and clinical utility as the criteria for evaluating tests, then how could we begin to think about discrete categories of genetic tests based on, and I should say, first of all, that we are thinking and have been in our discussions thinking about categorizing tests in terms of the risks that they raise for people who are tested.

In a general way, we thought it was useful just for simplicity to start by thinking about two categories of tests. That is, to think in terms of tests that might have high risks or low risks. Obviously, one could have many more gradations of categories of tests, but if we think in terms of high risk and low risk, the question becomes, how do you use criteria like clinical validity and clinical utility to determine what goes in a low-risk category, what goes in a high-risk category?

So if I can have the next transparency? The first conclusion that we came to is that categorization must depend upon looking at information about a test in aggregate. That is, you need to look at a variety of different characteristics, characteristics that have to do with clinical validity, clinical utility, that have to do with the various components that we identified as important to those characteristics and pull them together in order to be able to categorize tests as potentially low risk or high risk.

The examples that I have here, just for the purpose of discussion, are that a low-risk test might be one that had high predictive value, that predicted risk for a non-stigmatizing condition and had associated with it for people who tested positive a safe and effective treatment, and just for the purposes of discussion, I think we could go one step further and say even if the predictive value was low, if you had all of those other characteristics -- that is, a non-stigmatizing condition for which you had safe and effective treatment -- you still might be comfortable in thinking about that particular kind of test as falling into a low-risk category.

Now, as you begin to think in these terms, obviously a number of questions come to the fore pretty quickly. One is, what do you mean by low predictive value? What do you mean by non-stigmatizing? That is, the concept of categorizing tests into different risk categories does not by any means solve the toughest problems, which are the problems of drawing thresholds.

In terms of comments that Dr. Watson made a moment ago, there is, I think, particularly with predictive tests the question of what is it we're testing for, and specifically are we testing for a risk state or, when we talk about positive predictive value, are we talking about predictive value for the risk state itself or are we talking about the positive predictive value for the disease for which the risk state is associated?

And just to use a non-genetic example to make that point a little more fully, I think we're all very comfortable with the idea of universal screening for blood pressure, for elevated blood pressure. We've somehow come to think about hypertension as a disease that we test for and treat, but actually hypertension is a risk state, and the majority of people with hypertension don't get the end result disease

that we're concerned about. That is, it's a minority of people with hypertension who are prevented from having a stroke or a heart attack as a result of treating hypertension.

Yet we know in aggregate, that is on a population basis, we have very good quality data to say that we're providing a health benefit by treating hypertension, even though some individuals would be fine if left alone, and we believe we're doing it in a safe and effective manner, and we believe that this condition is on the whole non-stigmatizing, although there certainly have been reports of people who've had some social consequences from a diagnosis of that kind.

But it's really within that kind of context that we need to begin to have discussions about genetic tests, and they include what is it we're testing for? What are we going to do with the test? What are the social consequences of the test? All of those need to be looked at together.

The example that we have for a possible constellation of factors that might lead to a high risk are again a test with high predictive value but one that tests for a serious condition for which no treatment is proven to be effective, and here again, how high is high predictive value? What's the serious condition? What do we mean when there's no intervention?

Often we have interventions that are unproven, but where we have reason to think they might make a difference. In some cases, we truly have no intervention that we can think of. An example that would fit this profile, for example, would be testing for Huntington's disease. Same kinds of issues. How do we define the condition? How do we define whether something's serious? How do we define what's high and low predictive value?

Though it is worth thinking about in this latter category, the possibility that there might be constellations of tests that pose so many questions and so many potential risks, both in terms of social and health outcomes, that there might be a question of whether or not the tests should even be made available, and I would characterize those as tests with low predictive value for a serious condition for which there is no treatment. That particular profile might raise a lot of questions about even tests becoming available, let alone what kind of oversight might be necessary.

Well, what we have here, and I want to elaborate a little bit on it, is the recognition that if we are going to do this kind of analysis, if we're going to take the different characteristics that we have about a test and think about them and come up with different risk categories, we clearly have to have a process to do that, and particularly some of the comments that were made earlier about the possibility of including within our thinking about a test its potential use in individual marketing in a package that's covered by health insurance or in universal health screening were that to be folded in, that's an extra sort of layer that needs to be factored in with all the other aspects of tests.

What I want to say then about this issue of process is, first of all, that we think having gotten to this point, that that's a place where we really need input and thought, but we have a few comments to make about what we think needs to be incorporated within any process that we finally agree on.

The first is that there does need to be a data-handling/data-evaluation/data-analysis process. Questions that have come up there are what data are we talking about? Who provides that data? What is the source of that data? How is it analyzed? And then, most importantly, how is it communicated, and to whom?

I know that we'll be hearing tomorrow from Dr. Khoury about a process that has been begun to explore a public/private partnership to develop standardized data formats for looking at data, and it seems likely that there will need to be some standardized process that defines what kind of data we'd like to have about genetic tests, particularly because we've identified that we want to know when there are gaps.

So the way that you can ensure, I think, that you identify the evidence gaps that may be particularly important in communicating to people about the aspects of the test, it helps to have a standardized format. These are the boxes we want to fill. We've either got data in them or we don't have data in them, and both of those are important.

However, another part of the process and very possibly a process that should be separated from the process of collating and analyzing data is the process that really gets to setting the thresholds that need to be set in order to identify risk categories.

Here, we see the need to identify the stakeholders, to identify a process that's acceptable to the stakeholders, and to develop a process by which final decisions can be made that is open, that is equitable and acceptable to people interested in these outcomes, and as I say, at that point in our deliberations, we stopped and said it's time to get more input. It's time to get some conversation about how these data evaluation and then threshold-setting processes might go.

I do think it's important to note the value in terms of where we are of Dr. Buchanan's comment, his plea for particularism. That is, I think, inherent in our thinking. I think, also, Elliott's comment about being iterative is clearly important here. That is, as we define the kind of data that we would like to have for a test and set out the boxes and find initially perhaps that some of the boxes are empty, we know that over time, they'll get filled, and as they get filled, that perhaps should trigger a re-evaluation of that particular test.

We need to accept that tests have multiple uses. I think many of the examples that we've been discussing here make that point. That is, tests may be used in different populations with different social implications. Tests may be used both for high-risk families and families that aren't high risk with different kinds of implications for what the tests mean.

Tests may be used for both diagnostic and screening purposes with very different implications, and often, although we say we want to look separately at the implications of the test for each use, often in a given setting where a test is being made available, all of those potential uses are inherent in the tests being offered, being made available.

I want to just end by saying we've heard a fair amount of discussion about the inherent social and ethical issues. I want to underscore that they are not really separate from the health outcomes issues in that efficacy is fundamentally, I think we can argue, an ethical issue. That is, information about efficacy is we've identified a very important part of the information that both test providers and test takers need to have, and the quality of the information we have about efficacy is extremely important in determining what we know and therefore what might be appropriate oversight for a test.

I'll just stop there. Thanks.

DR. McCABE: Okay. Thank you very much. So open it up for a discussion from the committee now on Issue 2.

MR. HILLBACK: Maybe I could jump in with this discussion of the iterative because I think one of the questions we have to ask is whether we can say, well, you have a test that is static for some significant period of time, and then you have enough new data that you change to a new static mode.

I'm not even sure that that really captures how dramatically this information is changing with 10 or 15 or 20 parameters that we might include in the test. All those parameters might be moving at the

same time, some in opposite directions, and so I'm not sure if it's really a step function which could happen every two years or every year or every five years or whether it somehow needs to be a curved line which then gets back to how does oversight work on something that isn't step function but is a curved line?

I think it comes back to me to process, to thinking about a process of oversight rather than a set of fixed battles, you know. Maybe it's more like guerilla warfare. It's always there. You're always working on oversight. You're always working on improving the knowledge versus a situation where you make a decision, and you don't revisit that decision for two or three years, and in the meantime, you freeze the way you use that test. You don't change it. You don't modify it. You don't use it in a different way.

So I think this is an interesting point that hopefully some others will pick up on.

DR. McCABE: Well, I can tell you people already picked up on this. This morning, Pat came over, and I think it was you who came over and suggested that it was all so complex and so many variables, that we really perhaps needed some consultation from somebody who was looking at chaos theory, and we've already identified such an individual who might be able to discuss it. You know, the problem is the use of that term. It's really non-linear modeling is what it's about.

(Laughter.)

DR. PENCHASZADEH: Complex systems.

DR. McCABE: Yes. Non-linear modeling of complex systems, and in fact, that is part of what we're dealing with here, a lot of what we're dealing with, and genetics is complex enough to most people, given that it's predictive and not absolute, and then all the variables that we're dealing with on this moving target make it even more interesting. So we're going to look and see if we can have some consultation from such an individual.

Yes, Wylie?

DR. BURKE: I obviously agree about the complexity, and I think we've already had discussion and need to keep having discussion about how we keep all that complexity in front of us.

But I find myself frequently coming back to a point about efficacy of treatment that I think we need to hold in front of us, and I recognize that I'm sticking with a medical model when I do this, but let me use the example of PKU.

We really don't worry about labeling kids with PKU. We don't worry about it. We want to label them. We want to find them, and we want to treat them because we have a definitive, effective treatment that prevents a major health outcome, and that's really to me why the issue of efficacy is a paramount issue and one where it's tremendously important to understand the quality of the evidence that we have available.

I don't mean to diminish or say that the stigmatizing qualities of a genetic diagnosis disappear when you have effective treatment, but I would argue that they change dramatically, and I would go one step further and say it's really in the setting where we don't have that kind of intervention that a lot of the social concerns that get raised by genetic testing occurs.

DR. McCABE: Yes, Pat?

MS. BARR: I asked Elliott for my own information if he would provide me with a list of all the

genetic tests Genzyme does, so that I could personally see the variation and what they were used for, and I actually liked -- I don't know if Francis can do the same, in terms of what is being done clinically through your institutes right now.

MR. HILLBACK: Do you have the full list?

DR. COLLINS: GeneTests would be the place to go for this because we're talking about tests that are being used for clinical purposes. So this is this index that's maintained by Bonnie Pagan and her colleagues in Seattle, and it's about 900 entries, of which, as I remember, about a third of them are only available in research protocols, and the rest are available for clinical purposes, and most of them are for relatively rare autosomal conditions.

MR. HILLBACK: I'm not familiar with that, whether they would list all the different versions of a CF test, for example, or only the mutations that are done because almost every lab is doing something different, but Francis is going to crank up his computer here with his modem and pull the data for us, but I think it's an interesting question.

DR. PENCHASZADEH: I use GeneTests almost daily. I don't have my computer. Probably Francis will be able to get it, but they don't give you such detail about each test. They give you the list of labs that will do each test, and on what it's based, if it's DNA-based, whatever, and they give you a contact person. I doubt if they would put the specificity of the number of mutations, for instance, for CF.

MS. BARR: I tell you why I want to ask. We're focusing, which we have to do, on some of the more volatile areas of genetic testing. There is a climate in which we're doing this that is becoming more and more excited, which may in fact be appropriate.

But I think that we have a responsibility, and you may very well be far more informed than I am, I suspect you are, I may be the only one who needs it, to see that the range and frequency with which such tests are now being used for multiple purposes, they're very useful and very helpful.

It's about the conversation and the social climate in which we're having the conversation.

DR. McCABE: Sarah has a list that's about six months old. I'm sure there are additions since then. So we could get in touch with Bonnie Pagan and see if we could --

DR. PENCHASZADEH: Yes, but that would not give you the volume of tests being performed.

DR. McCABE: Yes, but we can get the lists. We may be able to get from her a list of the tests because I think the issue gets back to something that we've discussed before, and that is that analytes that we consider standard clinical analytes, clinical chemistry analytes, depending on how they're used, could be used as a genetic test, and we need to look at the spectrum of what is perceived as genetic tests.

Having any luck, Francis?

DR. COLLINS: I'm finding their site, but it's going to take awhile.

DR. PENCHASZADEH: If you really want to know how genetic tests are being used today, part of this information would not be the lab themselves but the genetic services who are ordering the tests according to what indication and for what purposes and so on and so forth.

MR. HILLBACK: Yes. I think the other point is one that Ed made, which is there are a lot of

tests that are not DNA tests but are for genetic diseases. There's a lot of biochemical tests that are done for various autosomal storage disorders, et cetera, that are still genetic diseases but are being tested in a non-DNA environment and may not be categorized quite the same way.

I don't know how GeneTests does categorize them, but I think if you really get to the breadth of how do we look at genetic disease, it's much broader than DNA testing.

DR. PENCHASZADEH: Enzyme-based.

MR. HILLBACK: Right.

DR. McCABE: I would remind you that Peggy McGovern's article is in our packet under Tab 8, "Quality Assurance and Molecular Genetic Testing Laboratories," from JAMA, March 3rd, 1999. There's an editorial that went with that, and then on page 8, under Tab 2, the consultation document on oversight in the second paragraph, there is information from GeneTests that lists the number, more than 300 diseases or conditions and more than 200 laboratories in the United States, and the development of tests for an additional 325 diseases is in process and goes into the number of tests that have been run over the previous years.

Yes, Muin?

DR. KHOURY: I'd like to sort of bring up a subject and challenge the committee a little bit here. I keep thinking of genetic tests in very simple terms, and I'd like to pick up on some of the threads of the earlier discussions on SNPs and polymorphisms and gene/environment interaction.

I think today, we're facing sort of the easy end of the spectrum in genetics, which is single gene conditions that may or may not predict for disease, that have a penetrance of anywhere from 10 to 100 percent, and we tried to quantitate that.

10 years from now, we are going to be faced with testing for common diseases where you have a kit. Maybe not "kit." I'm using a bad term here. But sort of an array of testing that involves testing perhaps for five to 15 genes, and I think Francis in his article in the New England Journal of Medicine illustrated that nicely, where your positive test could be based on a constellation of seven or 10 genes at different loci, and add to that the environmental factors, whether you smoke or not, whether you drink alcohol or not, and how much, and this and that.

I mean, that immediately calls for a high-level chaos theory and epidemiology and biostatistics in order to get those risk estimates, and I'd like to challenge us to think a little bit ahead and other than be confined to the realm of just single gene genetic tests, positive or negative, because the implication for the classification of how the oversight can go, whether it's high or low, and the process of data collection that will ensue from that can be very different animal from the current situation.

DR. BURKE: It seems to me, Muin, one of the things that falls out of that is that you're describing, and I think accurately, that the genetic test of the future is going to be a low predictive value test. It's going to be a test that contributes to risk assessment to some degree in combination with a variety of other factors, and that to me only underscores the point about efficacy.

DR. KHOURY: Yes. It could be low predictive value for one gene at a time, but if you combine seven or eight that fall in the pathogenesis of that disease or 10, the combination of different genotypes at different loci could be more than the low predictive value.

But what do I know? In 10 years from now, I might be proven wrong.

MR. HILLBACK: Francis may want to expand on this, but several years ago, I had the opportunity to go to a meeting in Santa Fe called "Beyond the Genome." I think it was Number 2 or 3 or 4 that year, and there were people there, many of whom are a part of NIH and other parts of the government, who were trying to model the multiple systems in various subsystems, I guess, as part of human systems to try to understand the interaction of multiple genes and how the different pathways worked.

I think you're right. You know, we're going to get much further, whether it's the comments we heard from Glaxo earlier or the comments that Francis made in that very interesting paper, that we're talking about a much more complex environment than most of us probably are thinking about when we think about the issues right now. So I think you make a valid point.

You were at some of those, right?

DR. COLLINS: I can't believe I actually missed one. I guess I would put in just a note of caution about trying to integrate the theories that have surrounded understanding of non-linear systems and chaos to this particular circumstance because they're not going to help you unless you have data, and it seems to me once you have data, you don't need them because then you know the answer from good epidemiology.

So I'll be a little skeptical about whether other theoretical analyses are going to save us from our current dilemmas. We've just got to roll up our sleeves and collect a lot of what's going to be mostly empirical information at first about genotypes and phenotypes, and if you have that tabulation, then you can make predictions, and if you don't, the theory isn't going to help you.

DR. McCABE: Muin?

DR. KHOURY: Just quickly. I agree fully, Francis. Let me throw another point of caveat here. If you have a disease where you have 10 genes that have something to do with it, and 10 genetic tests, and then maybe five or 10 exposures, and each one of these is a yes/no variable, you have 2 to the power 20 strata in the population, and that translates to a million cells. Basically the combination of Gene 1, Gene 2, Gene 3, Exposure 1, Exposure 2, Exposure 3.

I guess what I'm saying is that collecting data might take a long, long time. It requires a huge number of people, and I think we might have to rely on a little bit of some other either theoretical or experimental set-up to drive that process a little bit more. But I can't agree with you more. I think we need data, but the kind of data we're talking about is immense, is huge, given the number of the genes and the environmental variables.

DR. McCABE: Barbara?

DR. KOENIG: Well, I just was thinking about the individuals who are providing the data as we're going along, and one of the things I think we still need to address in our outreach -- and perhaps we can talk about it later, tomorrow, whenever it's on the agenda -- is the issue of how to deal with this uncertainty that Wylie talked about it this morning, and that we're all clear about. As we're collecting information to make these findings meaningful, what do we do with the problem of providing information to people, and I think that's something where we need more public comment, and we need more specifically to request that, and we need to think about how to build that into some process of oversight, whether it's regulation or consensus or however.

DR. McCABE: Yes, Wylie?

DR. BURKE: And I think that where that leads is, first of all, that we have to figure out methods for effectively disclosing uncertainty. I was talking recently to a non-science colleague, and he had heard about the ApoE4 test, and I was trying to explain a little bit of the hesitations within the scientific community about using that test, and he said, "Yes, but, you know, if it's going to predict my likelihood of Alzheimer's disease, I want to have access to it," and then he said, "Of course, I want it to be accurate," and I think that's the point.

He was a lot less interested when he understood that there was a fair degree of uncertainty about the prediction, and I think there probably is some empirical research that needs to be done, and I think it's within a doable scope which has to do with figuring out how to effectively communicate scientific understandings to a non-scientific audience.

MR. HILLBACK: I think we're back to the basics of communicating what we know and what we don't know, because whether you take genotype and phenotype and push them together or whatever, you're still talking about we know something, and we don't know other things.

DR. KOENIG: But just to make it clear that there are two sources of uncertainty that we're talking about here. There's the inherent that's not reducible uncertainty that comes about when you tell someone with accuracy that there's a 60-percent risk of happening, okay, or chance of something happening in the future.

Okay. But then there is the other sources of uncertainty that go into coming up with that 60-percent estimate, and those are two separate things, and I think we tend to sort of reify our 60-percent number, and it gets put out into educational materials, and we convince ourselves that it's true, and we don't usually disclose how uncertain that number is. So it's very complicated.

DR. McCABE: Ann?

MS. BOLDT: Somewhat on that line, I think just the issue of as long as we're telling people up front, that's one thing, but then where's the duty to recontact afterwards, and do we need to develop that into it? Is that onus going to be on the laboratory or is it going to be on the clinician that ordered the test? So those are things that I think we need to address, too.

DR. BURKE: And I think it's important to note those are not specific to genetics. Technology's evolving and changing all the time.

DR. McCABE: Pat?

DR. CHARACHE: I think we're all recognizing the need for data, and yet we don't have a good system out there to capture the results of this 175,000 tests that were run in 1996.

I wonder, though, if it might be relevant in information that's put before the public for comment to at least discuss the implications of systems that capture that type of data.

I'm thinking of the model of the cancer capture information that was initially pushed by surgeons and is now a national program which anyone with cancer is reported to a databank that's supposed to be secure, and I wonder how people who are getting genetic tests would respond to that type of information capture which would be the fastest way to collect data.

MS. BARR: I think one of the interesting things about it is that I suspect that the large, large,

large majority of cancer patients have no idea that's being done. So the question of response and level of education and at what point public policymaking is done is a very interesting one, and what have we done in the past, and what do we think we should do now?

DR. McCABE: And it's a very interesting model. We've been involved in this at UCLA, in looking at that as a model within our deliberations about genetic testing.

There are issues about informed consent in that model, at least in the state of California. Basically, the records are freely available for investigation by being enrolled in a cancer center study, and so that with the level of concern about genetics, I think the model is not straightforward in terms of its applications, given people's concerns about informed consent, and part of why people are not aware of it is that they don't necessarily consent to participate.

DR. TUCKSON: I need help on two issues. First, Elliott, I wonder -- and I don't know how much work you and the committee have done on this. Do you have a view of the contrast between an iterative model and a static model in terms of its implications for our recommendations? What would one look like versus another? What are our choices here?

MR. HILLBACK: Well, I certainly haven't planned it out in any level of detail. We'll talk about this tomorrow, but I think fundamentally, the way that occurred to us, and I've spent years thinking about this but as a part-time job, is to find some model where processes of oversight allow for and encourage the rapid assimilation of new comparisons between genotype and phenotype and encourage the constant updating of the information that's provided, and then to do that, you need some mechanism that isn't a static step function mechanism, but then you have to have some mechanism to make sure that people are basically being honest and saying what they know and what they don't know, back to that phrase that again I've overused, like iterative.

The oversight function therefore somehow has to make it clear that if you're going to say I know this, you have some way to document it, and you're also required to say in the same breath what you don't know.

I don't know how the mechanism is going to work, certainly not of the ones we talked about, because as soon as you move to a more static model, you basically limit that, and if you make it a lot of work, I would suggest that on a lot of these tests, people won't bother.

DR. TUCKSON: So a static model would look like you just simply say this is what it is, and if you want to change it, reconstitute another committee to come back and look at all this again a year from now?

MR. HILLBACK: Not another committee necessarily. It's more like the product model. If we produce a drug today, and we take it to FDA, and we say here's the drug, and this is what it does, that's approved as it is.

If we want to make changes to that, we go back with new data, and it's a relatively long process usually, not always. FDA's certainly changing and has done a great job in being much more able to move fast, but it's a big process to do a clinical trial, prove that, come with the data that proves something and change it, and I think in terms of testing one of the interesting parts of the question Pat asked me was, and I don't know the answer, but I'll try and find out overnight, is what are the relative volumes of some of the tests we do, and I would suspect that some of the tests we do, we do less than a hundred of a year.

There's no way for Genzyme to be in a business,it makes sense for us to spend that kind of effort

to go through a static study, filing, et cetera, but it does make sense for our lab director who signs out every case to try to collect as much data as possible to be able to sign out a case with the best knowledge available on that day. That's the iterative system.

DR. TUCKSON: Boy, Elliott, this is so important, because it's really taking us down, I think, some very important roads here. I think all of us will need to understand more about this.

I mean, I like what you're saying. I want to get there, but unfortunately, I'm slower than the rest of you are. I need to catch this.

Under the current static drug model, again you must collect -- if you're going to change an indication for that drug --

MR. HILLBACK: Actually, the same thing is true for a kit that's made for a test.

DR. TUCKSON: Yes. If you're going to change it, you've got to submit all the data, and people have got to look at it, and you've got to be able to prove or convince an organizational entity that this is legitimate, your claims.

MR. HILLBACK: Right.

DR. TUCKSON: Under a static model, you still -- I mean, under a fluid iterative model, you have the burden of proof.

MR. HILLBACK: Yes.

DR. TUCKSON: The burden of proof is still as strong as it was the first time you came forward and made your assertions. So how does this become less cumbersome than the other one?

MR. HILLBACK: Basically, you know, the situation that we're in at all times, and every lab is in, is that labs don't follow the patients. Labs don't manage the patients. So what we're working off of is we are doing tests. We are providing the data to a physician who works with the patient. Okay?

At the same time, we're looking at the body of knowledge that's created by all the people that are studying that disease to try to understand the clinical utility, particularly, but also the clinical validity, but particularly the utility, of that test.

If clinical utility is the crucial measure, we can't measure that on our own. Analytic validity, we absolutely can do. Clinical validity, if you want us to calculate the 2x2 square, we can do that, but in the long run, clinical utility is way beyond our scope and way beyond any other lab's scope, I would maintain, to do.

So what we're relying on is the collective wisdom, the collective knowledge, of the medical community in managing that disease, to continue to upgrade our ability to give advice about the clinical utility and relate that to individual patients and individual events.

DR. TUCKSON: So instead of the burden being on the company for the new assertation, the burden is on the collective scientific clinical community that then says this is the new -- based on our collective knowledge, a broader perspective than any one company could have. We now assert that this claim can now be made.

MR. HILLBACK: And this is what's happening today. This is the status quo, but there's no system that defines it. There's no oversight that's built into that. There are some in the sense that a lab director is accountable, and CLIA can come and say tell us how you calculated this, how did you get to this. The lab director would be accountable, but it's not a very formal system. It's certainly not organized. It is a very inefficient system.

DR. McCABE: Reed, I think from my perspective, the cancer model, there are some issues with that, but I think it is a model that we need to think about, and it may be in some ways a better model, at least for me, an easier model to understand in relationship to this, where it becomes a community pooling its information and obtaining information on a repetitive basis, so that you don't just check someone one year out and make a decision or two years out, that basically that individual is enrolled constantly, and there's a constant updating of the information, and it allows refinement.

It also is a nice model because of the fact that the protocols permit change in the drug therapies and are able to account for that change statistically. So you're not stuck with a static beginning point, but the beginning point can change for different patients as new information comes along, and I think that's why the cancer model, I think, does have some very nice positive benefits.

Mary?

MS. DAVIDSON: Yes. I just wanted to speak to the issue of our need for data, and there's no question about it because the public and patients certainly want the best tests possible.

But I can say that because of the Alliance, because we have a help line, and we hear from the public all the time, as well as from our members who now represent more common disorders, but by and large, it's the voice that we hear from the more rare conditions, and I guess the public is more and more wary about personal information being in central databases, and I can't imagine that there would be the kind of participation needed to build up that kind of database and information, and so I just want to bring that up as an issue, that we really have some basic changes in terms of protection of privacy and personal information and protection against discrimination that we wouldn't really be able to build up that database in the way it's needed.

DR. McCABE: Judy, and then Pat, and then we're going to take a break.

DR. LEWIS: I just think it's real interesting as I'm listening to us. I think sometimes we present different levels of confidence when we talk about what we know than when we talk about what we don't know, and I think that's a real critical issue sometimes. You know, we can say with relative certainty what we know, but we don't always have the same enthusiasm or the same confidence when we say what we don't know, and I think sometimes that leads to some of the issues of confusion and mistrust on the part of people because they can hear really well, and, you know, they start to get very distrustful when we waffle on those things.

So I think we need to pay attention to how we present what we know and how we present what we don't know, and living with ambiguity is really, really hard, but sometimes we don't present that with the same level of authority that we present what we know for sure that turns out not to be true anymore tomorrow.

DR. McCABE: Pat?

MS. BARR: I guess I wanted to say two things. I think the cancer model is an excellent one. I just wanted to draw the distinction that it was a public policy decision rather than an individual decision

to participate.

DR. McCABE: Right, and I think that was driven partly by the fear of the disease.

MS. BARR: Right.

DR. McCABE: And it was a public policy to deal with --

MS. BARR: Because I just wanted to make the distinction in terms of why that worked.

Then the other distinction I wanted to make is that at this point in genetic testing, when you have to go through a lab, it's not clear -- I mean, one of the questions we're dealing with is off-label use really, but in medicine, with drugs, we have off-label use all the time.

So you don't always go back to the FDA. I mean, that is the company might have to go back, but the doctors themselves do not. So I think we need to be sensitive about that as well.

DR. McCABE: Do you have a comment, Reed?

DR. TUCKSON: No. I want to ask one other question, and after that break, are we going to return to the Issue 2 or are we done with that for today?

DR. McCABE: Let me look. I think we are done with it.

DR. TUCKSON: Then let me -- is yours on her point?

DR. KHOURY: The issue is on data, and we come back to it tomorrow afternoon.

DR. TUCKSON: Okay.

DR. McCABE: Muin's going to present a proposal.

DR. KHOURY: I just wanted to put the bug in your ears at this point, that this is very complex, and we seem to be stuck in a situation where we need data, but we can't collect it, and I'm very sensitive to what Mary said.

I mean, your constituencies are very specific, and their voices are very clear and loud, but I don't know if you hear from other groups. You have very specific constituencies that are very worried, that primarily think of gene conditions as being used against them for one reason or another.

I think what we're talking about is this kind of a mushy data collection on, you know, the thousands of genes for common diseases, where it's really much more complicated, and cancer is a good example for that.

There are different ways I think of it from a public health perspective as a process of surveillance, and I hate to put surveillance and genetics in the same sentence because it carries a bad connotation.

On the other hand, it's an important public health function to keep your finger on the pulse, what's going on, what do we know, and what do we don't know at any given point in time. Therefore, it's a continuous process. It might be punctuated by policy forums at a given point in time to make a consensus statement about the use of a test or not, but it's a continuous process of data collection.

There are two options there. One would be individual-based level data, where you collect the information at the individual level. You link genotype or phenotype and outcomes, and that's where some of those issues need to be discussed. The other process would be an aggregate data collection mechanism where individual identifiers are removed, and we just see the empty -- I mean, the table shows that needs to be collected. We can come back to that tomorrow, if you want.

DR. TUCKSON: Yes. That's actually the two comments I had, one on that point of the data. I mean, clearly, you scared me to death, Dr. Khoury, when you made the calculation of the number of cells, and Dr. Graves' paper a moment ago, and he again talked about, you know, this gives us this frightening sense of the complexity of these multiple interrelationships between the environmental issues and so forth and so on.

Yet at the same time, you know, we are living in a reality where clinicians are faced with the choice of talking to patients, and patients are making decisions in fact, you know, on their own. So we've got to respond to the real world, and it seems to me, Ed, that at some point, maybe there needs to be a part of our paper that specifically deals with the question of data, and I don't know how we're going to pull that out, but it seems to me, depending on what happens tomorrow with the discussion, we may need to have a little subsection of people who are thinking about that.

The only other question I had, though, Dr. Burke, was I'm trying to link the Issues 1 to your Issues 2, and we got into that notion of the lump and splitting and now we're down to the high risk/low risk.

Now, I'm trying to think. Is it basically the logic that you're giving us that we will have our low risk, let's say, category, and then we go back, and we plug in all of our potential benefits of a positive test, analyze that list of things, start assigning those to which ones go to low risk, which ones go to high risk, take our potential risks of a positive test, plug those in?

I mean, we just sort of take the one and overlay it over the Issue 2 and then sort of see how they fall out in terms of the --

DR. BURKE: Yes, I think the point is that for any given test, all those characteristics need to be looked at in aggregate. So on the one hand, you might have for a given test certain potential risks, let's say, of economic harms from loss of opportunity for life insurance and disability insurance and so on. So that would be one thing that would need to be taken into account in the test, and on the other hand, the tests might lead to the possibility of highly-effective treatment. That would be a benefit.

There's no way to look at a test without looking at those things together, and I think we at that point said this is going to be a complicated process.

DR. TUCKSON: Now, are we obligated, in terms of as you fast forward to the report and our recommendation, are we obligated to solve that Gordian knot or do we basically say this is complicated? Here are the kinds of things that one would look at, give some illustrative examples at some level of detail to make the point solid and to give a variety of illustrations to give you a sense of, you know, more complex, less complex, pretty straightforward, and then say that's the way it ought to be thought through?

I mean, I'm trying to get a sense of what we're ultimately going to do.

DR. BURKE: And I think that's precisely an area that we need to discuss, and I think as we go through Issues 3 and 4, where there are some different options for oversight mechanisms, there will be the opportunity for further discussion of that.

It does seem to me, as the discussion goes forward, that one question really had to do with what's within the regulatory framework versus what gets played out sort of in -- you know, within the community, given all the different pressures that influence decisions about medical testing.

So just one example might be that the regulatory force might be behind insisting that certain information is disclosed. I mean, that might be the key regulatory step, and here are the boxes of information we want you to fill. Put in what you got, show us what's blank. That's what you have to provide when you propose to commercialize tests, and then maybe some of the decisions about test use end up getting made by consumers, providers, health care insurers.

I'm not saying that's the right way to do it, but I'm saying that would be one possibility, and I know Elliott and Kate will be talking more in detail about those kinds of issues.

MS. BARR: I just want to say that the members of the last task force that I would hope that we would actually come up with something more specific than this kind of test is what we need for this, and this kind of test is what we need for that because we actually did that at the task force more or less, and it would only make room for yet another one to try and come up with how to regulate what we've got to do.

DR. McCABE: Yes. I think that we are the product of the recommendation of the last task force, and we probably don't need to recommend that we reconstitute ourselves. I think it's going to be difficult for us to do, but I think we were charged with coming up with specific recommendations, and we're going to need to do that, at least that's my goal.

MR. HILLBACK: Could I just make one comment? Because I think one of the things to think about is whether, if you took this list and expanded it, and you ended up with 20 factors that you had to look at, because we started this on the last task force, was to then try to prioritize those 20 and to give numeric values to the ends of the spectrum of each of the 20, and some got double value and some got triple value, and we slowly -- quickly -- went insane.

One of the questions is are you really looking at a sphere? You're looking at a three-dimensional space, four-dimensional space, over time, Pat reminds me, and instead of saying I want to get a precise way to define whether this is high or low, I'm going to do it by looking at the shape of this blob here, and if we in the end decide we have to have high and low, which I don't know that we have to, but if we do, I think we can either drive ourselves insane and drive any oversight authority insane by trying to prioritize everything, lots of things we don't know today, or we can say it's really more about we've got to make a call, high or low, and let's try and do it in this four-dimensional space. It's a course I flunked in college. Anyway, three and a half-dimensional space that we need to deal with.

DR. McCABE: Okay. I think we need to take a break.

It was pointed out to us that the U.S. News and World Report that's on the newsstand, November 1, 1999, has an article by Jennifer Couzin, "Quandaries in the Genes: As Genetic Testing Expands, So Do Ethical Complications," and announces our meeting.

(Recess.)

DR. McCABE: We're going to resume now, and our goal is to finish by 5:30, and I really do want to have people have time for break before dinner. So we're going to move ahead at this point.

Now we're going to hear a report of the SACGT Working Group on Outreach by Dr. Lewis. The outreach document is under Tab 3 in the briefing materials.

DR. LEWIS: Thank you.

I'm going to report the recommendations for gathering public perspectives on oversight of genetic testing, and I want to acknowledge the members of the working group: Ann Boldt, Pat Barr, Mary Davidson, Barbara Koenig, Reed Tuckson, me, Dr. McCabe was with us ex officio, and also to especially acknowledge the work that Sarah Carr did in helping us, because we asked her an awful lot of information, and Sarah did a wonderful job of pulling it together and helping us keep focused. I just get to be the one to stand up here and give our summaries, but everybody was really involved, and I want to thank everybody for all the hard work that they put in to doing this.

The charge that we were given at the last meeting was to develop a plan for gathering public perspectives regarding the oversight of genetic tests and to present this plan to the SACGT at its meeting today. So we've done that.

Our process includes the use of conference calls. We did an awful lot of brainstorming in terms of listing possibilities for ways to gather public input. We narrowed the possibilities to a list, and then at that point, we actually consulted with the public on how to consult with the public, and Reed Tuckson led us in recruiting leaders of a variety of ethnic minority communities so that we could go out, and we could reach out, and we could say, hey, this is what we're thinking of doing. Are we on the right track? Are there other things we need to be thinking about?

So we wanted to be sensitive to what it was that we were doing was what it was that we needed to be doing, and we actually did consult with the public on how to consult with the public.

We recognized the fact that there are a broad range of public perspectives. We have those of us who have professional economic interests, such as health care professionals, researchers, representatives from industry, those who manufacture diagnostic devices, those who provide laboratory services, managed care organizations, health insurers, patient advocacy organizations, and academicians.

We also recognized that there were some individuals who were not members of organized alliances that had public perspectives, and that those individuals may be patients, they may be families, or they may be consumers in general.

We recognized the fact that there may be some special concerns from people who are members of ethnic minority communities, and that there also may be some special concerns for economically- and socially-disadvantaged members of the general public, but, in reality, we really believe that all members of the general public have concerns that we need to address.

So in terms of capturing the views of the broader public, we wanted to make sure that we were reaching out to diverse communities, and we wanted to make sure that we were paying attention to work that had already begun, that there were many scholars who had done work already in this area, on two areas in particular, both on the safety and the validity of genetic testing and on public attitudes about genetics and genetic testing. We wanted to capture the work that had already been done.

So after doing all of that and after spending an awful lot of time looking at the various methods and eliminating many methods that we might use to reach out to the public, we came up with a suggestion of five potential methods.

The first is the required mechanism, the Federal Register, but we knew that that alone was not sufficient. While it was necessary, it wasn't sufficient. You know, most people don't sit and read the

Federal Register every day.

So we wanted to do a targeted mailing, and we have come together, and we have started to put together our mailing list, and at this point, the mailing list is about 78 pages long, I believe, and it has members of various and sundry representatives of the groups that I talked about before, people who have interest, and that list has been contributed to by a lot of people, and it still has the opportunity to be contributed to, and so we thought that mailing our consultation document to a targeted number of people who clearly had vested interest was important.

We also recommend a Web site consultation, and that this be an interactive Web site that has the ability to have not just the up view on the Web but to have some push technology so that's it connected to some list servers so that we can proactively share the availability of our Web site with various and sundry people who would be appropriate to consult with us.

We also recommended an open public consultation meeting. That's an invited meeting, but it's open to the public in general, to be able to share our consultation document, give people the education they need, and then solicit their input, and the final one is to do a retrospective literature review and analysis so that we know what's been done, and we don't spend an awful lot of time reinventing the wheel, and we build our knowledge that's already out there.

Further, we recommend that there be a short version of our consultation document be available in both English and Spanish, and that this be used with targeted mailing and Web site consultation.

One of the things we did when we had our consultation conference call was talk about the availability of our document in multiple languages, and there's so many various languages that this could be available in, and we made the decision to recommend Spanish based on the criteria that it is the second most spoken language in this country today, and that we were told by our consultants that we need to have some rationale for why we chose a particular language, and that was the rationale for why we chose Spanish.

We were also told that in terms of reaching other communities, that we might not get as much response as we would like, but that the people who would have influence in being able to go into the communities and gather the input and help get the input back to us would probably be doing that back to us in English because we were concerned with how we were going to deal with input that came back in multiple languages.

So that's where we were at, and we look forward to hearing from people.

DR. McCABE: Thank you very much.

We're now going to hear from Professor Bonham, and the topic of the talk will be "Consulting with Diverse Communities on Issues in Genetics." Professor Bonham is co-investigator in the Communities of Color and Genetics Policy Project, University of Michigan School of Public Health/Michigan State University/Tuskegee University.

Vence Bonham is co-investigator on this project, the collaboration between these institutions. He is an Assistant Professor of Health, Law and Policy at Michigan State University, an Adjunct Professor at Detroit College of Law and the Center for Ethics and Humanities at Michigan State.

Professor Bonham obtained his J.D. from Ohio State University College of Law. His many interests include health care justice and vulnerable populations, race, ethnicity, and the Human Genome

Project. He also consults on health care issues for physicians and medical group practices.

Professor Bonham?

MR. BONHAM: Thank you. Thank you for inviting me as a representative of the Communities of Color and Genetics Policy Project to speak to you today and share with you our experiences in engaging minority communities in dialogues and development of policy recommendations.

On behalf of Professor Toby Citrin, the principal investigator, and the project team, I would like to share with you the following. First, information about the original project that the University of Michigan and Michigan State University was involved in, Genome Technology and Reproduction: A Community Dialogue Project. Secondly, a description of our current project, Engaging Minority Communities in Genetics Policymaking, and, third, I will present the lessons we have learned so far in the project that I believe may be helpful to you.

This project began in March of 1999, and we just now are entering the dialogue phase of the project. So we still have a lot to learn and a lot to hear from the communities that we're engaging in these discussions, but we've also learned a lot of lessons just in the process of engaging the communities, and that's what I want to share with you most today.

Finally, I will share my thoughts on the draft document that was provided. This report will take approximately 10 to 15 minutes, so that we will have time for you to ask me specific questions about our project and to discuss some of the lessons that we have learned.

I decided that the best approach was to provide you a written report, so that you could have my written thoughts as you further deliberate.

The initial project, the Genome Technology and Reproduction: Values and Public Policy Project, was a three-year project carried out by the University of Michigan and Michigan State University under a grant from the National Human Genome Research Institute Ethical, Legal, and Social Implications Program.

The purpose of the project was to develop a series of policy recommendations guiding the use of the rapidly expanding array of genetic technologies relating to reproductive decisionmaking in order to maximize the benefits and minimize the harms to society caused by these advancements.

These policies might be adopted by legislatures, governmental agencies, professional organizations, through their standard-setting or health care providers and insurance organizations.

To formulate these policies, the project utilized a process called the rational democratic deliberation. The broad essential feature of rational democratic deliberation may be summarized in terms of its premise, its process and its goals.

The defining features would be it is a deliberative process. It is a public discussion that emphasizes the giving of reasons to justify one's point of view and rely upon the best methods of analysis and argument and scientific evidence to come to a conclusion.

Second, the democratic part implies that all participants in the conversation are equally entitled to be heard. No one has more of a right to be heard because of social status, academic degrees or wealth.

The rational means that non-rational assertions, assertions emanating from mere authority or mere

tradition, have no weight or rational authority in the conversation. Those are not things that count as reasons.

A series of six evening dialogue sessions were convened in seven Michigan communities. These dialogues produced a number of guidelines expressing the views of the dialogue participants on the values and principles which should be incorporated into policymaking.

These outcomes were considered at a policy conference held in Ann Arbor, Michigan, when the participants shared their views with the project team. At the policy conference, the broad guidelines developed in the initial dialogue series were translated into specific policy options, forming the basis for the second series of dialogues carried out in the Spring of 1997.

The outcomes of this second dialogue series was used in the development of specific policy recommendations to be disseminated in publication at a national conference that was held in May of 1997 in Washington, D.C.

The project intended that a broad cross-section of the Michigan population would engage in the dialogues. While the percentage of minorities involved in the dialogues roughly equaled the percentage of all minorities in Michigan, Latinos and African Americans, Asian Americans and Native Americans, it did not achieve the sufficient engagement of the minority groups to assure that their perceptions, concerns and opinions were adequately reflected in the policy recommendations.

The initial study included a focus group made up of primarily individuals that identified themselves as African Americans, which disclosed a significant difference from non-minority groups with respect to trust in the research and medical care communities. These differences did not emerge from the dialogues, suggesting that their voices were muted and not given adequate expression in the dialogues.

The reasons identified for the failure to obtain the perspectives of the minority communities included selection of the agenda by an essentially non-minority project team, imposition of ethics and values framework inconsistent with the mode of typical conversation, selection of dialogue settings outside of the physical communities where the minority groups lived and gathered, and selection of non-minority dialogue facilitators, and the hesitancy of minority participants to voice views perceived to be contrary to those of the majority members in the dialogue groups.

Our current project, in which I am a co-investigator, is based on the body of research relating to the engagement of minority communities in activities aimed at understanding and improving health through education and advocacy and collective action.

The current project enables us to take the information learned and apply it to a more representative segment of the public. The aims of the project are, one, develop a process for engaging minority populations of diverse socioeconomic levels in the process of rational democratic deliberations regarding moral and political issues relating to genome research and its resulting technology.

Two, utilize the process of rational democratic deliberation involving African Americans and Latino populations and develop recommendations for laws, professional standards and institutional policies regarding the use and application of genome research and its resulting technology.

Three, to disseminate the findings of the project to the public, policymakers, health educators and practitioners, and four, identify any significant differences in issues of concern and policy recommendations developed by the minority populations as compared to the majority population participating in the initial project.

The area of research that is the basis of our project is the study of community engagement. The term "engagement" as used in our project refers to being actively and personally involved and committed to the activity.

Most of the literature describes projects to educate and empower low-income minority communities to engage these communities in research and to involve communities in health promotion and disease prevention programs.

Factors identified in the literature as promoting successful community-based projects include respecting cultural beliefs and values held by community members and developing literacy, appropriate and culturally-sensitive material for each group, utilizing local leadership from within the community in locating project activities at familiar locations and within the community.

The significant role of the church in the African American and Latino communities is a constant theme in the literature, and you'll see it's an important part of our project.

The researchers from the three institutions involved in the project have recruited 15 community-based organizations in the African American and Latino communities as partners in the project. Each organization has agreed to work with the project team to recruit members to participate in five dialogue sessions of two hours to discuss their concerns, opinions and values related to genome research and resulting technology, and to develop group opinions related to policy.

The dialogue sessions consist of individuals that are from the same communities where most of the participants are acquainted with one another. This enables a comfort level to be established quickly. Facilitators who share the racial or ethnic characteristics of the participants are chosen jointly by the host organizations and the project team.

The group consists of local chapters of the national organizations, such as the Urban League; Alpha Kappa Alpha Sorority, Inc.; Omega Psi Fraternity, Inc.; and local community churches, such as the Bethel AME Church of Ann Arbor, Michigan, and St. Andrew's Episcopal Church in Tuskegee, Alabama.

Organizations also include local groups that have very focused missions, such as the Clinic of Santa Maria in Grand Rapids, Michigan, which is a low-income clinic that's focused primarily on working with the Latino population in Grand Rapids, Latino Family Services in Detroit, Michigan, Faith Access to Community Development, a non-profit organization in Flint, Michigan, the Orchid Club in Tuskegee, Alabama.

As you can see, the project includes organizations that are diverse, some with long history of participation in policy development and others relatively new and not actively involved in policy development.

I believe this is important in understanding that there are many types of organizations within minority communities. Some organizations have infrastructure and large membership that can be communicated with and others are focused with very specific issues.

We are just beginning the dialogue phase of our project. The dialogue sessions have been rich. The participants have shared many concerns and views relative to genetic testing and genetic technology.

Some of the lessons that we have learned with our project so far is as follows, and I think these are the things that are really most important to this committee here today.

The first lesson. The lesson was learned from our first project, and that is, having the participation of minorities that reflects the total population does not mean that you will hear their concerns and recommendations. They can be diluted in the concerns raised by the majority population. It is important to reach out directly and work with targeted communities to make sure that their voices are hard.

Second, that you must establish a relationship based upon trust and understanding of what will be done with the opinions and experiences expressed.

One of the issues that's been raised already in our dialogues is what are you going to do with this information? You're asking for our perspective and our concerns, but how are you going to use it, and will it be used against us or will you go through it and dilute it in a way that if we looked at the information, it's not what we said, and you've changed it, and so it's very important to establish that level of trust.

There must be leaders from the communities who command trust to reach out to the communities. Surgeon General Satcher, whom I understand requested the special outreach effort, has that respect in the African American community. I think it's valuable to share that he is seeking this input and assets.

I think Dr. Tuckson's reaching out to various minority advocacy groups and using him also to reach out provides a level of trust and respect that's already there, and I think that's very important to use to really get input.

Have researchers and staff members of similar backgrounds of the populations of whom you are seeking input to be actively involved in the outreach process, to assist in establishing a trust relationship with the communities.

I know Dr. Tuckson's very busy, and so he can't take on that responsibility all by himself for this committee, but I think it's very important that you have individuals that have relationships that are already created within various communities and within various groups to make the links, to really make sure that you get the information that you desire.

Develop long-term relationships with organizations and communities and their leadership. Without a relationship, it is more difficult to build trust and get an honest and forthright input that is desired. That's been an issue in our own group.

There's been questions raised with regards to the principal investigators and the researchers involved from the University of Michigan and Michigan State really having any relationship other than an interest in research and going out to the various communities, and so we have to build trust in the relationship, that what we're doing is going to benefit all and not just for individual needs. So going out on an isolated occasion and asking for information and not going back and not sharing information is not going to help build that level of trust.

Go beyond existing power structures to seek input of communities. People do not want tokenism. People do not want lip service, and so developing approaches that are out of the norm are important to make sure that you're reaching communities of color.

My specific comments based on my review of the draft report, "Recommendations for Gathering Public Perspectives on Oversight of Genetic Testing." This committee must be connected to the community through national, state and local organizations. It's important to reach out to key minority community organizations with more than a letter. A personal contact, a request that they provide input to

the committee, may significantly increase their participation, and you've already started that process by reaching out through your conference call with various advocacy leaders, but that's the kind of way that you're really going to get input.

The letter by itself is not enough, and I think you have to identify those key organizations, those key individuals that you want to reach, and you've got to get on the phone, and you've got to make those personal contacts to really get input.

We recognize that your agenda and the scope of your recommendations are limited to genetic testing oversight, but it would be helpful if you are willing to share other concerns of the communities as part of your report.

We have learned in our project that the concerns raised by the communities identified broader issues than the implications of the Human Genome Project for policymaking. A willingness by this committee to communicate the concerns of the public as an appendix to your report beyond the scope of genetic testing oversight is an important statement of your commitment to reflect the concerns of the communities.

I think you're going to hear a lot at the conference that you're going to have in January with the public that's going to go beyond the specific focus that you have with regards to oversight of genetic testing, but it's important information for both the Secretary and the Surgeon General to hear, and so in some kind of way, recognizing your limited focus and charter, you need to be able to provide information with regards to some of the broader concerns that these communities have.

Ask the community organizations how best to obtain their input. You've already started that and continuing to do that is important.

I'm going to kind of get off for just a second. I've heard Dr. Tuckson talk on several occasions, and on two of those occasions, he talked about an experience he had in Los Angeles, of doing something for the community and no one showed up, and the issue was that they didn't engage the community to find out what the community's interests were, what they needed, and what was important to them.

This can happen to this committee if you're not careful, and so it's important to engage the community in that discussion with regards to what their concerns are.

Fourth, build trust and long-term relationships with community organizations to assist you in obtaining the constituency's input. Establish a group of leaders from the minority advocacy organizations that you update and seek input until your work as a committee is concluded. Let this group see and comment on your successive drafts to assure them that the voices of their communities will not be distorted. This group may be used by future committees in seeking input from diverse communities.

Too often, we'll go out, we'll ask for information, and we don't go back, and we don't provide them the final report. We don't provide them drafts of reports. It's important to have an ongoing dialogue with communities, and so I think that's an important approach that this committee can use.

People of color are interested with regards to the issues that you're dealing with with regards to genetic testing and will provide you their honest input, if you are willing to engage them and engage them in discussion. That's what we're learning in our dialogues.

It's interesting. You know, you start thinking about busy people and getting 20 to 25 people to come out for five consecutive weeks in the evening, and we're doing it, and people are not being paid to do this. They're coming out to share their opinions because they believe we're going to communicate that

information.

We have a dialogue group that's going on right now. It's Tuesday nights at 7:00, and I told the group last week that I was going to be coming to speak to this group today, and so they're seeing where in reality we can have an impact, and where their information and what their perspectives are are important, and so I think it's really important that you do those types of things.

The use of the World Wide Web, I believe, will be a valuable tool for the committee. However, you must recognize it will not reach the minority population at the same percentage that it will reach the majority population in this country.

I recommend that you seek to promote the Web site and the work of this committee in articles in targeted publications for Latinos, African Americans, Asians and Native Americans. The article that's now in the U.S. News and World Report is an interesting example of that. That's where the dialogue is really going on, and what people see in the media, and so to the extent that you can frame the questions and have an honest dialogue and get people involved through using things that people listen to or read, like publications, like getting involved in some of the national news media shows that people watch and have that dialogue go on, I think that you will get more information that will be helpful to the committee.

Finally, one of the things that we've learned with our dialogue group so far is people want information. People want to be educated, and they want knowledge, and issues with regard to genetics is an area where people have very limited knowledge.

I've heard around this table today how much this expert group raises questions about the level of knowledge that they have and all the uncertainties that exist. That's something the public wants, and I don't think that's limited to people of color.

The public wants information, and to the extent that you can provide them information and then ask them for input, you're going to have more valuable input, and it's going to assist you as a committee.

Thank you very much.

DR. McCABE: Thank you very much.

What we're going to do is now open the discussion for five or 10 minutes specifically to your presentation, but then at some point, I'm going to have us go back to the outreach document more generally. This has been very helpful.

Specific comments for Vence? Yes, Pat?

MS. BARR: I have some concern in terms of our ability to meet the obligation that you carefully outlined, and I think they are obligations. That is, in terms of our funding and our existence in terms of how long we're going to be here.

I think we can pretty easily be sure that drafts as we approve them go out to people, as we approve them as a public committee, but the possibility of a follow-up meeting may be very difficult for us. I don't know what our budget capabilities are or additional meetings on other issues, if we have time to do other issues, it may be very difficult.

So I guess I wonder how damaging you think that would be, will be.

MR. BONHAM: I guess I don't think there's a need necessarily for additional meetings with

regards to the public.

What I think is really important is the strategies that you use for, like for example, your meeting in January, and the advocacy group of people that you've already identified, making sure that there's communication with them. I think those are the most important things.

I also think it's very helpful to have things that go out to the broader public through literature, and if you're doing that, I think you're really reaching a lot of your goals. In the best of all worlds, if we had more time, you know, I know you've already extended from December to March, and I'm still surprised. The March date is coming quickly.

So we recognize that there are limitations. I think the key is, and I think one of the things that I think is very important and something I commend this committee, is the recognition of the importance of focusing on certain issues related to outreach to specific communities, and so I think you only can do the best you can, I guess, is what I'm saying.

DR. McCABE: I don't think we have any plan to have the final word on March 15th. So I think that one of the things that I got from your presentation is that perhaps part of the process for the future and part of the plan is to continue to have these relationships that we establish as a part of this program.

People's concerns from all segments of the community are evolving, and people's concerns now are very different than they were five years ago. So I think that this is true of minority communities as well as majority communities, and that I think it's important that we recognize that, and you've really heightened our sensitivity to that, I hope.

Yes?

DR. LEWIS: I just want to thank you for reminding us of the importance of the engagement piece, and that we're going out not just to get the information we want, but to go out to get the information people want to share with us, and that the problem then gets defined in community-based terms rather than we're going out saying give us the information you want.

I just think that's such a critical aspect, and I want to thank you for reminding us of that because it really is so important if we're to succeed.

MR. BONHAM: Thank you.

DR. McCABE: Reed?

DR. TUCKSON: You're early in the process you described of the community dialogues. Do you have any experience yet that helps us to understand the ability of the community to engage in this discussion over these complicated, difficult scientific concepts that are involved?

Is there a reason that we should be anxious about the ability of communities of color to give meaningful input on these scientific matters?

MR. BONHAM: Yes. The groups that we've worked with have been totally engaged, have asked for a lot more knowledge and information, now have Web sites, various articles and come back to the second and third meetings focusing on issues, and so I think there's really an opportunity to truly engage communities, that people are interested, they're knowledgeable to a certain extent, and desire to have their input, and so I think that it's positive with regards to what we've learned so far.

One of the things I think you have to recognize as a committee that's established by the Federal Government is the fear and concerns with regards to misuse of information, and you talked about that in a variety of ways with regards to discrimination.

But that is a concern, and it gets raised in a variety of different ways, and I think that's why it's so important that information is provided that's objective and factual to help people in developing their own perspectives.

DR. TUCKSON: By the way, you had somebody from the Tuskegee Orchid Club. Did Tuskegee come up?

MR. BONHAM: Tuskegee is involved. There are five groups that will be in Tuskegee, Alabama. Dr. Secundy is the principal investigator for that part, and they are involved.

DR. TUCKSON: But I mean did the issue come up of Tuskegee?

MR. BONHAM: Yes, it has. It's come up. It came up during our focus groups. We had focus groups over the summer to help us identify what the issues and concerns were for the communities, so that we could start to focus the questions, and it came up in a variety of our groups, and all of our African American groups and in some of our Latino groups, and so it's a major issue with regards to misuse of research information. The issues related to that are key.

DR. McCABE: I think it would be very helpful for you to share the information when you see fit to share the information from your project because certainly you've established this relationship and surely will get more in-depth information from the groups that you're working with.

MR. BONHAM: Right. We will be happy to provide that to the committee.

DR. McCABE: Joann, and then Barbara.

DR. BOUGHMAN: I actually had two different comments and/or questions. First of all, it seems to me that we've heard a message from Mr. Bonham that we need to be able to hear information that the community wants to give us beyond the scope of our charge.

I would urge us in the format for both the January meeting and in receiving information from the public that we allow that somehow in the format, but because these issues can and will go on forever, I believe, I think we're still going to need to delineate the charge that we have as a specific group seeking input there, but then allowing additional comment and for us to serve as a conduit of that additional information to the Secretary and others, but I think that to clearly so state in our document that other comments are welcome would be an important invitation.

Secondly, I'm going to turn the tables on you just a little bit. You said that you had mentioned to your focus groups, your discussion groups, that you were coming here. I would encourage you or challenge you in fact to go back and help us by re-engaging or continuing to engage those groups and/or any other influence that you might have in these various groups that are already entered into an active dialogue.

You made several comments about building relationships, long-term relationships, trust, and, so often, all of those things take a great deal of time and demonstration, and we're going to be hard-pressed to be able to demonstrate that, even if we have all of those capabilities.

So I would just turn the tables and seek your help as well.

MR. BONHAM: And we'll be happy to try to provide that help in a variety of ways.

DR. McCABE: Barbara?

DR. KOENIG: I just wondered if you had any concrete suggestions for us in terms of when we set up our public consultation meeting which we haven't done yet, we're just about to begin that process, of how to deal with the concern that you raised about particular people or individuals feeling silenced in certain contexts but not in others or if you or your people in your project might be willing to help us in the next few weeks as we set that up, if you have suggestions now or both.

MR. BONHAM: Yes. We would be happy to have further discussion about some of the specific strategies that we developed, but one of the comments I would probably like to make today is I think it would be important in that meeting to have different formats for your discussions, and at least one of those sessions would be set up with a facilitator to help to draw out people that are quiet and that are not as involved but decided it was important enough to come, and so they're there. They have something to say, and so I think to have a process where you really make sure that you get everyone that's there involved in some kind of way, I think, may be one of the strategies to do that. But we can talk about some of the approaches that we've used.

DR. McCABE: I think that's a good transition.

DR. PENCHASZADEH: I'd like to just ask the committee whether you have given consideration about, you know, how would be the process to reach whoever we think should be invited to these deliberations because once you go out to the communities, there may be different people, different representatives, and have you given thought to the actual process of reaching out?

DR. LEWIS: Well, as part of our telephone consultation with the leaders of the various communities, we asked them if they'd be willing to help us, if we were able to do this, and they have all agreed to sign on to be ongoing consultants. So we've made those connections.

The other thing, I think we had talked about wanting to do it, and you all can help me, is to make sure that we leave it open enough so that we're not systematically excluding anyone, so that if it's widely publicized, if we have overlooked inadvertently somebody, that they're welcome, that it not just be an invitational meeting, but that it be an open meeting, and that we identify people who are important but also ask people to share that information, so that it's not just a top-down process, but that it's a community-based process.

DR. McCABE: I think this is good transition to now begin to address the strategies for outreach and try and, you know, have the committee discuss those now, and Vence is going to stay at the table for those discussions to help us.

So the Federal Register, we can deal with that one quickly. We're going to do that one. We're obligated to do it. We also don't feel that it's sufficient. So then let's talk about the other strategies and what people think about them.

Targeted mailing. We've got 78 pages, did you say, of --

DR. LEWIS: We've got 78 pages on the list, and it's certainly a list that if anybody wants to see and add names to, we're happy to have people do that, but it's people who have a vested interest. Some of

it comes from that first group of people who have personal and professional interests.

Some of it is names that Mary's been able to get us in terms of various consumer advocacy groups. We went to the religious communities, and we've added from people within various religious communities, the key people that have been identified to us, and it's pretty -- and then the other thing, the other people we added to the list when we did our literature search, we added all of the people who have written because we want to know, even if somebody wrote something five or 10 years ago, we want to know what their current thinking is on the state of affairs.

So the list has continued to grow, and we sent the list to the people we consulted with on the telephone and asked them to review it and to make additions as well. Our goal is to make it as inclusive as possible.

DR. PENCHASZADEH: Is this a list of individuals or a list of organizations?

DR. McCABE: No. I can give you a few of the topics here, and it's not like one address per page. I had to count them here, but --

DR. PENCHASZADEH: Is it individuals or is it organizations?

DR. LEWIS: It's both.

DR. McCABE: It's organizations and, you know, just the first few names, Abiding Heart from Bozeman, Montana; Fred Abrams from the University of Colorado; Phyllis Acosta from Abbott Laboratories; and then it goes down, and I'm looking for some other organizations here. Alliance for Minority Participation in Pueblo, Montana. Alliance of Genetic Support Groups. Again a number of names. Amalgamated Clothing and Textile Workers Union from New York. American Association of Bioanalysts. American Academy of Family Physicians, and on and on.

DR. PENCHASZADEH: Okay.

DR. McCABE: So we've tried to be inclusive. We've used addresses that were provided to us from a variety of different sources. We're happy to add additional names.

Yes, Muin?

DR. KHOURY: Maybe this is not the right time to say it, but as a general question, maybe you addressed it in your presentation, and I was spaced out somehow. When you seek input, we will hear input. I guess you're concerned that we may not hear -- I think we'll hear a lot of input. What are we going to do with it in terms of massaging it, analyzing it, collating it?

I mean, to me, this is going to be a tremendous effort, and I think as we begin getting the input, I think we should have some clear plans for what to do with the information.

DR. LEWIS: We believe that this is going to come in two phases, and that presuming that our report is approved, that the solicitation period will start immediately after this meeting, and it will go for 45 days. So approximately till mid-December, till the first of the year, depending on when it gets started.

At that point, the staff will be working to analyze the data that we receive, and I presume some of us will be involved in a first run of looking at that, and then the tentative plans are to hold the public consultation meeting in January. So we'll be able to not only get additional input there, but also be able to

validate some of the input that we've already gotten because we'll have some preliminary analysis, and we don't want to bias the discussion, but it will be an opportunity to do some checking to make sure that what we're hearing is really what we're hearing, and then to be able to have all those data analyzed and be able to be presented to this group at its next meeting.

DR. KHOURY: What do you mean by data analysis? Is that going to be like a whole --

DR. LEWIS: I presume that there will be a fair amount of qualitative analysis that will be looking for themes, and that some of it may be some quantitative counting, but that a lot of it, I believe, is going to be thematic stuff, and I agree with Mr. Bonham entirely that we need to look not just at the themes that come forth a lot, but that the themes that come forth from a variety of perspectives, and that we need to really honor the diversity of perspectives that come forward and not necessarily discount something because we didn't hear it a thousand times.

DR. McCABE: Why don't we move on to the Web site consultation? Because I think that that may be even more difficult to analyze, and also, as was discussed, I'm concerned the representational nature of the Web site consultation.

DR. LEWIS: Well, part of what we did when we looked at the Web site consultation -- actually, it was Barbara, wasn't it, that was able to connect us with the people that put this Web site up, that gave us these ideas, and it's a firm that's got a lot of experience in dealing with diverse populations, and they actually have many lists to be able to do outreach to diverse communities.

Our goal is to have our consultation document on the Web site in both English and Spanish, to make the availability of the Web site widely known, and to make sure that there's sufficient access in a wide variety of communities, that it's not just in peoples' homes, but that we have the ability to have people access this through a variety of ways, and maybe working with communities around, bringing groups together in libraries and other places where they are able to get Internet access, but that the group that we're working with has a lot of experience in reaching out.

It's not just going to be here's the URL and do it, but there's going to be a lot of list serves that are going to send information out directly to people, and then they're just going to be able to click and get to our Web site, and it's going to be interactive, and people will be able to submit input directly from the Web site that's going to be able to come back to us.

DR. McCABE: Yes. I'm happy to have public comment on this, also. Did you have something, Dr. Buchanan? Can you please go to the microphone?

DR. BUCHANAN: I just had a question about whether you have made efforts to engage the following groups? Elderly people in the communities you're looking at, disabled people whose mobility may make it difficult for them to be included in the other groups, and young people. That is, say, late teenagers or adolescents.

I guess I just wonder if there's special measures that have been undertaken to make sure that those groups are represented as well as, I guess, I would say people who are not doing well in society or in the community, and that might include people who are recipients of certain public welfare services. It might include even people who are -- and by the way, these have nothing to do with the particular communities you're talking about. They would be true for any sampling. People in correctional facilities, for example.

DR. McCABE: To the extent for some of those groups, you could help us identify target groups that would be helpful to us.

DR. BUCHANAN: Well, I mean, there are services for people with disabilities, and there are disabilities rights advocacy groups that would be helpful. In some cases, churches would be helpful in accessing young people, you know, children. In some cases, they would be helpful in accessing elderly people, but not always.

I mean, there are some people who don't have a connection with the church or with a community group that you'll never hear from because there are barriers to their being heard. In the case of disabilities, it's only the most obvious tangible kind of barrier.

DR. LEWIS: For example, some of the groups we were talking about trying to make sure that we were targeting in terms of both the Web site, in terms of our public consultation meeting, things like parent-teacher associations, so that we could get to people who had vested interest but weren't necessarily members of any -- they were members of a professional community but not necessarily the health care communities, that we could go and make sure that we were exactly what you're saying, reaching out to.

DR. McCABE: Other comments on these two consultation pieces, the targeted mailing and the Web site consultation? I want to be sure we get on to the next one.

MR. BONHAM: I guess I would just like to emphasize with regards to the Web site is I think the Web site will be more valuable if you make sure that there's things that go out in the press, letting people know that the Web site is there, and that this committee wants information, and so that's going to give you a broader community that can't access the Web site.

DR. McCABE: Yes. I think that we had one reporter here this morning, Lauran Neergaard, who is planning to do a piece tomorrow. Her deadline's tomorrow evening. She is going to be back in touch with us after we've formally decided on these mechanisms, so that she can have more detail, but we're going to need to try and get publicity and publicity in a diverse group of publications.

Pat?

MS. BARR: I think that Kathy can answer this, but I thought that ELSI has funded a number of these kinds of groups in different communities that are trying to get some dialogue going. So I think we should be sure to have all of those on our list.

MS. CARR: ELSI grantees?

MS. BARR: Yes.

MS. CARR: They're on there.

MS. BARR: They are? Okay.

DR. McCABE: I just looked at the list and have one that we didn't have on there. So if others want to check the list and see if organizations with which you have contact are or are not represented, that would be very helpful.

DR. PENCHASZADEH: Which document will be circulated?

DR. McCABE: This is going to be a summary document.

DR. PENCHASZADEH: A summary document of the --

DR. McCABE: The big one, too, but there will be also a summary document in English and Spanish.

Let's talk about the open public consultation meeting then because there's some issues that we need to decide that have logistic and fiscal issues associated with them, like where we would have it. We have set a date, and that is February 27th?

DR. LEWIS: January.

DR. McCABE: January 27th. Sorry. January 27th, and I think we had talked at one point about trying to go around the country and have several different meetings in different places. We just can't do that and meet the March 15th deadline. Again, maybe that's something we need to address in our report.

Yes?

MS. BARR: What if we divide it up and went to different places? Can we still not do it? Or if we went to two places instead of just one?

DR. McCABE: Judy, did your group talk about this?

DR. LEWIS: We did not talk about that. Basically, we were concerned originally with the time frame as to whether or not this would be feasible at all, and once we were convinced it would be feasible, we went with, you know, let's go for it and let's do the best we can, knowing that we can't do as well as we would like to do, that the issue was we want to do as much as we can within the time and the resources allotted to us.

I guess I would just, you know, wonder in terms of whether or not that would be really feasible, given the time of the year and, you know, weather and all that good stuff.

DR. McCABE: Any thoughts on this? Because it's an important decision.

DR. BURKE: Well, I would just offer, I think we're a large enough committee that it's certainly feasible to divide us up into two or maybe even more regional groups, and it tremendously increases the opportunity for people from different parts of the country to have some input.

DR. McCABE: Yes. Just the logistics in terms of doing this as a formal outreach of this committee may be difficult and may be expensive because when we do it individually, we can do it informally. I know that some of you have been giving talks to various community and religious organizations.

Please try and document, do a quick summary of the issues that have come up, and please get that back to us. In essence, that's a focus group that you've done there.

There are packets of slides. I know of at least two. I've seen at least two sets of slides come through. Judy has a set, has her PowerPoint that she's willing to share with people.

DR. LEWIS: Absolutely.

DR. McCABE: And Kate has a set, also. So that if people want to use these for discussions,

certainly try and reach out, recognize the kind of communities we're trying to reach out to.

DR. LEWIS: If I could just ask one thing. I'm wondering, and I just would like some consultation on this, I think that the logistics in themselves might be insurmountable, but if we were to spread ourselves too thin, would we be perhaps diluting the ability to here or would we be maximizing it? That would be one of the questions that I would want to make sure because I was very concerned with what you were saying about not being -- you know, if you get to too many places, that maybe people won't feel like they're being heard, and I'd want to make sure that we were able to get the people that we wanted to make sure we were heard.

DR. McCABE: Plus the other important thing that came out of Mr. Bonham's presentation is having appropriate members of these minority communities who are doing this outreach, and that also limits our ability to some extent.

There was a comment from the audience. Could you please identify yourself?

MR. KNUTH: Dean Knuth, and just a thought for the committee. You don't want to dilute yourself by traveling in the middle of winter, and that you want to reach out to maybe the 20- and 30-somethings that are very capable and very happy with off-the-shelf net technology, like a chat room. It may not be familiar to members of the committee, but it's right there for you now, and the youth are using it all the time.

DR. McCABE: Thank you.

Yes?

DR. FEIGAL: One thing that FDA's done with facilities that we have but that we've made available to Dr. Satcher and others in the Public Health Service is in satellite downlinks. They've been co-sponsored often with the Food, Drug, and Law Institute.

Actually, we've done the strategy where we've sent people to different regions to hold face-to-face meetings that began with an hour satellite downlink live program where people could interact as an entire group, just seeing a central point.

There's a studio in Gaithersburg that has the satellite technology. It still takes a fair amount of logistics to plan these. FDA often has a more natural audience with industry that pays a little more close attention than shows up when we ask them to come and listen to the wonderful things we have to say.

I think the trick is to figure out if we were to do this, sort of how we would attract audiences on short notice of the kinds we want, but there is some technology available, and if you'd like to talk to the director of the studio that's put a number of these on for the Public Health Service, he might have some ideas and could brainstorm with you a little bit about how to do this.

DR. LEWIS: My only concern with something like that is wanting to make sure that people were feeling the personal connection because I've been teaching over downlinked sites, and I always just want to make sure that the people on the other end are feeling the same level of connection.

So I think it's a two-edged sword, and I think part of building -- you know, I appreciate the offer. I would just want to be concerned that we did enough of the leg work of building trust rather than being a talking head on a screen, and I'm not sure what that would do, and that would be something I think we'd need to sort out, too.

DR. McCABE: How expensive is that?

DR. FEIGAL: I don't know. I'd have to find out. Renting the satellite time, I think, is relatively expensive.

DR. LEWIS: It's relatively expensive.

DR. FEIGAL: Yes, but if you did it, for example, in three or four sites rather than trying downloading it everywhere, you might be able to do that. There are also some net technologies that could get used, but I think we're dealing with short time frames and busy times of the year to figure out how to do this.

DR. McCABE: Again, we may not do it perfectly on January 27th, but we may think about process for the future.

Do you have some comments, Mr. Bonham?

MR. BONHAM: Yes, I was going to make a comment. I mean, this committee's going to continue after that. I recognize that that's the first step where you're trying to focus, but there may be a need for a second meeting, and so that may be a way to continue to get input during your --

DR. McCABE: Well, let me tell you what my thoughts are, and then people can shoot them down. I think the logistics are not trivial, and I think that it may be best to have it in the Washington area the first time and learn from that and part of what we will be doing is thinking about the future when we might want to take it on the road as it were, but I think having been involved in these sorts of meetings, and also not knowing communities -- I had an experience with this with a border health issue in Texas, where there was a big problem with neural tube defects in the Rio Grande Valley, and we went into a community that was part of the epicenter for this phenomenon in the community, but we chose the wrong community, and we didn't realize that there were two communities that were really very competitive, that were only about seven miles apart, and it quickly became evident to us that we had really made a major tactical error in the choice of the community in terms of representation.

So there's all those sorts of issues, too, that I think we have to check out and would have to be very cautious about. I think it will be hard enough to do it here where we have a lot of staff support.

Do you have any thoughts on this, Mr. Bonham? Do you see any problems with having the first meeting in the Washington area?

MR. BONHAM: No. I think that would probably be helpful. I think the other thing is to the extent that you can get the support and active participation in Surgeon General Satcher, that will be valuable, and invitation to individuals to be the keynote or to open the meeting, I think those kinds of statements show that you really are concerned, and this is important, so to the extent that's possible.

DR. TUCKSON: The challenge is how to get the folks to come to D.C., and that's really going to be the issue. So I think maybe one of the choices in terms of the site really needs to be where you have enough of a diverse community locally, so as to be able to draw, you know, people in, and you get a pretty good diversity just from the local community itself, which D.C. actually is probably not bad in that regard. You certainly get the Latino community, you get the African American community, you get the white community. You may not get the Native American, and then we'd have to deal with some -- to get the Asian community. The Native American would not be here, and for that, we might have to look at,

you know, some subsidies, if necessary, an airplane ticket or so. I don't know, but that's something we have to deal with.

DR. McCABE: I don't know if it's on the list, but the Indian Health Service is headquartered over at Parklawn, or at least it used to be, and there may be some representation. In some of the aspects of government, there may be some Native American representation.

DR. TUCKSON: I doubt that we would probably want them to speak for, but I do think that the request from the Surgeon General to the Indian Health Service to subsidize somebody flying in for -- they must have to come to D.C. for other purposes. I mean, you know, how could they resist the Surgeon General's entreaty?

DR. McCABE: So one of the things we have to decide is place. We've already decided time. Are people satisfied? I mean, as satisfied as we can be with holding it in Washington, D.C.?

DR. LEWIS: Quite frankly, I think in terms of people's time and in terms of going places, sometimes it's easier to get from one post to the other than to get some place in the middle. So I think it's probably a relatively central place for people to get to, and it's probably a little more reliable than, you know, the Midwest in January.

DR. McCABE: But I think that as we're planning on this, we ought to be thinking to the future and not think that this will necessary be the first and last meeting. It may be, but if we are successful, perhaps we can then use that as a springboard to some additional activities in the future.

DR. TUCKSON: You know, Mr. Bonham, if it would not, you know, do violence to the project that's already got its own goals and so forth, it would be really wonderful if we could actually use in a formal way your effort, you know, as part of what we're doing here.

I mean, it's just like this low-hanging fruit that's right there. We might as well take advantage of it, if it won't mess you all up.

MR. BONHAM: We would be happy to share all the information that's coming out of the dialogue groups. The only concern I have is the timing issues. We will finish all 15 of our dialogues by next June. Okay. We will finish the first phase, which is going to be four dialogue groups, by December. So we'll have that data that we could share with you prior to your March date, and we may have all the data from the second phase by the time that you're finalizing your report.

But, clearly, our group is willing to share and communicate the kinds of concerns and thoughts as well as to use the meeting in January to maybe invite some of our participants to come to that meeting, and so we can do that and work with you with regards to those kinds of activities.

DR. McCABE: Yes, because certainly the people you've been meeting, they will have a different level of sophistication --

MR. BONHAM: That's right.

DR. McCABE: -- and may be able to help us substantially there.

MR. BONHAM: Right.

DR. McCABE: Is there any chance that the information that you will have from your first four

groups, I think you said, in December, that at least some level of processing of that could come back to us before our meeting in January to help us with framing the issues?

MR. BONHAM: Yes, we can work on that to make sure that happens.

DR. McCABE: Yes, Pat?

MS. BARR: I just heard Reed's question differently. I was wondering if you would/could take our executive summary and oversight documents in fact into your dialogue groups, so that we got responses from them to that as well as their concerns back to us, that you have an audience that you're already working with, and we have a document that we need comments on.

MR. BONHAM: Right, right. My answer is yes. We'll have to modify. We'll probably have to encourage them to participate in a sixth week, but I think we can do that, and I think that they would do that, based on your requests, and so, yes, we can do that.

DR. McCABE: Well, again if you would point out that we are a committee that was charged by Surgeon General Satcher, perhaps that would be helpful, also. I'm sure we could even get an invitation from Dr. Satcher to have your group help us, to participate.

DR. McCABE: Yes, Pat?

DR. CHARACHE: I was just thinking that as you set up the program here in Washington, you may want to consider adjacent areas to broaden the input, but certainly Northern Virginia, Baltimore are all very accessible, if they know about it and are solicited.

DR. McCABE: Yes, that's also one of the advantages of having it in this area, is that compared to some parts of the country, the distances are much, much closer here.

So Washington. We then need to find a venue in Washington that will be a venue that will be comfortable and accessible, and where we will try not to intimidate any one of these minority communities, and had you talked about that at all, Judy?

DR. LEWIS: No, we hadn't.

DR. PENCHASZADEH: Did you have any idea of size? Number of people that we may be willing to accommodate?

DR. LEWIS: I think we were thinking about maybe a couple of hundred.

DR. McCABE: But then I think we also heard that we ought to have different formats and break down into some smaller groups as well. So we would need some --

DR. LEWIS: But I think in total, we were thinking of probably about a couple of hundred people total.

DR. TUCKSON: I think that subcommittee work would be needed for that.

DR. McCABE: Okay. Sarah's saying that we need subcommittee member volunteers at this time. Did you want to take this on as an extension of your committee, Judy?

DR. LEWIS: Yes, no? Up, down?

DR. McCABE: Okay. So the members of --

DR. LEWIS: It sounds like our subcommittee is volunteering to be the subcommittee and if anybody wants to join us, we'll be happy to have you, but I'm getting a sense from people around the table that this is something that they'd be happy to continue with, yes?

DR. McCABE: Well, I know from the conference calls that I have sat in on that you've been thinking about this a lot. So if you're willing to do it, that would be terrific.

DR. KOENIG: With the caveat that I think some of us would like some idea of what the other assignments are before we make a final choice.

DR. TUCKSON: You get more than one.

MS. BARR: And the other thing is most of us don't know the Washington community well. So we have to rely on some other informant who will help us find the venue.

DR. McCABE: We will augment your group to help identify the individuals who -- and perhaps especially focus on people -- could be a large subcommittee, but we'll focus on individuals who live in the community.

DR. TUCKSON: In addition to the venue, it's structure. I mean, it's folks who know how to get a breakout, you know, like eight people per room and how many rooms does that mean, and there's just all that kind of -- you know, it's the conference planning kind of people who have experience with that sort of stuff.

PARTICIPANT: The committee has a support contractor, don't they?

DR. McCABE: Okay. That was one of the areas that I really wanted to get discussion before the end of the day because since we don't have another meeting before then, we had to know what we were doing the next time around.

There's also the retrospective review of the literature. That will be carried out by staff. Again, any help that people can provide, any angles into that literature that you might have, and Mike Watson is helping with this, also.

Mike has been very involved with issues about oversight for the American College of Medical Genetics and the genetics community. So he's helping to have that background now become part of this document.

Any other issues before we recess for the end of the day?

DR. TUCKSON: What time tomorrow?

DR. McCABE: It's 8:30, 8:30 tomorrow morning. So it's a half hour earlier than today.

DR. BURKE: Can we leave our stuff here?

DR. McCABE: The answer is no, don't leave your stuff here.

(Whereupon, at 5:21 p.m., the meeting was recessed, to reconvene at 8:30 a.m. on Tuesday, October 26th, 1999).