SECRETARY'S ADVISORY COMMITTEE ON GENETIC TESTING

Twelfth Meeting

Thursday,
February 14, 2002

Congressional Ballroom Salons II and III
Bethesda Marriott Hotel
5151 Pooks Hill Road
Bethesda, Maryland

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C O N T E N T S

C O N T E N T S

P R O C E E D I N G S (8:38 a.m.)

DR. McCABE: We're going to go ahead and get started while we're getting Elliott connected. I want to wish everyone a good morning and a Happy Valentine's Day. It was brought to my attention by Dr. Max Rubinowitz that in the February 14th, today's, New England Journal of Medicine, there is a whole series on direct-to-consumer marketing. There's a special article, three editorials and a sounding board piece, and Sarah will get hold of that and get it out to the Committee electronically, but anyone else who's interested in the audience ought to be aware of that. It looks like a very fine series.

We have a very full day ahead of us, including an extremely impressive panel of experts to help us explore issues in the collection, use and analysis of data on race and ethnicity in genetic research and genetic testing. The first item on our agenda is the presentation of the draft report on informed consent issues and clinical and public health genetic tests that has been produced by the Informed Consent/IRB Work Group. Dr. Koenig and her co-chair, Dr. Ben Wilfond, will be presenting the main elements of the report and then carefully walking us through the proposed recommendations that the group would like SACGT to consider adopting.

Before they begin, let me say a few words of introduction about Dr. Wilfond. Dr. Wilfond has a dual appointment at NIH. He is both head of the Bioethics Research Section of the Medical Genetics Branch at the National Human Genome Research Institute and head of the Section on Genetics in the Department of Clinical Bioethics at the NIH Clinical Center. Prior to joining the NIH, Dr. Wilfond was on the faculty of the University of Arizona, where he was co-director of the Tucson Cystic Fibrosis Center and the director of the Apnea/Bronchopulmonary Dysplasia Program. Dr. Wilfond's scholarship has focused on the relationship between empirical data and policy decisions, how information is communicated to subjects and patients and unique considerations of genetic testing in children. His current research projects are in

the areas of informed consent for gene transfer research and the use of stored biological specimens for research. He is also vice chair of the institute's IRB and Ben told me he has to leave early today because he is seeing patients Friday. Thursday afternoon is his clinic day over at Johns Hopkins. So he's still active in patient care.

Dr. Koenig and Dr. Wilfond, before you begin, I want to commend you for being ready to present the draft report at this meeting. Since I'm a member of your work group, I'm aware of the extraordinary efforts you have made to get the report ready for the full Committee's consideration. It took superb leadership on your part, and I want to commend you again for it. I also know that Kathi Hanna, who has been the contract writer for this project, deserves much of the credit as well. Thank you all, and please proceed with the presentation.

DR. KOENIG: Good morning. Ben and I are going to do this presentation together. So at some point, you may want to come a little closer together. So today, we're going to present the results of, as Dr. McCabe indicated, a very quick – we've really pushed to get this report to you, and I think it still needs some additional tweaking and tuning and one of the things you'll notice, I think, first off, is that even the title has changed and that reflects a change in emphasis in some of the comments from the Committee which I think will become clear in that we are trying to frame the issues in the broader sense of decision making, rather than simply in the more narrow sense of informed consent.

You have these slides. This is just a review of the members, a very, very wonderful group, including many of the leading researchers on informed consent in genetics in the country who have informed this process.

So let me review quickly where we are with our overall progress. We finished the information brochure for the general public which is now under review. Today, we're going to talk about

our report on the issue of defining the levels of consent needed for different types of tests, then the issues which are also very important, such as returning research results, the transition of research to clinical use, social risks, multiplex testing and direct-to-consumer marketing and multi-site protocols which is another research issue, we'll turn to next.

Let me just tell you the goals of today's discussion. We have an hour and a half. We've specifically done this first thing in the morning at the request of Dr. Khoury so that we can really focus on it because it's very complicated. So today, what we're going to do is review the draft of the report and attempt to reach consensus on the general tenor, not necessarily any specific sentences or content. We're also going to try and reach some consensus on the proposed recommendations. That's going to be the biggest part of our discussion and then hopefully agree to our next steps, including whether or not we need to solicit public comment on the informed consent report in general.

Why is this report necessary? Well, we really think that some form of national standards may be too strong but guidelines are needed in the area of clinical genetic informed consent for genetic testing because consent practices are highly variable, and if we can improve this whole process, the enhancement of informed decision making can help ensure appropriate test use, and you'll see that that ties in to our broader goal of oversight, and then patient participation in the testing process will be enhanced if this all works. Why is this necessary? It also is to follow through with one of the main overarching principles set forth in our original report, which is that documentation of informed consent must be obtained for tests requiring high scrutiny, the extent to which written informed consent should be obtained for all other genetic test requires further deliberations. We are now proposing a framework for that for this whole process.

In November, we presented some of our preliminary thinking on this and had some very useful

and helpful feedback from the full Committee and that feedback included the following points, and I'm going to go through it to remind you of it, and then hopefully it will become apparent how we have incorporated that feedback into our revisions about informed consent. One. In general, people felt that guidance for informed consent for clinical and public health genetic tests is needed and would make a significant contribution to the field. So there was general agreement about that, and the Committee also agreed that our efforts to identify the features of genetic tests that are important was a useful contribution and that those test features are very relevant to informed consent. However, there was some concern that the models we had developed were too complex and the Committee felt that a guide to decision making about level of consent should be simple and straightforward or more simple and straightforward than what we had presented in November. And finally, this was a very important point, that the guidance must be flexible and tailored to the individual patient's needs. So we've really tried to address these points.

One of the other points of concern. We had originally presented four consent models that were fairly rigid and involved putting consents into particular boxes and that was seen by the Committee as being a little perhaps too difficult to implement and so we have pulled back from that as you'll see, and then another important suggestion made by the full Committee was that genetic education and counseling should be an explicit component of at least the most comprehensive model of consent. So you'll see how we've integrated that. And then, finally, we have made some suggestions about FDA, and we have reconsidered and, I think, refined this issue of what the FDA's role should be in consent practices as a part of premarket review.

So I'm going to quickly do an overview of the report, then I'm going to talk about the details of the test features that we outlined as well as the informed consent process, and then I will come back to the podium and help us walk through the specific recommendations. So you'll see we've responded to your comments in November. Then we'll review the test characteristics,

suggest a continuum of approaches to informed consent that range from, and we've used this language, modest to robust as well as the many levels that fall between that without specifying a particular rigid set of guidelines and then the report recommends that a flexible framework be used in deciding what level of informed consent is needed in a given case. But most important, we also suggest that there is a threshold of consent that, if crossed, would require certain actions by FDA to assure that an intensive informed consent process is used when the test is offered, and as a way of doing that, we actually offered nine recommendations to the Secretary involving FDA, CDC and the Center for Medicare & Medicaid Services or CMS, as well as five recommendations targeted to professional societies, healthcare providers, disease and patient advocacy groups, patients, consumers, insurers and employers.

So why is informed consent so important in genetic testing? Just a very, very quick review. You all know this. The familial and ethical implications, the multiple applications with different implications, meaning that these tests can be used in so many different contexts. The results can be ambiguous or complex. Oftentimes they're merely predictive and the comprehension of the risk information conveyed can be very difficult and complex and of course, also, the potential for the misuse of genetic information. In addition, there's the very blurred line between experimental and clinical use of tests. Tests may move to the market prior to full evaluation of clinical validity. In fact, we actually expect that that will often be the case because of our general oversight recommendation that tests should be released, and then that there be a rigorous postmarket data collection process. So that just means the informed consent process becomes even more important and we're asking the informed consent process to do a great deal of work. Again, also, more tests are used all the time, more multiplex panels, all of those things we know.

Let me say a little word about the language used in this presentation, and again, this is why we changed the title. We're really thinking about informed consent as not literally being just the

process of the patient consenting, but in a much more broad way, that really we're talking about an informed decision-making process followed by the decision of the patient. So you can see that we've made this a bit broader and that was again at the recommendation of the full Committee.

To sort of conceptualize the whole process, what we're thinking of in terms of our guidance on informed consent for genetic tests is that a new test comes into being, is proposed, and then there is a formal process, a consideration of relevant genetic test characteristics which takes place, that sort of black box which we're going to flesh out, and then ultimately, as a result of this consideration, a level of consent for the new genetic test is proposed, and you'll see how that works out in the course of the presentation.

DR. McCABE: Elliott, are you with us now?

MR. HILLBACK: Yes, I'm with you now. Good morning, everyone. Sorry I couldn't be there.

DR. McCABE: Good morning, and we're just switching speakers right now, and the slide that we're on is we're moving from guidance on informed consent for genetic tests to patient/test characteristics that influence informed consent.

MR. HILLBACK: Okay. These aren't numbered, so it's hard to --

DR. McCABE: It's on page 5.

MR. HILLBACK: Thank you.

DR. WILFOND: So what I'm going to try to do in the next five to seven minutes is to talk a

little bit more about what's in this box here, what are the relevant test characteristics, also talk about what the various levels of consent would be and to try to make some suggestions how we get from here to here.

So after a lot of discussion, we came up with essentially five major patient or test characteristics that we think would have some influence on informed consent, and these include the ones I have listed here: the purpose of the test, certain characteristics of the disease the test is for, clinical validity, clinical utility, as well as specifically psychological and social implications of the test.

There can be a range of purposes of testing and some may pose more specific challenges than others for informed consent. So for example, there's perhaps less concern often when it involves the diagnosis of the disease than it might be for screening healthy populations for disease or providing for reproductive and prenatal information where the issues are much more complex and based upon people's personal values requiring a more detailed explanation and discussion.

Additionally, the characteristics of the disease itself might have some bearing on how complex the consent process ought to be and these considerations would include the severity of the disease, what degree of disability is associated with the disease, whether there's any particular stigmatizing characteristics. So if we're talking about behavioral disorders, alcoholism, there would obviously be much more concerns that would need to be addressed in the consent process along those lines.

Clinical validity would be important, also, with regards to the need for additional explanation to explain the probabilistic features of tests when those occur. And fourthly, clinical utility plays an important role in this because different types of tests might have different sorts of

clinical utility. In some circumstances, when interventions are available, the approach to consent may be more simple than when the value of the information is going to be based upon individual's own personal preferences of what's going to be important for them. So using the example of Huntington's disease, where the clinical utility of the test is to allow people to make life-planning decisions, that might require a more involved consent process than, for example, newborn screening for PKU, where the clinical utility is involved in preventing mental retardation and the assumption is that this is a value that most people share and there's not a need for a lot of discussion about the importance of that.

Additionally, some tests have specific psychological and social implications which, as I suggested from my previous comments, might vary with the particular test, but the point is that when a particular test has special psychological or social implications, that that might require a more involved consent process, so the person can weigh those considerations in making their decision, and again part of the point of this is that not only tests share each of these features.

So to try to put all this together, and this is again the idea of moving away from specific descriptions of each feature, is to note that the features together, each of them independently, sometimes can suggest a more complex process or more straightforward process of informed consent, and our suggestion is that we look at these five characteristics for any particular set of circumstances or any particular patient and ask ourselves whether or not in a particular circumstance a particular patient would need a more complex approach to consent or a more straightforward or simple approach to consent.

What I'd like to do now is to talk a little bit about what would be involved in those different approaches to consent, and this slide is more for background, just to remind us of the various components of consent, and we're not going to be talking much about decision-making capacity. We're going to assume that the people we're talking about have that capacity.

Obviously that's a very important issue as we're talking about children, but we're not going to be discussing that today. We're mainly going to be focusing on issues of disclosure of information, assessment of comprehension and voluntariness. Through our discussions, we've identified four key components of the consent process that could be modified based upon our interest in having a more straightforward or a more complex approach to consent, and this has to do again with information disclosure itself, how we assess comprehension, what sort of input the provider engages in in helping to make the decision and documentation. These first three are often what we think about as the decision-making process, the encounter that goes on between the provider and the patient to make a decision. Part of why we have documentation as a separate thing is again to make the important point that, you know, consent is not synonymous with documentation but is really one more feature of a consent process that may have some utility in some circumstances.

So again, for information disclosure, depending upon where a test falls in this continuum that we showed you before, that we could have a very basic to a very comprehensive approach to information disclosure that would depend upon what the relevant features of the test are for that person, and the elements would include the purpose of the test, if there are any specific personal, familial or social implications, the risks and benefits of having the test, availability of alternatives and that these would be the things that would need to be described, and you can imagine that this can be described in some cases in 30 seconds and in other cases, information disclosure might take a much longer period of time, might involve multimedia information, whether it's through CD-ROM or the Internet or pamphlets. Other times, it can be a very simple conversation.

The assessment of comprehension is also important in this with regards to particularly when information is complex, when there's very important decisions to be made based upon people's personal values, to have some opportunity to actually engage in a more back and forth sharing

between the provider and the patient to make sure that the information is understood, and again you can imagine again this continuum going from sort of an assumed to -- which might be do you have any questions versus a much more detailed discussion with the patient.

Another aspect of this has to do with the stance that the provider takes in engaging in this conversation, engaging in the information disclosure and the assessment of comprehension with how involved they are and what the decision is, and you can imagine in some circumstances being much more directive with regards to what ought to be done. Again, you know, newborn screening for PKU would be a wonderful example of somebody saying we really think this is an important thing to do, whereas in other circumstances, particularly as it relates to reproduction, we may want to take a much more hands-off approach in terms of what we recommend for the patient but still be actively engaged in helping the person make a decision that is consistent with their values.

Finally, documentation also might vary. In many circumstances, there may be no documentation whatsoever. I know what's missing from here on this slide is making a notation in the medical record which may be important in some circumstances. We discussed the issue of when it's important for the laboratory to be aware that an informed consent process has occurred and having some sort of a checkoff box as well as having a signed consent form.

So, again, similar to the slide that I showed you before with the continuum of the test features, we also can think of the informed consent components that I described before, disclosure, comprehension, provider input and documentation, and we can envision circumstances where all four of these are done in a much more robust way versus circumstances where these are done more in a minimal way. So we can see that when tests fall towards that straightforward side, that a minimal consent process is probably sufficient. Those that are more on the complex side, a more robust approach would be needed, and there might be a variety of

approaches that we might choose to use for those tests that fall in between, and so the one big difference between what you heard in November versus now is trying to sort of be a little less precise about what we think would happen in this middle field and sort of just point out that this could vary and leave a lot of variation to people involved in making the decisions. However, we also realize that what's most critical are to identify those circumstances when a more robust approach to consent is needed and the fact that FDA might have some role in helping to make that judgment about that. So at this point, I'm going to turn the presentation back over to Barbara, and she's going to talk about the FDA component and our recommendations.

DR. KOENIG: So now, we're going to show a couple slides which are meant to represent graphically what we've just talked about and in a way, these next two slides will summarize the recommendations. So we'll first go through this graphically, and I'm hoping Ben will help me because this is somewhat complex. But if you look at this, what we're trying to do now, you've seen each of these two parts separately before. The genetic test characteristics, for example, the purpose of the test, and then the components of informed consent, and what we're basically suggesting is a process whereby as a first step, you consider or FDA or a clinician or anyone consider those test characteristics, go through a deliberative process and make an assessment about where on this informed consent dimension that test should -- which features of it you would need to do, whether it needs to be robust or whether it needs to be minimal and that would be something that would happen for all tests.

Now, however, we're also proposing that there will exist a threshold of test complexity which we have not specified completely but which, in the report itself, there are many indications of what would be included in that which would basically trigger a process of mandatory robust consent. Okay. So basically what we're proposing is, and this is just to summarize the recommendation, that as a new test is presented to FDA, the test developer would make a

recommendation about what kind of informed consent should be recommended when that test is used clinically, and then as a second step, FDA would have an independent review of that recommendation, and in some cases, the recommendation when the test crosses this threshold of complexity, that certain tests that FDA would require that they only be administered with this most robust level of informed consent. Ben, do you have any comments?

DR. WILFOND: I think you said it quite well.

DR. KOENIG: Any questions at this point before we do the specific recommendations? Everybody's with me? Okay. So what we're going to do now is I'm going to summarize very quickly. I'll go through all nine recommendations just to give you a sense of their flavor and then we can come back and go through them one by one. We actually have them on the slides, the full text, so that we can consider them. So these are the recommendations that we came up with. First, that FDA should require submission of information to assist decision-making process from test developers and make it widely available. This is what I said, that when a test developer presents a new test, as part of the data template, they would make a recommendation about what level of informed consent is required or what it should look like.

The second recommendation is there's a role for FDA in assessing the level of consent necessary for tests and that for tests that cross the threshold of complexity requiring the robust consent process. Now, we are stating up front that we expect this to be a rare situation that tests would be in this level requiring robust consent.

Third, we think that FDA, in implementing this, should employ the framework that we have just suggested and that's suggested in our report, including that very system of going through and thinking seriously about all the features of the test.

And then, fourth, FDA should require the test developers to make the consent determination publicly available and to state that it applies only to that particular intended use. So for example, the specific consent process applies only to a specific intended use of the test. So if, for example, an intended use of the test was for diagnosis, if a test was then going to be used in a predictive context, it might require a totally different kind of informed consent.

Fifth, FDA should require test developers to include the need for robust consent on labeling and marketing. So for those rare instances where the test goes to the threshold of needing robust consent, this would need to be indicated on the label and in any marketing materials.

And then, Number 6, in parallel with that, we are suggesting that FDA, in collaboration with the FTC or the Federal Trade Commission, should monitor advertising, but we're suggesting a priority, that the highest priority in the monitoring of direct-to-consumer advertising would be for those tests where there is a requirement for robust consent. So we're suggesting an order of prioritization.

And then, 7, for tests requiring robust consent, CMS or the Center for Medicare & Medicaid Services and CDC should augment CLIA to require the lab to verify the consent occurred. Basically, this recommendation just recognizes the work that CLIA has already done on the lab's role in assuring that consent has been appropriately obtained.

Eighth, and again these are our recommendations to the Secretary, we're recommending that Medicare and Medicaid should be modified to cover the cost of the provider's role in an informed decision-making process and to allow the reimbursement of the services of an appropriately-trained genetic education and counseling provider, particularly when robust consent is warranted, and please note that we have changed the language. We noted a small mistake from the version that you have in your handout. We always meant the phrase "genetic

counselor" to include any qualified and trained genetic professional and not just a certified genetic counselor. And then, 9, agencies should hold -- let's go back to 8. I should say that this also reflects more the Canadian approach that we heard yesterday that the testing should be considered as a full service and that you have to in some cases consider the counseling to be part of the testing process.

Nine. This is a recommendation that we came to partly at the suggestion of Joe Boone from CDC but also after our own reflections on how complex this whole issue is, we think that all the agencies involved should hold a conference on informed consent for clinical and public health genetic tests to further clarify these issues and get more perspectives and that this conference could serve as a forum for further reflection and consideration on our recommendations.

We also have some recommendations for the private sector as well as those to the Secretary, and first, we think that using this framework that we've developed, professional societies should develop guidelines for specific tests and for education, and if you can imagine it, we wouldn't ever want to have every provider out in practice going through such a complicated document and a complicated process. What we're suggesting is that using this framework, professional societies could make recommendations specific to tests or to categories of tests and that that might be helpful, similar to practice guidelines.

Number 2. Professional societies should discourage off-label uses of tests without careful consideration of the consent issues, again on the assumption that the consent really needs to be tied to the intended use.

Third, for tests requiring robust consent, providers should only offer the test if that form of consent is provided.

Four. Healthcare payers should cover the cost of provision of an informed consent, particularly for the robust consent process. Reimbursement of genetic education and counseling services should be allowed. So that's basically a recommendation to the private sector, but paired with that in Number 5 is basically – this is back to our discussion yesterday. This is a suggestion for the demand side. We're suggesting an increased demand for this on the part of consumers, so that we think that there should be a process of advocacy for informed decision-making processes and that that could help influence coverage and reimbursement policies of third party payers. So this is basically a recommendation to disease interest groups.

Okay. Let me quickly go over the public comment, the questions that we might ask the public to comment on, and then we'll open this up to discussion of the recommendations and comments. So what perhaps the next step we think might be to begin by asking have we identified all the test characteristics that are relevant to consent? Are there any that we've missed? Then the appropriate process. Are the consent components complete? Have we adequately specified the consent continuum, and does it work to just specify it as a continuum, rather than a series of boxes? Remember our first iteration in November had four separate categories of consent. Or do we need more specific consent practices? Would these guidelines be too burdensome for test developers, providers or laboratories to adopt is an important consideration, where we might want public comment. Are the recommendations appropriate? The public recommendations, now we're on the public recommendations, is the role of FDA appropriate? Will professional societies and consumer groups be able to contribute sufficiently to the development of specific guidelines, and are there any other suggestions? So anything? Ben, do you have anything to add?

DR. WILFOND: Not at this moment.

DR. KOENIG: So I have also the full text of all of the recommendations here in the

PowerPoint and can move ahead if anyone wants to consider those, but let's open this up to comment.

DR. McCABE: Is there any general comment before we move on to the specifics? We have about 45 minutes for this discussion.

DR. BURKE: I really appreciate the work and the philosophy that informs this process, but I'd like to raise a general concern that I think might bear on the wording of some of the recommendations. You mentioned that you feel that the bar should be set relatively high for requiring a robust informed consent process, and I agree with that, and we've also said many times that we want the FDA review process to be streamlined. I think it's logical that FDA should a checkpoint in this process, if we are going to require certain tests to be labeled in essence as requiring a robust informed consent, and so I would propose that the analysis needs to be simplified, and I'll actually make a suggestion that I think is consistent with the reasoning that you've just given to us. What I'm really saying is to require test developers to suggest a level of informed consent and then to ask FDA to review that and figure out if it's correct and generate a labeling requirement is only going to work if it's a fairly straightforward process, and you've well identified all the complexities. So it's hard to take complexity and make it straightforward.

But I would propose that there are actually three criteria that are fairly easy to determine, that make it possible to determine whether a robust consent process is needed, and they all have to do with test use, which I think is a very important feature of your presentation. If the test is to be used for reproductive decision making, I think that could be a pretty straightforward simple requirement. Now that would require us to think carefully about how we currently use triple-screen testing, but I think the logic of your argument is that when a test is used for reproductive decision making, that is the purpose of the test, there should be a robust consent process. I'd

also argue that your reasoning suggests that if a test is predictive, there should be an assumption in favor of a robust testing process with one caveat, and this is where it would get complex, but I think we have to have the caveat. That is, if the clinical utility is very high and very well-established and broadly recognized, then we don't need a robust consent process, and your PKU example illustrates that. But I think in general, we should say predictive tests do, unless they meet that criteria, and that should be readily documentable, I would think, largely by published data, and third is when a test is done on one person for the benefit of another. So I think when a test is done in a woman with cancer to determine whether a BRCA1 mutation is present, primarily so that her daughters or sisters can be tested, that's a complex, and I don't know if what I'm suggesting are the right criteria. I guess what I'm really saying is I don't think we can move forward with these kinds of recommendations unless we're satisfied that we've got a pretty tight and fairly objective set of criteria for the robust consent.

MR. HILLBACK: Can I get in at some point in the queue?

DR. McCABE: Go ahead, Elliott.

MR. HILLBACK: Sorry I'm not there. Again, it's hard to do from a distance. To me, the goals here are fabulous, and I totally agree with the need for informed consent. I think all of us on the lab side of the world and people that provide tests would totally agree. Where I have a concern is I don't understand the whole front end of this of trying to get FDA in. As Ben said, the concept of informed consent and carrying that out is primarily, almost certainly, between the provider of the service and the patient, and it's customized based on a whole series of factors that are only known at that point in terms of the patient's understanding, in terms of the various complexities of the patient's condition, the patient's family condition, the patient's mental condition, the patient's medical history, all sorts of things, and it seems to me we're trying to impose order on disorder when disorder is unfortunately the order of the day. I'm

sorry for the pun, but I have to get one in at least. So I don't understand why or what FDA can do. FDA, unless they're going to try to enforce the training and education of physicians, and we've been down that loop before, or unless they're going to try and enforce what a physician actually does and hold them accountable for the quality of their informed consent, which is a private discussion between a physician or other healthcare provider and a patient anyway, and none of us are there at the time, I don't know how this FDA piece of this really helps, and if you're going to say, well, every time you change information, you're going to go back to FDA, ask them to review the new information to make sure it's complete, maybe change the level of informed consent, and then somehow disseminate that, I don't think FDA is interested in being in the role of disseminating this information either. So to me, all the recommendations late in the process make a heck of a lot of sense, and I think as part of whatever we end up doing with FDA, yes, labs ought to submit the kind of information that's going to be needed to give informed consent, but I don't think that's a reviewable, let's set levels, let's decide what a provider should do in the privacy of their office with a patient from a distance because I'm not sure the provider's going to act any differently. We're still going to get back a signed form or a checked form, and none of us are going to know whether it was any different or not.

DR. KOENIG: Can I just respond quickly to Elliott?

DR. McCABE: Yes.

DR. KOENIG: To clarify one thing, Elliott, we actually had you in mind when we were thinking through this recommendation, and it really is meant to deal with your concern that the important thing about oversight is to tell people what you know and what you don't know.

MR. HILLBACK: Right.

DR. KOENIG: And that we are in no way saying that FDA should specify what the informed consent process should be or to in any way interfere with that doctor/patient relationship or provider/patient relationship. Rather, what we're suggesting is that there may be certain situations in which tests can only be offered safely if informed consent is part of that clinical process, and we just want to flag those and make sure that that information is included on the labeling in rare instances.

MR. HILLBACK: But see, my reaction would be I don't want to be the patient where you've decided I don't need urgent or strong informed consent. I don't want my mom to be that patient. I don't want my kid to be that patient. I want the same level of informed consent whether I'm going to have my male pattern baldness test or anything else. I want to know what the issues are, and so as soon as you start saying, well, there's a bunch of them that are just checkoffs, if I'm the practitioner, I say, well, I don't even need to really give you informed consent because everybody's decided this isn't important. I think you almost devalue the concept, and I would rather strengthen the concept. I think informed consent is very important, and I think an awful lot of people just wave at it, and I think that's what you're trying to get at, but I don't think regulating what the labs do or getting FDA into this is going to change that. I think there are lots of other steps in your later recommendations that might, but I don't think we're going to solve the problem by a number of these parts of the regulation. I think other parts, I applaud very strongly, and I think we should strengthen everybody's commitment to doing informed consent and maybe strengthen how CLIA gets involved and certainly the professional societies as you've recommended.

DR. McCABE: Barbara or Ben, any response to that?

DR. WILFOND: Actually, I have a question for Elliott. I want to see what your response is to Wylie's first comment because what Wylie did was try to be much more specific in being clear

about a very limited set of tests in which the point was these are the ones that for everybody, we would want to try to make sure that a certain approach is done and that this is where possibly FDA may have a role in trying to at least be clear what that standard is. But what Wylie did was being more specific about what those limited ones were. Would that make you feel more comfortable, if you had a clearer idea of when this sort of activity would occur?

MR. HILLBACK: Well, again, my reaction is twofold. I guess my reaction is what can FDA do if they've come to this conclusion that Test X needs some high level. They could say that, but they have no influence unless the practice of medicine is now in their purview. They have no influence over whether it happens or not. Let me finish. If I'm the patient, if I go for some other test, I don't think I want people to be feeling, well, this test has a lower urgency because again it's personal, as you said, I think.

DR. McCABE: I have a number of people in the queue here.

DR. LEWIS: I really think that this is a wonderful document, and I think it's going to spark some great discussion, and I really appreciate the work that you've done. I have several comments. The first is along the line of what Elliott was saying, which is, I'm not sure that the test developer is the appropriate person to determine the level of consent needed for the test because to me that's a clinical decision, not a decision that relates to the science of the test. So I believe that the level of consent really is a professional responsibility and it's the clinician that needs to be making that decision because I think it's the clinician who's responsible for the practice of their profession.

In terms of the language in the report, I'd rather see it say patient education and counseling because I think that there's lots of parameters that go into patient teaching. Part of it is the genetic issue, part of it are other issues, and if we call it patient education and counseling, then

it gives this document a much broader and doesn't infer who the clinician is that should be doing it.

In terms of Wylie's comments, I don't know how you tell why somebody is seeking a test. If you say that it's for reproductive decision making, I mean, that's really clear, I think, if somebody's pregnant and is going in for prenatal counseling, but if I have a two-year-old who is diagnosed with cystic fibrosis, that diagnostic test may be used by me for future reproductive decision making, and you have no way of knowing that, and I think that just targeting reproductive decision making at some level has issues that relate to women's issues that may or may not be fair, but I also think that presuming that -- and somebody else may have a test and be pregnant and be having a prenatal diagnostic test that they're using for information and not for reproductive decision making. So I think that why everybody is having a particular test at a particular time becomes an intensely personal thing and trying to mandate what people do with that information becomes really problematic. So I think that while I agree with what you're saying, what might be an important decision for you might not be an important decision point for me and that again it gets to the level of personal, and to me, what it gets to is the clinician and the patient having an informed discussion and some of those issues to me are broader than just genetics.

I know we're here to do genetic testing and that part of what we're looking at is this in the realm of genetic testing, but I think this document can serve as a model, and I think that we need to be careful and not get into the point where we say that there are some things that are the same for all clinical practice, which is a partnership between the consumer and the provider and a discussion that's mutual and is based on respect and not just a checkoff. The documentation I think is a different piece, and how one documents what is done, I think, is very important, and to me signing a form is just signing a form, and I know lots of places where people are signing very complex forms that would be looked at as very robust consent, and it's here, read this and

sign it, and you've got documentation of informed consent but that the process hasn't happened. So I think it's the process that we want to focus on and the documentation of the process is secondary, but I agree with Elliott that I'm not sure having FDA and the test provider be the people who determine this, I think that's really something I'd want to look at again.

DR. KOENIG: Just one point of clarification about that, Judy. We're not proposing that the test developer be the final word about whether a robust consent is required. We're just suggesting that if the person who develops the test might have knowledge that they should make a suggestion, and this was very carefully thought out by the group with a lot of input and everyone thought that there should be an independent assessment of what kind of consent would be ideal. So if we didn't make that clear, I just want to get that on the record.

DR. LEWIS: That helps a little.

MS. BOLDT: I agree with Judy in that I didn't think it was in the hands of the test developer, and you just answered a little bit of my questions, too, Barbara. But I guess I do think that there still needs to be a role of FDA, and I don't know if FDA has expertise at this point to help establish this robustness in terms of informed consent, but I think we can't leave it totally in the hands of the health providers at this point until they understand the complexities and nuances of all this genetic testing.

I do disagree with Judy in saying that we shouldn't call it genetic education and counseling. I do think that to make it so broad to cover a patient, I think we still have to hone it in because it is different to me for healthcare professionals, and they do know what they're talking about maybe with patient education, maybe not as much with genetic education.

DR. McCABE: Steve, do you want to respond?

DR. GUTMAN: Actually, I do. We always like it when people who are formulating ideas for us formulate what they want fair and square, and then we will take those ideas and deal with them in the best way that we can. To be perfectly honest, there are actually two issues at hand here. One is that you are very much at the edge of our legal framework in terms of where we have historically been. We do have precedent for pushing the envelope when we get worried about tests and all kinds of either traditional or untraditional ways, but we certainly haven't visited this particular enterprise before, and you're correct, we don't have any particular expertise. We're growing expertise. We can seek expertise, but we don't have expertise to bring, and I think that there is this -- so what's easy for us in terms of this charge is it's easy for us because we feel so passionately about honest labeling. It's easy for us to try and focus on having the information there so that anybody who does bother to read the label might be able to figure out and maybe to have the label lead towards particular decisions. It's important to us as we're looking at different models to make this more publicly available, so not only providers but maybe interested patients have access to this labeling and can understand if they're worried about their own disease management. It might be harder for us to mandate informed consent. I don't know. It might be something we could do, but there is a subtext, I mean, a very profound subtext. I don't know who here has had a medical procedure in the last year or two. I have. I've seen what informed consent in much more mundane situations are. I had an instance where I was naked on a gurney, having been pre-medicated and asked to sign, and I would have complained to the department head except it was the department head. And so the deal here is that this is a very small part of a very complex problem and we're from the government and we're here to help, but I don't know that we will actually be able to solve all of the problems.

MR. HILLBACK: Could I just add, Steve, because I would ask how you guys would have any chance of keeping the information up-to-date on a "label" copy back to our iterative situation that we're in. This becomes a massive update process which I think becomes onerous and in the way.

DR. GUTMAN: Well, I actually think we would look for it, if we had public databases that either we used or that we leveraged, we would look for mechanisms for update, but I think that the issue here of when the test tips over from a test where you really become alarmed versus the background test where you worry, and I actually treasure your notion that I don't think you should devalue even male pattern baldness. Maybe I'm becoming more sensitive about that particular disease. But I think that the number of instances when you cross that threshold, based on new information, would actually be relatively small. So I don't see that as particularly problematic.

DR. LLOYD-PURYEAR: We also have significant problems with actually the purpose of this document because it's gone from, I think, being a guidance document, which is what I thought the original purpose was, to actual standards and recommendations, and I think there are many papers on guidance and national standards or recommendations generally don't exist because we generally cannot mandate the conversations and the kinds of conversations that take place between healthcare and public health practitioners and their patients. I think to think that this just affects FDA, part of CDC and CMS is also a significant oversight because this will have far-reaching, if these recommendations are carried out, would have far-reaching effects on both other parts of CDC, HRSA and NIH. These recommendations will affect newborn screening programs, public health programs, AHRQ, I forgot, practice guidelines, public health and healthcare professional behavior in general. So I don't think you can narrow it to an FDA requirement or just an affect on FDA and CMS and because I think these issues are also relevant to research in public health and in the clinical setting, if you look at the aspect of tests being a continuum between research and clinical practice, especially with genetic tests. Generally, FDA spoke up because I was going to point out this is not an FDA role nor a CLIA role to mandate this kind of or have oversight of this kind of clinical behavior. And there is something similar that was done with vaccines and it was done by regulation, the National Childhood Vaccine Injury Act. They required vaccine information sheets to be handed out

with every vaccine that was given and that was the conversation, that was the informed process and that, I think, is similar to what FDA is focusing on that label of what you know, what you don't know, what are the possible adverse events, what are the problems, what are the risks, and I think that is really where we have to go. But I think FDA already answered that this is not going to work for FDA.

DR. KOENIG: Can you be more clear about what you mean? I'm sorry. I don't see how this is establishing standards.

DR. LLOYD-PURYEAR: Well, because you talked about national standards and requirements, and when you start making recommendations, --

DR. KOENIG: Strike the word "standards" because that was just a mistake, and I corrected it when I was actually reading it to say that this was guidance. So take out the word "standards," which I agree is a loaded one.

DR. LLOYD-PURYEAR: When you start making recommendations to a Federal agency to have something done, that becomes national standards, that trickles down and that has far-reaching effects, and it goes back to what Elliott said. I mean, this is a conversation between people, and I don't think you're going to have one size fits all.

DR. WILFOND: Actually, Michele, I think the entire working group would agree with you entirely, and I think that we're being perhaps slightly misunderstood, and I think the reason for that is because the order of our recommendations has all the FDA recommendations up front. I think in general, our thought is precisely what you said, what Elliott said, that what's most important is that conversation goes on between providers and patients, but all we want to do is to say there might be some limited circumstances in which it's very important that a certain

more robust approach to consent be taken and perhaps FDA could be one of the places where that decision making occurs, and I think we intended to think that this would happen in the limited set of circumstances, that the vast majority of times, there wouldn't be any involvement at all, other than that the importance of information be provided to FDA and a decision be made in collaboration, that it did not reach that threshold of complexity.

DR. CHARACHE: First, I certainly have enjoyed the thoughtful assembling and integration of the factors that go into consent and the concept of a continuum between robust and not as opposed to tabular forms, but as we look at these factors that go into it, it seems to me that they're really separable into very distinct populations. One is a set that pertain to an individual patient and that includes the purpose of doing the test when there are multiple purposes for doing the specific test. The other component are those things that are test-dependent. Now, obviously FDA can't deal with things that vary by patient. They could only deal with things that are test-specific. So examples of test-specific factors would be the purpose of doing the test that was submitted by the sponsor which is what FDA has to work from, and the second factor would be the robustness of the test, how secure the validity information is known, what kinds of limitations or what kinds of data you want to be sure is provided in the result returned. So there are test-specific things which can be very clearly delineated that FDA could monitor if this were considered desirable. The advantage of having FDA indicate according to guidelines what tests need a robust type of informed consent is that it can be monitored, and I think we're all aware of the fact that doctors or healthcare providers or patients will order tests that should have a robust factor to it that don't and there's no way of monitoring it. Now, in terms of the monitoring, we can come back to how that should be, but I will strongly urge that it be only a check box that somebody has done this and that is documented for various purposes, that it has been done and doesn't get into the issue of the relationship between the person who asked for consent and how this was done because we can't monitor that. That's patient care. So if we separate those concepts, it should be practical for a sponsor, based on the characteristics of the

test, to suggest what level of consent they feel is warranted. Clearly FDA would need deemed status to refer to others with expertise in a given disease state the decision making on what kind of recommendation to make, and it would then be feasible, if FDA felt it was warranted, to indicate either that informed consent is required or, if that's not legally possible, that informed consent is strongly recommended with the sponsor choosing the wording for why this should be the case. It would have to be test-dependent. It would have to include a statement that indicates that these are minimum standards and does not suggest that for a given use or a given individual, they might not be more stringent.

DR. McCABE: I have Muin, Wylie, Victor, Kate, and Joann, and I would ask anyone else who then goes after Joann and in fact these individuals as well, we need to start giving some specific guidance, probably not as blow by blow as you had anticipated, but some specific guidance back to the co-chairs who can take these back to the work group and make the changes in the document.

DR. KHOURY: Actually, I do have very specific guidance here. We need to be careful not to throw the baby out with the bath water here. There is a lot of good stuff that this document represents, a lot of hard work, all the elements are here, and I think once we start going through the recommendations, you might see that we have more agreement than disagreement around the room. When Wylie said something, it triggered the chain reaction in my mind, which is about this sort of having selected situations for that higher threshold robustness, if you will, and that reminded me in a way of the work that the initial Data Group and the classification issues we did way back when, and at the end of the day, we abandoned it, and I'd like to propose here a similar approach, and I think where you guy sort of ended up was kind of in that vein, this continuum. But I'd like to propose a three-pronged approach that the Data Group has adopted. One is an FDA process, a CLIA process, and a postmarket data collection process specifically around informed consent and the psychosocial and ethical issues. The FDA

process could be as extensive or as simple as the labeling issue that this premarket template that people are feeling would give an indication to the level of complexity and maybe they can monitor. We can discuss that FDA piece, but I don't think you should push them too much to the edge of their legal landscape as Steve said earlier. So an FDA piece that may be all there is to it is what we know and what we don't know at the time the test is submitted for certain intended use and borrowing some of these elements of complexity which are some -- these are data issues. I mean, clinical validity, clinical utility and then psychosocial implications, and then the CLIA will take over from there. They have a piece around sort of working with the labs, maybe working through a box and they're going through that as we speak. And then we shouldn't forget that after all this is done, as these other parameters are being refined in the real world, clinical validity, clinical utility, that the funding agencies can begin to sponsor studies that would look at the use of tests in the real world, including informed consent decision-making processes, as part of the ELSI framework. I was going to suggest that the Data Group work with the Informed Consent Group as we begin to do those case studies, Wylie. I mean, when we start going through the BRCA1 and the newborn screening, since we have all these piles of information that came down from the agencies, that we would consider in that time line whether in the postmarket phase there are any data that have been collected specifically about these issues for the case studies that we have, we are considering.

So anyway, in summary, three-pronged approach, an FDA process that could be as simple as the labeling, the CLIA process, and then intensive postmarket data process, because we can never ensure that tests will not be used outside in the off-label phase, and we need to document what's going on in the real world, so that if FDA needs to intervene and that probably is in the rare situation, at least they will have the real data in hand, rather than just concerns of people. These are my specific comments.

DR. BURKE: Well, I'm going to get even more specific. I thought when I first heard this, that

I liked the general idea but it felt too complex, and so I threw out that maybe we could simplify. I think what I'm hearing from comments, particularly Judy's comments and Steve's comments, that simplification is hard to achieve and it would be difficult for FDA to implement as a mandate for informed consent, even a simplified definition of what meets the need for robust counseling. I'm also very impressed by Elliott's comment. I do think that if you boil it down to a threshold and say above here, you need robust informed consent, you are implicitly saying below here, you don't need to worry about it very much, and I think there's a fair amount of danger there.

So I'm wondering if maybe the right approach here, and actually I'm going to propose this, is not to have FDA involved in this process in any way, except that the labeling standards that FDA monitors as part of its review process include comment about the importance of informed consent, but I don't want to lose the threshold work that you guys have done. I'm going to propose that maybe the most important recommendation you've made is to CMS, that what we may be talking about here as our most important operational recommendation being to say that there are certain tests with certain kinds of characteristics for which CMS should agree that genetic counseling services are an appropriate adjunct to the test.

DR. McCABE: I quite honestly must agree with that. I was very impressed with that recommendation because we are adding a burden to the health professional here, and it's a very important burden because it really has to do with a very realistic education of the consumer of this test, and I was impressed that we might be able to get CMS' attention and pay for this and that's an important concept.

DR. PENCHASZADEH: Yes, I agree with Muin, that we have many more agreements than disagreements and that I would take issue with Elliott's concern that putting a threshold for high or robustness of the process means that unless you reach that threshold, you are not

required to informed consent or to simply discuss with a patient what you are going to do and what type of tests you are ordering. I don't know exactly whether this is a role for FDA, if FDA can really legally do that, but I compare this simply with labeling for drugs and medicine. After all, FDA does tell us what is the appropriate use for particular medications. I don't know why we can't have some system by which some agency protects patients and consumers in the sense that makes sure that some kind of a discussion occurs between professional and patient. I think that the example that Steve just gave about his own personal experience tells us what occurs in the real world of medicine, and one should try to put some protections there to use a test. We heard yesterday that this is a very intense investment market, that tests are going to be marketed directly to consumers more and more. So where will the health professional be when a patient decides to go for a test because of the direct-to-consumer marketing? So I think that some provisions have to be there to make sure that this is done and monitored in a way. I would second what Muin proposed regarding this three-pronged approach. I still think that there is a role for FDA, at least that's what we heard in our working group, that FDA can have some leverage to at least determine according to some guidance and in consultation and with deemed status characteristics of tests or use of tests that will require robust consent and that's all that we're saying in the rule.

DR. McCABE: I have five people in the queue. I'd ask that you be very brief, so that we can end in time for the break.

MS. BEARDSLEY: Yes, I'd like to put aside sort of the question of FDA involvement which strikes me as in some respects a detail of enforcement and think a little bit, at least to me, what maybe is really important here are a couple of things. One is the notion that a test developer when it develops its test is going to create some kind of piece of paper that's intelligible to consumers about this test and that it's going to make that piece of paper available. That strikes me as a really important thing, and we ought to make sure we don't lose that. Secondly, that a

test developer when it develops a test is going to think about informed consent. Now, I agree with you, Judy, that the test developer can't figure out how an informed consent should be implemented one way or the other, but I do think that the test developer's in the best position to think through sort of the big picture general items and that it's important that they do that and it's important that that gets communicated in some way. So I think we need to make sure we preserve those two things and maybe think a little less about the FDA piece.

DR. BOUGHMAN: The last two or three comments actually lead in very well to the kind of larger box issue that I wanted to raise. We've been talking about informed consent, and it seems to me that it is the informed part of this process and the labeling, the way Kate just put it, that if not the test developer, who should be able to in fact give the best information about use, intended use, whatever. It is the consenting process, the sharing of information and feedback between the clinician and the patient that came along with the total package of informed consent that I think our colleagues around the table are feeling uncomfortable about. So that, if in fact we kept the informational part, the informed part of the informed consent process applying to those issues up front with FDA and make it absolutely clear that the consenting process which is a patient/provider relationship and that's where it could even be emphasized more clearly, that sometimes that process is so complex that we would urge that formally-trained individuals in the area be involved in that process. I think we could make it even stronger, yet simpler, by dividing those two components.

DR. LLOYD-PURYEAR: Actually, I agree with that, and if you could phrase your or put the framework of your document more clearly as points to consider when engaging in informed consent, I think that --

DR. KOENIG: That's what it is, actually.

DR. LLOYD-PURYEAR: Well, yes, but that wasn't even clear to me because of the recommendations at the end, that you were leading up to those recommendations, and your audience was the Secretary. I can't remember what you said, but it was a different audience than healthcare professionals.

DR. KOENIG: We're not writing a how-to document for healthcare professionals.

DR. LLOYD-PURYEAR: Except that I think this is the basis of it. I think these points to consider should be the basis of what a physician, a public health practitioner, are going to need to consider when engaging in the process of informed consent.

DR. KOENIG: Well, that would actually be a different task. We're not trying to write it --

DR. LLOYD-PURYEAR: But that's what I thought the original task was. When I questioned this a long time ago, that was what I was told the original task was and Wylie's shaking her head yes.

DR. BURKE: I'm agreeing with you that I think that's what they've accomplished.

DR. LLOYD-PURYEAR: Yes, because that's what I think this is.

DR. BURKE: I think it's a wonderful --

DR. LLOYD-PURYEAR: If you take away the recommendations, I think it's a wonderful document on informing people who are going to be engaging in giving and talking about genetic tests of what they need to consider. It's great for that, and if you limit, going back to what Ed said, ourselves to two or three of these recommendations, the one for CMS, which I

think needs to be done and they need to be brought to the table on the issue of reimbursement, and I think this is a concrete thing that they need to address because we're not being covered for that and the convening of the conference, and I don't know about the issue of the FTC, but I think somehow they need to be brought in to look at the issue of direct marketing to consumers. So those are three areas.

DR. KOENIG: That explains your hostility to the document, I think, the fact that there's this misinterpretation.

DR. LLOYD-PURYEAR: It's not hostility, just disagreement.

DR. KOENIG: But just to make it clear that we were interpreting our task as figuring out how informed consent relates to oversight and that is an important issue. It's not a trivial issue. This is not just about education for providers. There are also serious oversight issues in this.

DR. CHARACHE: Coming back to Kate's point, I think the key thing is the goal as opposed to the details of the how-to, but certainly if the laboratory did not have to worry about check boxes, it would be an incredible relief. This would be a very cumbersome and expensive thing to have to do and the suggestion was made because it can be monitored. One of my questions is, whether it would be possible to see how significant the problem is at the present time with two pilot thoughts. One is to get some developers and these can be people in the laboratory-developed test arena, it doesn't have to be commercial outfits, to consider the tests they offer and what kind of informed consent and what criteria they feel is necessary or what tests they would consider robust and see what kind of a consensus we get, separating what's patient-based from what's test-based. The second thing that might be interesting is to choose a few tests, and I can think of some in our own institution, which everyone would agree should be robust, and these are largely neurologic predictive diagnostics and monitor what's going on. How often is

there a documentation of informed consent in the patient record? What really is the problem that we're trying to answer and how severe is it, and therefore what type of stringency is essential?

MS. CARR: I'm sorry. Could I just ask you two questions? Because I thought earlier, you were suggesting that the check box idea was a good one.

DR. CHARACHE: It is a good one but only if there's a legal basis for having it, and the only legal basis I can think of would be a strong recommendation or requirement by FDA that this test, based on test characteristics, warrants the box.

MS. CARR: So if you would take away the FDA role, then that would go away as well?

DR. CHARACHE: There has to be some group that makes that decision, and I think that it would most likely fit in the purview of FDA, if it were test-associated as opposed to patient-associated, and if FDA felt they could meet that charge and again it would require deemed status groups to help them.

MS. CARR: And secondly, who would you suggest do the monitoring of how the tests are -- the ones that we all agree might need robust -- how that would happen?

DR. CHARACHE: This would be done through the regular reviews. They look at requisitions when CAP or Joint Commission or somebody reviews a lab, and they can just ask for the stack of requisitions for genetic tests and see whether the specific kinds of tests that are of concern have check boxes.

DR. McCABE: And that would be CLIA?

DR. CHARACHE: That would be CLIA. That recommendation was made by the Genetics Working Group of CLIA, that for those tests in which others decided this was required, this would be the mechanism that was recommended.

DR. McCABE: I have Steve, Reed, Judy and Ann, and I'm going to cut it off at that, so that we can wrap it up.

DR. GUTMAN: I don't wish to suggest FDA isn't willing to consider helping here. I just don't want to promise something we can't deliver since it's not clear to me exactly where the limits are in terms of -- certainly we can require all kinds of clever labeling. I'm not so certain we could actually mandate informed consent. We're certainly willing to explore that, however.

DR. TUCKSON: I guess I'm getting a little confused by what we have left, but let me just then succinctly say, I think what I want to just make sure that doesn't get lost here is, that we're not losing this, is that somehow the only place I can imagine is FDA is the only place that can assemble all of the information that is absolutely necessary for informed consent to occur and as long as that's not being lost, and we also have to understand that the test developers do not have a natural incentive to make this information available, not in the way in which people need to make rational decisions. They have an incentive to sell a test, many of them, and to market a test, and so while there may be some good folk, there are some people that are trying to make some money. So I would urge that there is some explicit determination that all the information that's necessary to overcome any conflicts of interest around that information is necessary.

Second, and I don't know if it is part of this report or some place else, but we are making an assumption that that information can then, on consent and issues of cost, can be somehow connected and made available through some mechanism to people called "counselors." Now, I

don't know how that's supposed to happen, but that's an essential part of the thesis here, and then, finally, and I don't think it's for this group, but I don't know whether our Committee has dealt with it, there is this assumption in the recommendation, which I agree with but unproven, that these counselors can take this information and somehow or another participate in a rational decision-making process that people then don't get preyed upon or protected and that, you know, rational use of limited healthcare resources and all those other sort of things and we're recommending that that be paid for. By the way, we need to at some point have one of our subcommittees start to look at who actually does that work because at the end of the day here, what we may be liable of doing is making a recommendation that drives up healthcare costs like crazy because of all these new tests and driving up healthcare costs by paying more people to participate in the process of irrational use of limited healthcare resources and you have two inflationary things going on at once which is a frightening proposition.

MR. HILLBACK: Yes, Reed. I'm sorry to jump in.

DR. McCABE: Keep it brief, Elliott.

MR. HILLBACK: Giving someone wrong information. Having them do a surgical procedure they don't need or having bad healthcare and ending up costing the system more money. So I'd be careful to judge this on economic grounds. I'm sorry to jump in, but I just don't accept that argument as appropriate.

DR. McCABE: Okay. Please, everyone, keep your comments very brief.

DR. LEWIS: I was just going to say that the recommendation in terms of reimbursement for counseling services through CMS is something that fits very nicely with the current work of the Access Group as we're working on looking at both guiding principles and reimbursement

issues. So as that gets fleshed out, that may be an appropriate place for that one to play out.

MS. BOLDT: Ditto.

DR. McCABE: Barbara, I know you had a couple of questions.

DR. KOENIG: Well, first, I just want to reiterate the fact that we knew that we were pushing the legal limits of FDA, and we did that purposely and on the advice of our FDA representative that we should not confine our thinking to the current situation but actually look at the ideal situation. So just to throw that in.

I just want to see if we can understand which things we're agreeing on, which we're not agreeing on very, very quickly. So maybe to start, it sounds like there's general agreement about that as a recommendation. It's going to need to be refined, though, because we certainly don't want to suggest that you have to have a genetic counselor every time you do a pharmacogenetic test. So that's why this needs to be tied to some standards and some threshold when it's important. So that's why this is all tied together.

Then secondly, what about the issue of the conference to further identify and define this issue, possibly to identify some of the current practice issues, such as what Pat suggested? Is that something that there is consensus and agreement on? I just want to raise that so that we could get some consensus. If there are any dissenting voices about that, could we get them out?

MR. HILLBACK: Ed, could I propose something?

DR. McCABE: Briefly, Elliott.

MR. HILLBACK: Yes, briefly. I think what I would like to propose is that we, as an umbrella statement, we come out strongly in favor of increasing the effectiveness and the performance of informed consent and then start to list things under that that would help. I agree more information out from the labs is probably on that list. I certainly agree that some sort of reimbursement encouragement to allow the time for this to be done is partly there. I think we're back to our education and training of the practitioners. There's a number of things that could go on that list, but I think the strong statement we ought to make is if you don't have informed consent, you have a great opportunity for error here, and we need to reinforce informed consent and then laundry list things under that that will help do that. But I'm still very much against FDA getting in that loop. I think there are lots of other better ways to do it.

DR. McCABE: I'd just remind everyone that the origin of this goes back to our original oversight report where we basically stated what Elliott has just said and what we had asked this work group to do was to flesh out what is two sentences in our recommendations in the oversight report.

DR. BURKE: I wanted to make a comment that I think is in direct response to Barbara's question, and it's based on what I think I'm hearing, but it's also a very specific recommendation. I would recommend that your Recommendation Number 9 to HHS should be the first recommendation and that actually that should be combined with your first recommendation to the private sector. That is, I would move that we support a recommendation for convening of a conference that is not just HHS agencies but includes professional organizations to talk about a threshold issue that remains.

From my perspective, in terms of what we have left in your first set of nine recommendations, I'd say we're still very interested in Recommendation Number 1. That is, we'd like informed consent recommendations from the test developers to be part of the labeling, and there's a very

clear interaction between the conference that defines some guidelines and standards and the labeling. I haven't heard any dissent from Recommendation Number 6, which is to think about a good oversight process for direct-to-consumer testing, and I think that's all of the recommendations really that this conversation supports in the first nine. If you look at the last five, what I've said is I think the first one and the set of last five is really part of the conference, and I think we are supporting everything else except Number 3 which I think falls out.

DR. KOENIG: Which is?

DR. BURKE: When a genetic test is labeled as requiring an intensive consent process, and if we're no longer going to have that formal standards requirement, then we don't need that recommendation. I think the intent of that recommendation is folded into others.

DR. KOENIG: Could I just raise one thing, though, about this issue and resisting somewhat? We were working on the assumption that there were some tests which could only be safely offered in clinical practice if a robust consent process accompanied those tests. Is that a generally-shared assumption? Because if that's the assumption, then we can think of different mechanisms to deal with that in terms of oversight. Now, again, I'm not talking about practice but the oversight elements of that. Is there agreement? How many people agree with the idea that there are some tests that can only be safely offered in practice if there is a robust level of informed consent attached to them?

MR. HILLBACK: I do. I think you're trying to create something artificial personally.

DR. WILFOND: But the question, though, is whether there should be oversight of that, though. Barbara, I want to make sure that you're clear that you're separating out whether the process should be robust or whether there should be oversight to ensure the process should be

robust. Which are you asking or are you asking both?

DR. KOENIG: I'm asking them in sequence. So first, if we're in general agreement about that, then the second step is should we tie our suggested oversight process to this need?

DR. McCABE: We're going to have to hold some of this discussion till this afternoon. We have guests that are to appear before us. I think that you have some general guidelines. I think the issue really has to do with that you don't set a threshold and say everything below that is trivial. I think that's one of the messages that you should get. I think the other issue is how you would deal with the robust consent in a way that doesn't create an artificiality that begins to infringe on the health professional/patient relationship. With that, we're going to take a 10-minute break. We will resume sharply in 10 minutes.

(Recess.)

DR. McCABE: Well, our next session is on exploring the collection, use and analysis of data on race and ethnicity in genetic research and genetic testing. I want to thank all of our presenters for coming here and being with us today. We certainly appreciate your input on this, and now I'm going to turn this over to Dr. Wylie Burke, who will chair this session. Wylie?

DR. BURKE: Well, I also want to welcome all of the members of the panel. Thank you very much for taking time from your busy schedule to come here and talk with us and to help us to understand the collection used in analysis of population data, particularly as they relate to genetic research and to genetic testing. We appreciate your help in bringing us up to speed and helping us to understand the issues and in particular to help us to identify what are the policy issues related to the collection of population data and to the use of identifiers related to racial and ethnic identities, how those relate to policy and how those might have relevance to the

tasks of this Committee. So today, we will, with this esteemed panel, explore how and why racial and ethnic population data are collected and analyzed and used in social and health policy; how and why the categories are used in genetic research and in the provision of genetic testing; what the concerns are about the use of the race and ethnicity categories that are used currently; and to what extent a testing context, the purpose of a test or the particular research in question might be relevant for the collection of these kind of population data.

So obviously we have a lot of ground to cover, and with apologies to the panel, what I'd like to do is rather than making formal introductions just briefly describe the flow of the panel. I do want to mention to and remind Committee members that we do have biographical data, both in our notebooks and in our folders, for each of our panel members. So let me just outline how we'll proceed. We're going to begin with Dr. Claudette Bennett. Dr. Bennett is Chief, Racial Statistics Branch, U.S. Census Bureau, and she's going to be reviewing the types of data that are collected by the Census Bureau, about the racial and ethnic background of the U.S. population and explain why that data is collected and used. She'll also discuss a recent change made in the categories and give us some indication of what the data on race and ethnicity from the 2000 Census tell us regarding the U.S. population's racial and ethnic background. Next, we'll hear from Dr. Olivia Carter-Pokras, who is Director of the Division of Policy and Data in HHS's Office of Minority Health. Dr. Carter-Pokras will describe what health-related data by race and ethnicity are collected by the agencies of HHS and why these data are important from a health policy standpoint. Then Dr. Robert Desnick, who is Chairman of the Department of Human Genetics at Mount Sinai School of Medicine, will describe how race and ethnicity population categories are used in genetic research and in decisions about clinical genetic testing related to disease mutations. Then, Dr. Steven Mack, who's a Visiting Scientist at Roche Molecular Systems, will review why and how race and ethnicity population categories are used in genetic research and also clinical genetic testing with respect to pharmacogenetic applications. Then Dr. Charles Rotimi, who's an Associate Professor in the Department of

Microbiology and Director of Genetic Epidemiology for the National Human Genome Center at Howard University in its College of Medicine, will talk about his work which includes a longstanding scientific interest in the patterns and determinants of common complex diseases in populations of the African Diaspora. Dr. Rotimi will review what is currently known about variation in disease susceptibility among populations, what scientific research is underway on genetic variation, including variation among groups, and how the groups and their genetic differences are categorized and reported. Then Dr. Joseph Graves will talk with us. He's a Professor of Evolutionary Biology at Arizona State University, West. He's also the author of a new book called "The Emperor's New Clothes: Biologic Theories of Race at the Millennium." Dr. Graves will review those theories, discuss why the concept of race is especially problematic when it's associated with genetics and suggest other population categories that might be used in research and clinical practice. And I just want to note that members of this Committee, you may remember the public comments that Dr. Graves has given previously to this Committee in October 2000. Then Dr. Lisa Brooks, who's a Program Director of the Genetic Variation and Genome Informatics Program at the National Human Genome Research Institute, will talk to us about a new project underway, under the auspices of the Genome Institute, called the Haplotype Map Project, and how that will advance knowledge of human genetic variation and the genetic contribution to complex diseases with particular attention to how samples of different population groups will be identified. And then, finally, Dr. Jean McEwen, who is a Program Director also at the National Human Genome Research Institute in the Ethical, Legal and Social Implications Program, will review studies that are being funded by NIH to advance knowledge of the ethical, legal and social implications of research in genetic variation in different populations. So we really appreciate all of you being here and the detailed and very interesting conversations that we're going to have with you, and I will now turn the podium over to Dr. Bennett.

DR. BENNETT: Good morning. In the presentation, "Exploring the Collection, Use and

Analysis of Data on Race and Ethnicity," we're not going to talk about the genetics part. We're from the Census Bureau. We talk about the collection. So we're going to leave all the genetics to everybody else to talk about. With respect to the outline of the presentation, we were basically given a list of questions, and the presentation is going to follow the order of the questions that we were asked to address. The first one being what type of data are collected by the Census about the racial and ethic background of the U.S. population. We're going to talk about why are these data collected, what racial and ethnic categories are used to collect these data, why were the categories changed recently, and how has the data on race and ethnicity from the 2000 Census been analyzed and, if so, what do we know about these data as it relates to racial and ethnic population?

Just a little bit about the type of data on race and ethnicity collected by the Bureau of the Census. First of all, let me say that the categories used by the Bureau of the Census to collect information on race, Hispanic origin and ancestry reflect social and cultural uses. They do not reflect biological, anthropological or genetic, but we use three separate questions to collect information on race and ethnicity and those three questions are: race, where we also get detailed information on American Indian, Alaska Native tribes, detailed information on the Asian population and on the Pacific Islander population; and we asked a question on Hispanic origin; and we asked a question on ancestry. I'm going to talk a little bit about the question on race and the question on Hispanic origin as I go through the presentation. The question on ancestry is asked only of a sample of the population. So I'm not going to talk about any of that information because that information is not available yet, but some of the results from the 2000 Census are available with respect to race and Hispanic origin.

So why are the data on race and Hispanic origin even collected? The data on race and Hispanic origin are collected to fulfill a variety of legislative and program requirements, such as state redistricting, monitoring local jurisdiction compliance with the Voting Rights Act,

implementing Acts, such as the Civil Rights Act, the Public Health Act, Fair Housing Act, Equal Employment Act, Healthcare Improvement Act, Job Partnership Training Act, and a whole mirage of other legislative or programmatic requirements.

I just want to talk about the question on Hispanic origin because this is a question that was used in the 2000 Census to collect information on Hispanics. Most of you in this room probably already know but I'll say it just again. The Federal Government treats race and Hispanic origin as two separate and distinct concepts. Persons of Hispanic origin may be of any race. So in the 2000 Census, in compliance with the 1997 Office of Management and Budget's directive, which pretty much revised the 1977 directive, gave us some instructions that basically said that, first, we wanted to sequence the question on Hispanic origin before the question on race, that was the first thing. And we did that to try and reduce the non-response of Hispanics to the race question and also to reduce the non-response of non-Hispanics to the Hispanic origin question. So you see that there's a note on the top of this question that says "Answer Both Questions 5 and 6." This was our clue to the respondents that there were two separate concepts. The Federal Government is treating these as two separate concepts, one on Hispanic origin, where we asked every household to identify the members in the household whether they are Hispanic or not Hispanic. If they are Hispanic, we asked them to indicate whether they are Mexican, Puerto Rican, Cuban, or some other Hispanic, like Guatemalan, Dominican. Those are other types of Hispanics.

Then we had the question on race. The question on race had 15 separate check boxes, plus three write-in lines. A whole lot of information we collected in the 2000 Census is on race. You look at this question, you're going to say, well, there's some ethnic groups that are included in this question and that is in fact correct, because you see the listing of the detailed Asian categories. Well, the detailed Asian categories are listed on the Census form because they were initially included to capture the immigrant population that started to come into the United

States in the 1860s, and every Census, we have pretty much added categories to capture the immigrant population, and in preparation for the 1990 Census, where we did some research to take the detailed Asian and Pacific Islander categories off and have a category called Asian or Pacific Islander, the Asian and Pacific Islander community lobbied the Congress of the United States to have their separate listing because they had a history of having those groups listed. So you see the categories on the form includes what the OMB called race category, and OMB, in 1977, identified four racial groups. In 1977, they identified white, black, American Indian or Alaska Native and Asian or Pacific Islander. In 1997, after an extensive review, those groups, Asian and Pacific Islander was split into two separate categories, one called Asian, the other called Native Hawaiian and Other Pacific Islander. So you see that reflected on the question. We tried to format the question in such a way that there was a delineation between the ethnic groups that comprised the Asian population and those that comprised the Native Hawaiian and Other Pacific Islander population as well.

You also see a category called Some Other Race on this question because the Census Bureau in about 1950 started to try and systematically collect information on persons who were of more than one racial parentage. In preparation for the 2000 Census, after the Office of Management and Budget made the decision to separate Asian and Pacific Islander, we did not go back to them. This is a special category that Census had that all other Federal agencies don't have. The Census Bureau went to the Office of Management and Budget and got an exemption to include the Some Other Race category, and I'm going to tell you a little bit about this Some Other Race category when I start talking about the data because it's a very interesting category in terms of who reports in that category.

All right. From the 15 check boxes, we are able to take the information and collapse them back into what we call the six alone categories. The six alone categories are the five Office of Management and Budget categories being white, black or African American, American Indian

or Alaska Native, Asian, Native Hawaiian or the Pacific Islander, and then we have the Census Some Other Race category.

When tabulating this information, it is always desirable to have the numbers add to 100, and one of the other new things that we had, I should have mentioned, for the 2000 Census was to allow persons to report more than one race, there was an instruction to the question on race that allowed persons to mark one or more boxes. So in order for things to add to 100, when you have persons being able to report more than one race, you have what we call six alone categories which would be the white alone, black or African American alone, American Indian and Alaska Native alone, Asian alone, Native Hawaiian and Other Pacific Islander alone, Some Other Race alone, and two or more. If you add those categories, they're going to add to the total population. Okay. Somebody may be thinking where is Hispanics in all of this? My first thing that I said, Hispanic is treated as an ethnicity, not as a race. So persons who report as Hispanic also are in the numbers for the race. If you want to treat Hispanic as a race, what you have to do is cross-tabulate the race variable by the Hispanic origin variable and come up with categories called white not Hispanic, black not Hispanic, American Indian, Alaska Native not Hispanic, Asian not Hispanic, Native Hawaiian not Hispanic, Some Other Race not Hispanic. Okay? When you treat Hispanic like a race, you have to take them out of the individual race categories. For comparative purposes, when the Census is showing information, we also show information for persons who are white alone not Hispanic, and the distinguishing things that you need to keep in mind is when we're using the alone, we're telling you that those are persons who only reported that race and nothing else. So let's just see if I can summarize this a little bit. Coming out of the 2000 Census, there are two approaches that one can use to look at the data. You can look at the data in terms of those who report that race alone. So the race alone, for example, would be responders who reported only one race. All respondents who reported white and nothing else are considered white alone. Persons who said that they were white and, say, American Indian, they are in the race in combination category because they reported more

than one race.

Then we said what can we do to confuse the American public? And we came up with a wonderful concept called the race alone or in combination. Okay. Now, the race alone and the two or more will add to the total population. The race alone or in combination is not going to add to the total population. It's going to add to greater than the total population because it becomes a tally of responses and not respondents. Okay. So the individual using the two or more who reported that they were white and American Indian, they're counted in both the white alone or in combination population and in the American Indian alone or in combination population. Everyone in this room's got that, right? Got it.

All right. Now, why did the categories change between the 1990 Census and the 2000 Census? During the decade, for about 20 years, the Office of Management and Budget was receiving our letters and telephone calls basically saying that the concepts no longer reflected the increasing racial and ethnic diversity. So they started a review in 1994 and coming out of that review were the 1997 revisions to the standards. The major revision that most people know about is that of allowing persons to report one or more races, but there were also statements that allowed the question on Hispanic origin to be placed before the question on race. We also made changes in terms of the terminology that were used, and there was also the discussion about whether or not the new directive was going to reflect new classifications because there were persons from the Arab community who wanted Arab to be treated as a race, and the Office of Management and Budget basically said no, not for the 1997 to that. Okay?

What are some of the major findings on Hispanic origin and race from the 2000 Census? One of the major findings is the fact that the nation is much more diverse in 2000 than it was in 1990. The diversity is more complex, and as I indicated earlier, we measure diversity using two concepts, the question on race and the question on Hispanic origin. We don't use, we

being the Census Bureau, in the demographic directive, do not use the term "minority." So one way to measure the nation's diversity is to combine both race and Hispanic origin and come up with categories called white not Hispanic and All Other Races and Hispanic or Latino groups.

We had about 281.4 million persons, and I'd like to thank everyone in this room for participating in the 2000 Census because I know you did, and as a result of the 281.4 million persons, about 87.5 percent of the population reported as not being Hispanic but 12.5 percent or 35 million persons reported as Hispanic in the 2000 Census.

What were the major findings with respect to race? Although the 2000 Census was the first opportunity that respondents had to report one or more races, the overwhelming majority of the U.S. population reported only one race. Ninety-seven point six percent of the 281.4 million persons reported one race and 2.4 percent or 6.8 million persons took advantage to report two or more races.

So what does that mean when we talk about the racial distribution of the U.S. population? Seventy-five percent, and I'm using the alone concept here, not the alone and in combination, okay, using the alone concept, 75 percent of the total U.S. population reported as white alone, about 12.3 percent reported as black or African American alone, nine-tenths of a percent reported as American Indian or Alaska Native, about 3.6 percent reported as Asian alone, one-tenth of a percent reported as Native Hawaiian and Other Pacific Islander, 5.5 percent or 15.5 million persons reported in the Some Other Race category.

The Some Other Race category on the Census for the most part is a Hispanic category in that 97 percent of the 15.5 million responses in that Some Other Race category were Hispanic ethnicities, and this is not new to the Census Bureau. We saw that increase in the 1980 Census. We saw it in the 1990 Census and again in the 2000 Census. We think to a large extent that

maybe there may be confusion on the part of some Hispanics who don't know the difference that the Federal Government used in terms of treating race and Hispanic origin as two separate concepts. Others may very well be persons of Hispanic origin's effort to have Hispanic treated as a race. So that's what that reflects, and again the 2.4 percent reflecting two or more races.

I've covered a lot of information. A couple of things I want you to keep in mind. The concept of race, Hispanic origin and ancestry used by the Census Bureau reflects self-identification. It is not enumerated identification, it is self-identification. The data coming out of the 2000 Census with respect to race are not comparable to previous Censuses. They're not comparable because in 2000, we allowed persons to report one or more races, but in addition to doing that, there were methodological changes. We changed the ordering of the question. We changed some of the terminology used in the question. All of those things are factors that leads to a lack of comparability with respect to the data.

I'll try and answer questions if there are questions after this, and if there are additional questions, you can reach me at the Racial Statistics Branch at 301-457-2402, and we have an Ethnic and Hispanic Branch to talk about ethnic and Hispanic statistics. So I will stop at this time. Do we take questions?

DR. BURKE: Thank you very much, Dr. Bennett. I think what we're going to try and do is go through all of our panelists because we've got a lot of material to cover and then try and save questions for after, and in particular, I want to note for the Committee that we have a discussion period right after lunch. So with that, Dr. Carter-Pokras?

DR. CARTER-POKRAS: Great. Can everybody hear me? I really appreciate all this assistance with the audiovisual equipment. It's unusual to have so much assistance, and I do appreciate that, those of us who are literally challenged when it comes to AV equipment. I've

been asked to talk about racial and ethnic data in HHS data systems, but I went a little further beyond that because I also took a look at some of the questions that I was specifically asked to address in regards to the role of racial/ethnic data in assessing genetic testing, screening, counseling, access to services, et cetera. I also reached out to folks who were members of the Spirit of 1848 listserv for the American Public Health Association and met with the Deputy Assistant Secretary on Health Policy for our Department to get their views because they weren't able to attend in person, and they wanted to say the bottom line to your question, should this Committee delve more into the use of racial and ethnic data in regards to genetic testing, and it's an unqualified yes, because we really need some policy guidance in regards to this. So I'll just go back to the bottom line, but hopefully I'll give you some other things to think about.

Why do we use racial and ethnic data in health policy? We use it for a lot of reasons. We use it for monitoring trends over time at national, state and local levels. We use it to identify high-risk populations so that we can target interventions. We use it to evaluate programs, to understand the etiologic process and identify points of intervention, and to ensure equitable access to services, particularly to monitor and enforce the Civil Rights Act as well as other anti-discrimination legislation.

There are two particular efforts that our Department is interested in at this moment. We've got an initiative to eliminate racial and ethnic disparities in health that focuses on six health areas, which include cardiovascular disease, cancer, diabetes, infant mortality, HIV/AIDS, and immunizations, many of which, of course, overlap with your interests with genetic testing, and we also have our national goals and objectives for the Year 2010 for disease prevention health promotion, Healthy People 2010.

Now, as you know, the Institute of Medicine has been interested in the quality of care for some time, and in summarizing some important aspects of the report in regards to how do we

improve quality of care across the entire system, we need to be able to answer the questions, do all parts of the population have access to needed and appropriate services? Do the services meet or exceed their expectations? And is their health status improving?

So what kind of health-related data are we collecting within the Department by race/ethnicity? First, we've developed an inventory of our data systems that are funded and maintained by the Department, and they're compiled in a directory which I gave you the Website. Many of these data systems, of course, do not collect information on genetic information but some do, like the National Health and Nutrition Examination Survey. In this inventory, we have almost 200 data systems. I think it's 198 at last count. Ninety percent or more of those do collect racial/ethnic data, and they are compliant with the Office of Management and Budget standards.

We recognize that there's some of the data systems that were not collecting racial/ethnic data or were not consistent with the Office of Management and Budget's standards, and so in 1997, the Department of Health and Human Services issued an inclusion policy to require the Department's agencies to collect and report racial/ethnic data consistent with these OMB standards, but again this is limited to those departmental data systems that are funded and maintained by the Department. We are more limited in our ability to improve racial/ethnic data for those data systems in which we are dependent upon data that are supplied to us from other entities, which is why we had an Interim Final Rule published last summer for the State Children's Health Insurance Program, or SCHIP, and why we had a Notice of Proposed Rulemaking that was published, also last summer, for Medicaid Managed Care to require the collection and reporting of racial/ethnic data to ensure that we have equal access and quality of services that are delivered. The Health Insurance Portability and Accountability Act is another area which we have been working with other businesses and industries to identify business needs for the collection and reporting of racial/ethnic data via electronic transmission of this information. Vital statistics is another example I wanted to give you where we depend very

much on decisions that are made by other entities, because what we recommend to the states is a recommended certificate for collecting the information on birth and death, but it's up to the states whether they decide they want to go along with that recommended certificate.

And how do we collect the data? Well, it depends on the data system. It varies widely. We have the National Health Interview Survey that's a household-based interview survey and self-report is the method of use then. We report by proxy. For example, the Census is an example where we have a mailed questionnaire which it may have been -- my husband may have filled out the questionnaire for me, for instance. Observation. Typically, the funeral director doesn't ask the decedent what race or ethnicity they are, and they rarely gather that information from family members. We may also link to other data sources. For instance, with the link to infant-birth death files, we link information on the infant death with information on the race/ethnicity of the mother that was achieved through the birth certificate.

The question of wording and categories are also important considerations. We just wanted to reiterate that the OMB standards are considered minimum standards. You may collect additional information on subgroups as well as other information, such as economic status and risk behaviors. We can have open-ended questions, such as we oftentimes do for the death certificate. If you have an in-person interview, you may have a card with a list of categories. You may have a list of categories that is included in the mailed or telephoned questionnaire or form.

When and how often do we update these categories? Well, the Office of Management and Budget clearance process is one opportunity to update the information as well as implementation for the new standard from the Office of Management and Budget of January 1st of 2003.

Now, in addition to the two collection issues which I've mentioned already, the fact that collection is not required by the Federal Government of racial/ethnic data and the inclusion policy only encompasses those data systems that are funded and maintained by the Department, there are concerns about confidentiality, privacy, legality and potential uses of these data, and I think this is where your interest and efforts are particularly needed. We've had two reviews in the Department. One is with SHIRE, funded by The Commonwealth Fund, by looking at our Federal laws and regulations governing the collection and use of racial/ethnic data. We found out that there are no laws or regulations that prohibit the collection of racial/ethnic data from Federal agencies. Of course, there are anti-discrimination laws in the use of these data. Our office has funded a review by the National Health Law Project of state laws and regulations governing the collection and use of racial/ethnic data by health insurers and health plans, and we found that there are only four states that prohibit the collection of racial/ethnic data at the time of application.

Missing information on data systems still continues to be a problem. For instance, the National Hospital Discharge Survey finds it very difficult to present data by race/ethnicity because we're missing such a substantial amount of information by race and ethnicity.

Discrepancies between self-identification and observer identification have been well documented, and what we considered the gold standard for the collection of racial/ethnic data is self-report. We do need information on subgroups, socioeconomic status, risk behaviors and other information to help explain when we do find that there are disparities.

Now, one question I was asked to answer is are race/ethnicity data needed to measure disparities and access to genetic services, and that's an unqualified yes. Congress, after many folks went in and talked to them about disparities in healthcare access and quality of services that are received, they passed the Minority Health and Health Disparities Research and

Education Act of 2000 and requested an IOM study to assess the extent of disparities and the kinds of quality of healthcare received by the U.S. racial and ethnic minorities and non-minorities. They actually called it the "Ethnic Bias in Medicine Study," but IOM now calls it the "Understanding and Eliminating Racial and Ethnic Disparities in Healthcare." They've asked them to explore factors that may contribute to inequities in care and recommend policies and practices that may eliminate these inequities. In the reviews that were presented by Jack Geiger from New York as well as others of the literature in regards to this issue, there are well-documented disparities in access to specialty services which is of particular interest to you here, and they found that insurance coverage is not the only barrier. There are additional barriers, and it seems like the role of the patient/provider communication is part of that as well as perceptions by the provider about the willingness of the patient perhaps to follow treatment. So when we talk about ethnic biases in healthcare, we're talking not only in screening but testing, counseling and treatment.

One of the pieces of literature that was discovered by Jack Geiger in this review of the literature that he presented to the Institute of Medicine was the term "application error" by Van Ryn, where they talk about the fact that epidemiologic information about a population group is inappropriately applied to any member of that group without consideration of individual characteristics, and this is certainly a concern in the realm of genetic testing.

What can we do to prevent? Recommendations from Jack Geiger are to track patterns of care by patient race and ethnicity, to include discussion of problems and nature of stereotyping and racism in medical curriculum and to move race/ethnicity to the social history, not the initial discrimination description when we're talking about a particular patient's medical history.

Now, how have we used race/ethnicity data to date in the realm of genetic testing? Here are just some examples from a review of the literature. We've used it to provide prevalence

estimates in the screened population, for instance neural tube defects and sickle cell. The State of California has actually used it to document support for universal screening for sickle cell because they said that they would in a single year have not detected over 6,000 infants with sickle cell trait if they had not been practicing universal screening. We've used it in the past to target group for screening, to assess satisfaction, understanding residual risk and anxiety levels, to assess attitudes about autonomy and confidentiality, to assess interest and intentions to obtain gene testing and counseling. We've used it to assess familiarity with genetic tests and actions anticipated based on the genetic test, to assess response to pretest education strategies, and my fellow panelists, I'm sure, are going to give additional examples.

But there are continuing concerns regarding use of genetic tests, and this is what our Deputy Assistant Secretary for Health Policy Beato wanted me to share with you. The issue is not so much the collection of racial/ethnic data, it's how we use that information, especially to inform policy. Here's an example, unfortunately, one of the first genetic testing lawsuits out there, which predominantly focused on minority populations, where, for almost 20 years, the Lawrence Berkeley National Laboratory secretly tested African American employees for sickle cell anemia until the workers filed a lawsuit that resulted in the '98 decision by the U.S. 9th Circuit Court of Appeals that preemployment testing for genetic illness violates the ADA, unless the employer can prove that it had a clear business-related reason for conducting the test. The military has had ongoing discussions regarding this. Pilots at one point in time were not allowed to train if genetic tests showed a trait for sickle cell anemia, and in fact, in the late 1990s, also, the military issued an order saying that unless there was a concern about dehydration, that we should not be universally applying or targeting a particular population for genetic tests for sickle cell.

We do have protections out there, but they are limited, and examples of the protections, as you know, are the Executive Order 13145 issued a couple years ago, state genetic discrimination

legislation. Most states have passed state genetic discrimination legislation. HIPAA, ADA. Title 7 of the Civil Rights Act of 1964 has also limited protections, but what they don't protect is against stereotypes, unfounded beliefs and prejudices, and in fact, a piece of legislation that came to my attention was a law in the State of Vermont, and I'm seeing some nods, where the sponsor for this particular piece of legislation wanted to use DNA to classify potentiates for Native recognition, but in his comments that he made in support of this piece of legislation stated that "only people that need to fear this are those who aren't what they say they are," which suggested that he wants to use this to limit access to services.

So, is race/ethnicity needed to assess the extent to which health disparities are correlated with biological factors? This question I found much more difficult to answer, and luckily, it's the last question, and I look forward to the other panelists to help out with this question because I have problems with the way this question is phrased. First, we don't see race/ethnicity as a surrogate for a biological or genetic variation. Instead, we see it as a social/political construct, one that talks a little bit more about social ordering and is considered by many researchers as an exposure variable, rather than, as I said, a surrogate for biological factors. I understand that you have in your packet of materials a framework for understanding the relationship between race and health that's been published by Dr. David Williams and just briefly, it shows you what he has developed a few years ago. He has one that's much more detailed with many more lines, but I like this one because it's a little easier to understand. What it says is when we observe racial and ethnic disparities in health, it could be due to a multitude of factors. There are some biological components, but what we have found with the studies, such as by Richard Cooper and others, that a very small percentage of those observed disparities in health, for instance cardiovascular disease, maybe 4 percent are explained by this genetic variation. There are cultural factors. There are socioeconomic factors, and in fact, the socioeconomic disparities have a big role in explaining these observed disparities in health. The role of racism and discrimination on health is getting increased attention in research as well as political, historical

and legal factors and how they operate on health practices, psychosocial stress, environmental stress, psychosocial resources and medical care, and they impact on biological processes and eventually health outcomes. Gene expression is really where many of these operate. We know that socioeconomic status is a powerful determinant of health. We've observed disparities between individual and household socioeconomic status and morbidity and mortality that's well established. The association of socioeconomic status and Health has been found in different populations using different indicators of SES and different health outcomes, and it's been observed for over 100 years, and we have observed that the impact of income is strongest at the lowest level. So it's not necessarily a linear effect. When we do see unexplained health disparities after we have supposedly controlled for socioeconomic status, it doesn't necessarily mean that what remains is biological or genetic. It could be that we have actually problems in our measures of socioeconomic status, and we have inadequately controlled for differences in current social class. We may also have failed to consider the effects of social class in earlier life, including childhood, or failed to include intergenerational effects of social class. We may also have failed to include other variables that are important, such as nutrition and non-economic aspects of racism.

So finally, I would like to end with an example to help you think this through. This is information for the linked infant birth-death files from the National Center for Health Statistics. What you can see from the blue bars of non-Hispanic blacks, that they have higher rates of infant mortality at all levels of education for the mother, educational attainment of the mother. And in fact, if you observe the right-most bars, those women who have received a college education or greater, you'll notice that that infant mortality rate is higher for African Americans than it is for white mothers with less than a high school education. Now, when we take into account the mother's socioeconomic status at the time that she was growing up, we find that many of these remaining disparities that are depicted in this go away. Okay. So it's important that we take into account socioeconomic status at all points in our life span.

So I hope you can give us some policy guidance, and Dr. Beato said he would be very pleased to meet with you in the future, if you would like to do so, and to also share our additional concerns, and I did promise that I was going to give a list of suggested reading materials that have been suggested to me by many members from the Spirit of 1848, so other researchers can also share their thoughts with you. Thank you.

DR. BURKE: Thank you very much. We'll move on to Dr. Desnick. While we're waiting for the audiovisual to be worked out, I'll just note for all of us that we are on a pretty tight time line, and at the same time, we want to make sure that we get the full benefit of this wonderful panel of experts, and it's possible that we may want to look at shortening our lunch hour a little bit, and it's possible that we may want to move one or two of the last speakers over to the beginning of the afternoon session right before our roundtable. So we'll see how things go. We don't want to rush anybody. Probably, also, I should ask our panel, we would certainly really appreciate your being able to stay for our roundtable discussion after lunch. We're going to break for lunch and then start our roundtable at 1:00 and want to have a very lively discussion and appreciate it if you can participate in that.

PARTICIPANT: Can we eat here?

DR. BURKE: Actually, we can go get food and come back. Perfect.

DR. KOENIG: While we're waiting, can I just ask the last speaker, the Spirit of 1848, some of us on this part of the table don't know what that refers to. If you could just clarify it?

DR. CARTER-POKRAS: Certainly. The Spirit of 1848 listserv is just sort of like an e-mail listing from one of the caucuses of the American Public Health Association, which is the largest organization of public health professionals across the country, and so this particular

caucus is interested in the social classes of health.

DR. KOENIG: Yes, we know what the American Public Health Association is, but why is it called the Spirit of 1848?

DR. CARTER-POKRAS: That's just the listserv. It's to --

DR. KOENIG: What happened in 1848?

DR. CARTER-POKRAS: It goes back to efforts that have been made to kind of improve public health at that point in time in this country.

DR. DESNICK: I apologize for being MacIntosh, but sometimes we're incompatible. I'm Bob Desnick, and I appreciate the opportunity to come and talk about race and ethnicity and genetic research and testing, and what I'm about to tell you is that I'm going to make three points. One is that there are racial and ethnic populations that have a higher prevalence of genetic disease than in the general population. The second point I'm going to make is that knowing that fact, there are certain considerations that one makes in genetic research and in developing genetic tests. Finally, if I have a moment, I'll be provocative about what may be the future of genetic testing and give you something to talk about later on. So if we can get this beamed up, we'll be in business.

Now, I'm going to focus on two experiences that we've had, one that we've had a great deal of experience with and the other that we're now having an increasing amount of experience with in terms of genetic testing and that will relate to Jewish genetic diseases and the recent advent of mass screening for cystic fibrosis, and I apologize for this delay. So as I just pointed out, I'm going to use as examples prenatal and premarital carrier testing for Jewish genetic diseases and

for cystic fibrosis.

Let me begin by pointing out that in every ethnic, demographic and racial groups, there are certain genetic diseases that are more prevalent than in the general population, and I think we're all familiar with the ones that are depicted here. These are the common ones that we all know about. I just want to point out to you, though, that if you look at any given ethnic, demographic or racial group, you'll find certain other diseases that are very common, and there's a catalog here of a few of the 22 recessive Finnish genetic diseases where they have a major founder mutation frequency which you can appreciate here and the list goes on and on. Now, I've been particularly interested in my career in diseases that occur in the Middle Eastern populations, those among Arab populations and among the Jewish people, and these two books are catalogs of the different diseases, both Mendelian and complex traits, that occur in these populations, and there are quite a few different disorders. Now, in these populations, you have founder effect, and in fact in some of the populations, in fact, as shown here, here's prevalent recessive diseases in Saudi Arabians and these a partial list of the disorders that you can find in that population and most of these, it's of tribal origin. So they'll be in a particular demographic area or in a particular tribe and because they have a high degree of consanguinity in this population, it brings out these recessive genes.

Now, in terms of Ashkenazi Jews, there are a number of diseases that occur in this population, and you can see that the incidence of the disease is as high as one in 1,500 for Gaucher's disease, actually much higher if you look at disorders that are not medically as concerning, like Factor 11 deficiency, but you can see Tay-Sachs is one in 2,500. That means a carrier frequency of about one in 25. So there are nine different diseases that I've listed here, and these are all nasty disorders. Now, just to make the point that although they are frequent in the Ashkenazi Jews, even in the Jewish populations, where you take Gaucher's and Tay-Sachs that are common in the Ashkenazi, they're rare in the Sephardi and absent in the Oriental Jews, and

in fact, there are ceratin Sephardi Jewish genetic diseases which, for instance, Familial Mediterranean Fever, and there's certain diseases that occur more commonly amongst the Oriental Jews. So in each of these populations, there are discreet disorders that occur more frequently among them than in their relatives prior to the Diaspora.

Why the high frequency? Very simply, founder effect. There's either a single or a major mutation. Some people have suggested that there's selective advantage for heterozygotes and has been shown for sickle cell and G6PD deficiency and, of course, consanguinity in those populations where there still is a high frequency of marrying relatives.

Now, what are the implications in terms of genetic research? Well, we're in the era of the genome and what we've learned is that we can identify disease genes and susceptibility genes in groups with a higher prevalence. So it's easier to identify them, and here's a brief list of examples where we've positionally cloned the disease or susceptibility genes. I just make the point, it was an Arab pedigree that allowed us to clone the Hipepcin-K gene for pycnodysostosis. As you probably know, familial dysautonomia, so far, we only know it occurring in Ashkenazi Jews. That took a long time to clone because it was a new gene and a very tricky mutation. Some say that for breast cancer, if they would have just focused on the Jewish Ashkenazi population, they would have gotten the genes much quicker. Certainly with Crohn's disease, where we know the incidence in Ashkenazi Jews is about the relative risk if a first-degree relative has the disease is 16 times higher amongst Ashkenazi Jews and, of course, this is the first complex trait in which a susceptibility gene was identified and, of course, you're going to hear more about pharmacogenetic traits in a moment.

But once we've cloned a gene, we can identify the group's specific mutations. We can develop DNA-based diagnostic tests and test panels. We can investigate the penetrance a la, for instance, hemochromatosis and establish genotype-phenotype correlations and, finally, we can

develop screening and counseling programs, and let me turn to a couple of examples, because if you think about ethnic-based genetic diagnosis and screening, there are several levels that we can look at. If we take prenatal as the example, I think we're all familiar with the fact that Tay-Sachs disease has been the prototype for the prevention of recessive diseases, started it back in the '70s by Kaback. You can see that now for this rare disease, in the Ashkenazi community, there have been over a million and a half individuals tested, and in that group, over 1,400 couples where they have a one in four risk. The impact of that has been dramatic because what's happened is this has gone from a Jewish genetic disease to a disease in which there are more commonly non-Jewish babies born in North America than in the Jewish population. Prior to the advent of the testing and screening programs, you can see there was something like 45 to 60 babies born in North America to Jewish couples and following screening, you can see there's been a small number that have escaped the screening or for other reasons have been born, whereas in the non-Jewish population where the carrier frequency is 100 times less, you can see that there are more babies born, and in fact, if you go to the Tay-Sachs parents groups today, you see that it's changed from Jewish families to non-Jewish families in the main. Now, back in '97, we were the first to introduce what we called "triple disease screening" or multiplex screening for Jewish genetic diseases and that now has reached the point where most centers are now testing or offering testing for nine different Jewish genetic diseases that cause severe disease, and as you can see, the frequency of affecteds range from one in 1,500 to about one in 100,000, but if you look at the carrier frequency and you add them all up, if you test for all nine of these diseases, one in every six Ashkenazi Jews is a carrier. This just shows you the common mutations that you're testing for, and it's a total of 26 mutations. If you only do five for CF, which gives you 95, 96 or 97 percent detectability, and for all these diseases, I think you're going to appreciate this, there's pretty high detectability, greater than 95 percent.

Now, every year, being in New York, there were always babies born in the religious community in New York, and they brought forth prenatal screening. This is the Hasidic

community. There's about 250,000 Hasidic Jews in New York City alone, and in this community, prenatal diagnosis is not feasible, abortion is not permitted, artificial insemination or birth control are not options, and marriages are arranged. In fact, in this community, which I'm speaking now to meaning the cultural or social needs of a particular ethnic group, the marriages are arranged, and it's the quality of the match that really makes the marriage. So how many generations of Biblical scholars or bankers or whatever you have in the community decides how you match up your daughter to their son, and in fact, what we did is we organized what now has been very successful and that is compatibility testing, genetic screening prior to the matches, and we can talk more about that later but basically I want to show you the impact of premarital screening because maybe it will have some implications on the provocative discussion I'm going to lead at the end. There has been, since '83 when we began this, a total of over 132,000 singles before marriage screened in this community and actually we've now got this worldwide, but look at this. The number of proposed matches of carriers prevented is over 340. Now think of this. What they do is the boys get tested in their schools, the girls get tested in their schools. They have confidentiality. They just have a computer number and a birth date, and then when the parents want to make the match, what they do is they call a central computer in Brooklyn. They give the match numbers and then they're told either compatible or non-compatible. So if you had Tay-Sachs in a family or one of these other diseases, your normal or even carrier kids are not tainted by that because they can be matched up in this way and these people, as you can see, have very large families, and in over 340 instances, there have been marriages avoided that would have ended up with a one in four situation and having large families, you know that in almost every case, you're avoiding a birth of an affected child or more. Now, recently, I was in Saudi Arabia, and we had a conference because they're very interested in premarital testing because they have high level of consanguinity within the tribes and they're quite interested in advancing this concept and had a whole symposium on premarital screening, and I think in certain populations, this is going to be very effective.

Now, what about cystic fibrosis? This is a complicated one, and let me just tell you and remind you that there was an NIH Consensus Conference back in April of 1997. To summarize that consensus conference, it recommended that CF genetic testing should be offered to couples planning a pregnancy or seeking prenatal testing and follow-up of that was an implementation workshop held a few months later in which the groups, the American College of Medical Genetics and the American College of Obstetrics and Gynecology, together with NIH, came together and recently you know that there was a document that was produced from this combined effort of the two Colleges and NIH on preconceptional and prenatal carrier screening for cystic fibrosis, and this is now available nationally. There's been education programs of the obstetric and gynecologists by ACOG and everybody appreciated what the problems here were because the problems are significant. The problems are that in different ethnic, demographic or racial groups, the incidence of CF varies from one in 2,500 to one in 3,200, the carrier risk proportion at least so, but the percent detectability, in other words, if you're doing DNA tests, varies considerably, to almost 100 percent down to around 30 percent. Of course, you really have to realize that this has a residual risk associated with it. So carrier detection here is an issue.

Well, recently, we published the laboratory standards and guidelines for population-based carrier screening for CF, and this is a document that was recently published in Genetics in Medicine and what we proposed was a core panel of 25 different mutations, and the way we came up with this core panel is we got all the data from the Cystic Fibrosis Foundation, where they had screened over 15,000 and genotyped over 15,000 CFs in America and what we did was we took every mutation that was .1 percent or greater in that population, so that was the basis of it. But I think that you also have to realize, as Fred Gilbert recently suggested, that you can expand that panel to look at particular ethnic, demographic and racial groups and in fact that might be wise. So there is a role here because of the risk in these different groups in making available testing that is meaningful. Of course, what we realize in cystic fibrosis is

even with the testing, we're going to end up with situations where if both parents are negative, well, fine, that's going to make these people very comfortable, but the difficulty here is if one parent is positive and one parent is negative, what we're doing is decreasing it here but increasing it in these other populations, so that where the risk was low to begin with, now that one is a carrier, they have a greater anxiety. So there's both good and bad with these tests, and I think we all have to appreciate the importance of genetic counseling and being able to help these people get through and understand what they're getting into when they have testing.

I'm not going to talk about newborn screening, presymptomatic and dispositional testing, but I think you can all have discussed that in great detail and appreciate it. I think that we all appreciate the issues, stigmatization, confidentiality, privacy, genetic discrimination, and all appreciate the need for education and counseling.

Let me just give you a little speculation of what I think's going to happen in the future and maybe we can use this as a basis of discussion. You know the Human Genome Project is now rolling along. We've got a first draft, and what we're going to end up doing in the next number of years is identifying all the disease-causing genes for monogenetic disorders and for multifactorial polygenetic disorders and also the susceptibility genes for common disorders, cancers, even environmental toxins, and you can see in the future that you might be confronted with the following situation, where you have an interactive computer with this following disease gene menu. Now, I've put this up at 2010, but we're in the era of prediction prevention, and what we're going to do is we're going to be able to offer people choices, and you decide where you are. Which button are you going to press? This one says test me for everything, and I've listed 1,200 different nasty diseases you might not want to have a child with. Here, I don't want to know. You have the right not to know. I don't want to be tested for anything. On the other hand, there's the intelligent consumer who's going to say, oh, I want to take each one of those diseases, disease-by-disease, decide which ones you're going to test me for, and then what

you're going to do is you're going to take your little finger and put it in this little DNA collection port because they're going to get your fingerprint and do your genome off of that. And, of course, they're going to put their credit card right here because I don't think the insurance agencies are going to pay for it, but eventually they will because it's actuarial. At any rate, the question I'm going to raise is whether we're going to have a second screen and that second screen is going to be ethnic-based and racial-based, where you not only provide your family medical history but you might provide your race and ethnic history as well as your demographic history, and the question is will that help in working out which diseases you're at risk for? Now, what I think will be the future is that young people who are computer literate will be very attracted by this. I don't know how long it took you to find your spouse, but just think of this, you put your finger in there and put your credit card in there, and a week later, you get a printout and it tells you all the different diseases you're at risk for and what you can do about it. And your pharmacist gets your computer genome because he knows about pharmacogenetic traits and also what particular things that you can do to make you better. It might be vitamins, lifestyle changes, whatever, those recommendations will come to your physician and pharmacy. On the other hand, at the very bottom of the page, there'll be a psychosocial little thing in there and it will say if you go to the Bethesda Marriott and in the Grand Ballroom on Saturday night, everybody in that room will be genome compatible. So let the hormones roll. I think that that kind of computer dating may be or genome dating may be what we're embarking on in the future, and with that, I'll stop and look forward to the discussion later on.

DR. BURKE: Thank you very much, Dr. Desnick. We'll now move on to Dr. Mack.

DR. LANIER: It certainly gives a unique twist on Valentine's Day.

DR. MACK: I want to thank the Committee for giving me this opportunity to talk to you about

these issues, and my bio says that I'm a visiting scientist. I've been at Roche Molecular Systems and the Children's Hospital Oakland Research Institute for about eight years. So I've been visiting for a long time, and I apologize in advance for any glare from my head. Recently, I've been working with administrating the Anthropology Human Genetic Diversity Component of the International Histocompatibility Working Group. So my interests lie with molecular evolution and population genetics and what they call molecular anthropology. I'm going to talk about pharmacogenetic, and I want to talk in the larger context of developing diagnostic tests, and at the end, I want to tell you a little bit about the study design that we've come up with for the anthropology component, so that we don't have to use racial categories in collecting data.

So just to get to the basics. The point of pharmacogenetics is to determine what the molecular basis is for differential drug metabolism in individuals which are given the same drug, and there are a number of points in the drug metabolism pathway where there are opportunities for differential metabolism. You have absorption and excretion of drugs in the intestine. You have a slow or rapid response in either case. The drugs are actually metabolized in the liver, and we have three different classes of metabolisms which I'm going to talk about at great length.

Drugs are both activated and cleared in the liver which complicates the entire issue. Then there's the actual receptors in the body, it's more than just the brain, but where the drugs are actually active and then the drugs have to be excreted. And so we have to consider all of these points when we're considering the genetics of drug metabolism. But what I'm going to be speaking about today primarily pertains to the liver where the actual metabolism occurs.

I want to make it clear that in addition to just issues of pharmacogenetics, issues where you're thinking about race and ethnicity apply to genetic test design in general. So we have pharmacogenetic, which is basically genotyping to predict the outcome of drug metabolism,

and what I'm going to be talking about primarily is the cytochrome P450 gene, which has a class of about 50 different genes, only two of which seem to be active and have substrates which are endogenous to the body. So the other remainder of the genes in this family are acting on drugs which are exogenous which come from plants, it's thought, and other foods that people eat that have to be broken down or otherwise metabolized, and the idea is that as people spread throughout the world, they encounter different environments and develop different genetics to cope with them.

These issues also hold for HLA issues – that's human leukocyte antigen -- of autoimmunity and transplantation, where you're developing a test to do tissue typing for a bone marrow transplant or a kidney transplant, and so there are issues of donor-patient matching where we know that racial data are collected, so that you can fill the database of potential bone marrow donors. We know that in one population, say the European American population, you have a certain chance of finding a match, and based on that chance, you need a certain size donor base in order to find that match for a given patient. And when you're looking at other populations, like the African American population or the Native American population, the size of the donor base has to be larger or smaller in proportion to the genetic diversity of the population in question. So Africans, Subsaharan Africans and African Americans are genetically more diverse than other populations because the human species started in Africa and Africans have been in Africa the longest, so they've generated more diversity, and so if you're going to do transplantation using genetic screening, you have to have a much larger donor database of potential donors for African American community than for the European American community. Conversely, for the Native American community for whom genetic diversity is much lower for a variety of reasons, and you really only need to have a smaller database in order to ensure that you're going to find a match.

Similar issues are true for autoimmune diseases, like type I diabetes or nasopharyngeal cancer.

I'm not going to really talk about these too much. Maybe we can talk about them during the panel discussion, and the same thing is true for the genetic test used to diagnose genetic diseases, like the beta-thalassemias. There's two distinct regions in the world where you have endemic malaria and the beta-thalassemia genes that provide some protection for that malaria are very different in different parts of the world. And if you want to have a genetic test that's comprehensive, you have to take into consideration the genetics of people from North Africa or the Mediterranean as well as people from Southeast Asia, where you have two very different classes of beta-thalassemia.

We already heard about cystic fibrosis, so I'm not going to talk about that very much, but if there's one take-home message from my presentation, I want to leave you with the idea that the genetic contributants to these various diseases and issues of transplantation and autoimmunity and pharmacogenetics, they're not evenly distributed among global populations, and as we're developing a test, a given population will be inadequately served if their genetic diversity is not considered during the development of the test. So we want to be able to include everyone, and we need to have some sort of model or a scheme to make sure that we've done that in a statistically significant fashion.

The next few slides are going to be probing some population genetic issues. The basic concept here, the take-home message is that there's a couple of different ways that genetic differences can be used to distinguish populations. For most of the populations that I'm talking about today, I'm going to be using geographic descriptors, and when I use a geographic descriptor, I'm actually talking about the modern descendants of people who lived in that place about 1,000 years ago, before everybody started moving around, to make things clear.

If you look at the way that polymorphism and diversity is apportioned throughout the human population, you'll see that about 86 percent of all the variation is shared between all

populations. So most populations are very similar mutationwise, and then there's a small number of mutations, about 14 or 15 percent, 10 percent of which are shared within a continent, that is specific to a particular continent, and then only 4 percent of the actual diversity is what we call private polymorphisms which is particular to an individual population, and so these are private polymorphisms to a given continent. But when we're developing a genetic test, we have to make sure that we include the pertinent private polymorphisms, otherwise the test won't be accurate for whatever it is dependent upon on that mutation. When we consider this 86 percent public polymorphism, the allele frequency distributions in each population differ and they can differ to a great extent. So that even if a given mutation or a given polymorphism is shared among all populations, it might be very high frequency in one population, very low frequency in another, and in some cases, perhaps improperly, the identity of the population can be used as a surrogate for genotyping or has been used as a surrogate for genotyping to determine the individual's degree of risk based on what population they come from. So that's the correlation between population and allele frequency distribution.

I'm going to present a couple of slides from a recent paper that we published just to outline some of these issues, and we did a study of the HLA markers in the Pacific and Asia and these are of five different population groups that are based on historical linguistic distinctions. We wanted to know how the markers that we see and that are used for the immune system in determining self and non-self as far as transplantation goes correlate with the history and the geography of these groups. There's six groups, Austronesia, Melanesia, Micronesia, Polynesia, Australia and Continental Asia, and I just want you to keep these colors and the regions in mind for the next slide. In particular, I'm going to talk a little bit later about this group of islands down here, I want you to keep that in mind as well. The basic result of this study was that there's a strong correlation between the genetics of these immune system molecules and the demographic definitions of these populations. So all the mustard-colored populations are Polynesian. I'm not going to be able to talk about why Hawaii is an outlier here, but it's an

interesting story. We can discuss it later. Micronesia and Austronesia, Melanesian populations form one group. Continental Asians form another group. Australians form a third group. The basic take-away message from this slide is that if you're Polynesian or Melanesian or a Micronesian, your best chance of getting a transplant is from someone from your similar demographic group. There are a number of shared polymorphisms that are at high frequencies and as we know from the transplant community, your best chance of getting a transplant is from a relative, and then once you go outside of relatives, you want to use this demographic information to give yourself a strong chance of finding a match. You can extrapolate this sort of thing to the probability of determining risk for a particular genetic disease.

So let's talk about pharmacogenetics in particular. There are a number of different phenotypes that we have to consider. I'm going to be talking about genes that all follow this nomenclature. CYP stands for cytochrome P450 and then the individual locus as denoted by this three- or four-letter code, 2D6, 2C16, like that. So we have what we call extensive metabolizers of drugs which possess at least one functional allele; intermediate metabolizers of drugs which possess one reduced activity allele and one null allele, meaning that there's no function; poor metabolizers carry two alleles and this results in a complete loss of enzyme activity for a particular locus; and then there's a fourth category called ultrarapid metabolizers who carry multiple copies of functional alleles, from 3 to 13 copies, and they have enzymatic activity which is far in excess of activity of extensive metabolizers. And these are phenotypes, that I'm going to be talking about phenotype and genotype, and I'll try to keep them straight as we go because there are also ultrarapid alleles to a particular locus, poor metabolizing alleles of a particular locus.

The whole issue is further complicated by the model in which drugs function and this is pertinent to the entire issue of why we do pharmacogenomics, pharmacogenetics, which is that when you have normal or extensive activity, there's two modes of activity for a given enzyme,

P450 enzyme. Some prodrugs need to be modified by the enzyme in the liver into their active form. For example codeine is modified with hydroxyl and made into morphine, and then other drugs which are active are cleared by the enzyme and removed from the system, and so when you have poor activity, you have no enzyme activity, and you build up a large amount of prodrug and you never activate it to the drug or you can build up a large amount of a particular drug and never clear it from the system. So individuals who are poor metabolizers never, for example, will respond to codeine or respond very weakly to codeine, and you have to give them very high doses of codeine in order to get the desired effect because of the drug activity, the modifications are very low, whereas for other drugs, the drug is very slowly cleared from the system, so they will need a much lower dose in order to get the same effect, whereas with ultrarapid activity, prodrugs are very rapidly metabolized into drug form, whereas other drugs are very slowly cleared. So with ultrarapid metabolizers, you need to give them a much lower dose of, for example, codeine in order to get the desired effect and a much higher dose of a drug which is cleared in order to get the desired effect because the drug is cleared much faster. So when we are designing pharmacogenomic tests, we have to consider both the poor activity and the ultrarapid activity enzymes and the diversity in the populations that leads to these two activities in order that we can make sure that the patients are getting the right amount of each drug.

Now, the rest of the slides I have for the most part are going to be talking about the distribution of different alleles and cytochrome P450 genes, and I think this slide is particularly pertinent to the discussion that we're having today about the use of racial and ethnic categories. This is the distribution of an ultrarapid allele of CYP2D6. 2D6 is one of the best-studied genes in this field. Here's the world, of course, and the numbers in black, I hope you can see them in the back, are allele frequencies of this particular allele distributed across the world. You can see the highest frequency is here in Ethiopia and in Saudi Arabia, 30 percent and 20 percent, and then obviously this is not a high-resolution map of the allele frequency of this gene. In the

Americas, it's 4 to 5 percent or 2 percent. In Europe, it dwindles as you go north to about 1 percent. In Asia, it's even lower than 1 percent. In some parts, it's 0 percent.

So the second take-home message of my presentation is going to be that we need a much higher resolution and much more geographically-related means of assessing diversity on a global scale. Obviously the racial categories that we use, the five plus an other categories that we heard about earlier, really don't adequately reflect the actual units of diversity that we're looking at on the global scale.

Another way to look at this is by looking at phenotype, and this slide shows the various phenotypes of metabolizers, of debrisoquine. It's not actually a drug. It's just a test compound used to determine phenotype and debrisoquine is oxidized and converted to hydroxy debrisoquine, and this perhaps just shows the ratio of debrisoquine to 4-hydroxy debrisoquine in both the Chinese population and the Swedish population, and each of the bars represents the number of individuals in the population that show that particular ratio and so each bar represents a particular phenotype. You'll notice a couple of things right off the bat, which is that in the Northern European population, there's a significant percentage which are poor metabolizers. This constitutes about 25 percent of the population. So the poor metabolizing alleles are at a fairly high frequency in this population, whereas in this Asian population, the number of poor metabolizers is much lower. So you can see right here that you're going to have to a different set of alleles which are detected in this population and this population. The second point is that the entire curve has shifted, if you notice, between the two populations because the high frequency alleles in this population are different from the alleles in this population. So this curve in general metabolizes debrisoquine more poorly than this curve or this population than this population and this is the sort of thing that you can do on a population-by-population level to get an idea of the phenotypes at work, so that you can get a qualitative idea of how you're going to use a particular drug in a particular population, but it doesn't give

you a quantitative idea of what the actual alleles are.

This slide shows the global distribution of some cytochrome P450 alleles. These are the major variant loci, CYP2A6, CYP2C9, 2C19 and 2D6. There's not going to be a quiz, so you don't have to memorize all this stuff, but the important thing to notice is that most of these are of loss of function because you have inactive enzymes and no enzymes, reduced activity, various things like that, and so when people inherit these particular genes, they're going to be poor metabolizers or intermediate metabolizers and the drug is not going to affect them the way that you expect, and these drugs range from things like morphine and codeine to malaria drugs or tricyclic antidepressants. Any number of drugs that you can think of are metabolized by these genes. So you'll see here that, for example, for these inactive enzymes at the 2A6 locus, they're at fairly high frequency in Asians, low frequency in Europeans. They're not even detected or haven't been tested in Subsaharan Africans or people from the Middle East and East Africa, and you can see, as we go down the list, that especially at loci like 2C19 or 2D6, the differences between populations are extremely different. So for example, this 2C19*3 allele is at 10 percent in the Asian populations, and it's not really seen very well anywhere else. 2C19*2 is seen in almost 30 percent in some Asian populations and never comes up above 20 percent in other populations. And the same thing is true for 2D6 where you have 51 percent of 2D6*10 in Asians, 20 percent of 2D6*4 in Europeans, and a totally different allele, 2D6*17, in Subsaharan Africans. All of these alleles need to be taken into account if we're going to develop a test that adequately covers the variation.

Now, when I had up the map earlier, I asked you to remember that group of islands. This is another example of the distribution of 2C19. This is a poor metabolizer genotype. So it's a measure of phenotype. So the frequencies mean a little bit different, but if you look, you'll see that there's a decline basically between Europe and Africa, moving into Asia and then out into the Pacific Islands. In particular, the islands of Vanuatu have 61 percent poor metabolizers for the population, and since this is genotype, this number actually means that the frequency of the

poor metabolizer gene in this population is closer to 70 percent, and if you divide the island chain between north and south, you'll see that there's an even greater disparity in the southern islands. The frequency of poor metabolizer genotype is about 75 percent, so that about 80 or 90 percent of the population have at least one copy of this poor metabolizer gene. I think this makes the point again with the map that I showed you that even within a particular population or a particular island chain, which is somewhat arbitrary depending on how they were determined, there are differences on the subpopulation level that would have to be taken account of, and all of these mutations are accounted for by only two genes, two alleles in this population which aren't seen to a great extent in many other populations. Part of the problem that we face in developing these tests, especially in the U.S., is that an allele, like these 2C19 alleles, occur the square root of 2 percent in the population, and there's only limited space when you're making a test for accounting for all the alleles. So the chances are very great that these alleles might not necessarily be included in the test, whereas for another population, it's very important that these alleles be included if they're going to served properly by the test.

Here are the U.S. I have some numbers for the D26 allele frequencies, and this is important for the next slide as well. The *1 and *2 alleles give you normal activity, and you can see that they're at comparable levels in the European American community and the African American community in the U.S. The distribution of the null alleles is rather different. Twenty percent of the null alleles in the European population are *4 alleles, where that number is almost a third in the African American population, but the same thing is true for these reduced activity alleles. Fourteen percent of the reduced activity alleles in the African American population are *17, and these are not even detected in the European American population at all. And then with these duplications, *1 and *2 are ultrarapid metabolizers, *4 is a duplication of this null allele, and so this contributes to the null allele frequency in the African American population. So 2 percent allele frequency in the European American population for ultrarapids is fairly high, and you see a similar number for the African American community, but you don't see that number

here.

In the next slide, I have a list of the alleles which are detected by one of the early gene chip assays for these P450 genes. This slide is about four years old, but the point I want to make is that the original alleles which were selected for the chip were selected based on their frequencies in the European American population. So you see here four particular poor metabolizing alleles cover about 90 percent of the poor metabolizing genotypes seen in the European American population, but these alleles only cover about 10 percent of the poor metabolizer phenotype seen in the African American population. So obviously -- I mean, this is an old slide, but the chip assay had to be redesigned in order to accommodate all of the diversity that we saw in the previous slide.

So to sum up for pharmacogenomics and genetic testing in general, the distribution of these alleles is not even around the world, and we need to be able to look at all the alleles possible in order to develop a test that's going to serve the global community to the best degree possible. So the question that we've come to, and this is kind of an outline of the thought process that we went through when we were devising the experimental design for our project, is how do we organize our data collection to best account for the observed genetic substructure of the species. We're talking about race and ethnicity today, but we came up with five categories of structure to think about the data. First is the species level but that assumes no population substructure, and if you assume this, then you risk false-positives and false-negatives in your analysis and you're really not going to be getting anything useful out of the data at all. We considered using racial categories, but they're very arbitrary, and as I hope I've shown you, they don't really reflect the global distribution of diversity on a scale which is useful. I left out a word here. They serve as only a very, very weak estimate of heredity, and it's too weak in many cases to be statistically relevant. What we were left with was smaller units of demographic distinction, ethnicity population on the individual level, and ethnicity distinctions reflect social distinctions as well as the historical and geographical context, and so one of the

things we wanted to do was to try to use this information, which people self-identified, but the number of categories is very large, well over 6,000 categories, depending upon how you define ethnicity. Populations are the actual biologically-functional units where evolution of population genetic forces are in operation. This would be a very nice way to collect the data but again the population is difficult to define, and there are many more possibilities for populations.

So what we decided was a combination of these two categories, and I've put this in for thinking about the future. Diversity is generated at the individual level and as a possible future goal using high-resolution genomic maps after a global survey of diversity has been completed, I think one of the goals of pharmacogenetics and DNA testing in general would be, as we heard in the last talk, to be able to look at people on the individual level instead of having to break up the world into geographic groups, to really look at the diversity on an individual basis instead of having to lump people together into any sort of groupings. But this is something that's going to be far off in the future, unfortunately, I think, later than 2010.

Then finally, the classification of the demographic model that we decided to use was hierarchical and it just breaks the world down into different regions based on the distinctions that we see in the data at a certain level. So this scheme has about 14 different distinctions which are below the racial level but above the ethnicity level and each of these is hierarchical. So they break down into a number of smaller divisions as well, and we allow people to self-classify ethnicity. We collect data on whether or not samples were collected and where they were born and all this is keeping in mind the idea of modern descendants of people who were alive 1,000 years ago in terms of classification. So this is the classification scheme for data that we've come up with, and one of the things we're doing now is testing this against racial categories to see which is more useful in terms of data analysis. So thank you for listening, and we can talk about this at greater length later.

DR. BURKE: Thank you very much, Dr. Mack. We'll move on to Dr. Rotimi.

DR. ROTIMI: Again, I was sitting down there listening to Dr. Mack and I was saying that, wow, he covered quite a bit of what the issues are here and the way he ended was really music to my ear in the sense that in the future, what we're really going after is individualized medicine. I don't know how we can accommodate that in terms of cost, but I think that is the direction that we are going.

My talk today, I really wanted to give the message that for most of these diseases that I think we are beginning to consider in terms of complex diseases, I think maybe we are overemphasizing the importance of genetics in all of these diseases. So my presentation today will be an attempt to maybe take us back to my discipline in terms of epidemiology, to say, hey, maybe we need to look at the environment. Maybe that is really what the issue is here. But in the process, maybe also say that genetics is important, but maybe not as important as we are thinking about it.

But I want to start with a series of questions because as I listened to all the presentations and some of the talks I have given before and have heard that other people gave, it becomes very clear to me why the public is confused about what we are saying. We are saying there's no difference and we are saying there is difference. We are saying we don't know what is important here. So it's very, very confusing. Why is the study of human genetic variation generating so much heated debated? Why we do we find it difficult to accept the fact that we have 99.9 percent of our DNA sequence in common, a major finding of the Human Genome Project? Why the difficulty in explaining the fact that group behavioral differences are primarily due to culture rather than biology? I think it's as a result of several things. Probably most important of these is that we are generating new information, and we are expecting people to take this information and accept it right away. I think also the nature of what we are talking

about is complex, and I think sometimes we are not allowing science to take its natural course, which is incremental knowledge, and we are expecting science to give us the answer right away. I think, also, the debate has not been very honest because we are not quite clear of where we stand as the scientists or the people who are trying to deliver the message to the public.

Like I said earlier, we are saying there's difference and we are saying there's no difference, but when you really look at it in terms of the evolutionary history of various populations, you do see differential distribution. For example, this was a study done by Marc, I think, when he was at Case Western Reserve University. When you looked at the 75 human genes, for example, you do see an average that African population tend to have two more SNPs gene compared to other populations. Does this mean that Africans are radically different from – no. I think what it's saying, this was reflecting the history of the age of the African. They probably had more opportunity to have varied over time.

This is an article, and if you have not seen it, I will really, really recommend that you read it. You may not agree with everything in there. Quite a bit of my presentation today is based on this article because I really enjoyed it when I read it, and quite a bit of the issue that we are grappling with here was talked about. Given that we know that geographical differences in distribution of these various mutations that we are interested in, what is the best way to start to say to the public, to make sure that we are not sending the wrong information, and I think Olson here made what I consider a good attempt. "Not only do all populations have the same set of genes, but all groups of people also share the major variants of these genes," and I think that has been said earlier, also. "Geneticists have never found a genetic marker that is of one type in all members of one large group and of a different type in all the members of another group." I think that is the real message here, that the human and the variation that we see is a continuum. Of course, you have differential frequency but that doesn't mean you can draw neat

boxes around different populations, and I think that is where the message gets lost.

This is what we hear in the news, and this is what really confuses the public. "Researchers find genetic markers unique to Africans." "Asians biologically less susceptible to alcoholism." "All Native Americans descended from a small number of founders." This is really confusing, and at the same time, we put up a slide that we are 99.99 percent similar, but this is what gets in the New York Times, and this is what the public hears. So how can we begin to phrase these things in a way that we are not confusing ourselves and the public?

I think probably the question, also, is the interest of those that develop drugs. I think we all agree that the larger the group that a drug targets, the more cost effective that drug is going to be. So it is really not in the interest of pharmaceutical companies to target some as opposed to all Nigerians. If you target all Nigerians, then you are going to produce a drug that you're going to quickly recover most of the money that you are investing.

So how do we marry the fact that there's an economic interest and there is an individual interest and there's this group identity issue? Much of the medical interest in human genes lies not in the similarities among people but in the differences. That is the reason why we metabolize drugs differently. But that difference, again, the emphasis here is that there's no neat way to use it to identify groups. And I'll just use this example, and I think people who have heard me give a talk before will have heard this many, many times. I go back to my days in Nigeria where I used to get malaria and quinine in relation to my mother. When I take quinine, I find my malaria is gone, I itch quite a bit, but my mother is fine. She doesn't react to that. So even at the family level, there's that distinction. So when you use Nigerians, for example, as a mode of developing drugs for malaria, you're probably going to miss somebody like me. So we really have to be careful what we are calling groups and how we are using that group to drive design strategies.

Again, the current focus here, this is what I'm trying to refer to, superspecialization of drugs I think it's not in the interest of pharmaceutical drug companies, and that is where I'm afraid, as we do this research, given that African population have this long evolutionary history, more than any other group, it stands to reason that quite a few of the variants that we are going to see in the African population, especially the rare ones, I mean not the represented, are in the populations that have stronger economic and political power. Therefore the drugs that may be designed for those rare variants may not be of interest to the pharmaceutical companies because it's not going to generate enough resources. Even if the group is large -- for example, the HIV drugs are a very good example. Most African countries cannot afford it. It's there. So how do you marry, you know? I think this is our question. This is probably beyond individual scientists.

I put this here because this was a story that when I read it, I was very, very taken by it, and I think it's part of the problem. You start by asking the wrong question. About half of Asians have this and therefore they are more susceptible to the effect of alcohol intake, and your objective was to determine whether Asian Americans with this particular variant differ from Asian Americans without this mutation, and they went ahead and did it and said yes, there was indeed differences. I said, this is the issue. The scientific question is not properly developed. Is this a problem of Asians or a problem of persons who carry the variant? You see, when you start with the wrong question, your answers are bound to be wrong.

This is another example. This is a study that was done by one of my colleagues at the National Human Genome Center at Howard University, Rick Kittles, where he showed very clearly this group that we call African Americans, we better be careful because we tell the African American population you have substructures and those substructures reflect evolutionary history, and if you don't properly account for them, you're going to find associations just because of that substructure, not necessarily because it's related to the disease or to the gene.

So using large groups, like African Americans or Asian Americans, represents a poor research strategy for understanding genetic variation and its implication for drug development. We need to go do better than that. This is again to drive that message home. I actually disagree very strongly with this premise here, but it does show, even if using these so-called population-specific allele, there is nothing like that population-specific allele. All that this is saying is that there's differential distribution. But if you use this constellation of alleles, you do see a dramatic difference between admixture rates or estimation of European genes in the African American pool, with the highest rate in New Orleans. If you know the history, you know why that is true. Again, the interracial marriages was again more acceptable in this part of the United States. When you go to Jamaica, the rate is as low as 7 percent. So again, this tends to drive why you need to be careful who you're calling African American and how you are using that group to define your strategy in terms of drug development or even preventive strategies.

How can we explain the genetic variance without suggesting that groups are inherently different? I think that is a challenge. Human groups are extremely fluid. I think that we all would agree with. The word "race," for example, cannot begin to capture the commonalities and differences of our shared history. Most African Americans have European ancestors. All European Americans have African ancestors. It makes no sense to talk about races when we are all complex mixtures of different peoples. I think this, however we are going to say, we need to get the message out. Group attributes we are very, very good at identifying. We are so good at it, before we look at it, we see all the differences in the world. It's driven by the way we live our lives and the culture that we have acquired over the years, and I think, again, part of the message here is as we learn more about our genetic susceptibility to disease and our relationship to the past, we need to find better ways of putting genetics in context. People tend to attribute great importance to the findings of geneticists. But the striking homogeneity of our DNA actually emphasizes the centrality of the environment and our experiences in determining who we are, and I will show a few slides to drive this message home.

This is a study we did some years ago -- again, Richard Cooper at Loyola Medical Center was PI for this study -- where we actually measured blood pressure and other related risk factors, including diabetes, in different African populations, what we refer to again as the African Diaspora. These data here represent over close to 11,000 men and women from West Africa, the Caribbean, the U.K., and in the U.S. The U.S. here is Maywood, Illinois. What you do see again is as you move from West Africa to the United States, through the Caribbean and the U.K., you have this monotonic increase in the risk of diabetes as your body mass increases. Your body mass again is your weight divided by your height squared. That is basically how heavy you are. Now, I know you also see the risk by men and women. So what is going on here? The tendency, when I first came to the United States, when you hear the discussion between black and white, the differences when you compare black and white, you almost think that some of these attributes are driven by biology the way it's presented, and again I try to make this point here, that we see that obesity is not a universal attribute of black people but it's influenced by social and environmental conditions that people find themselves. It doesn't mean you don't have genetic susceptibility. It always amaze me when I find, for example, somebody with all the hazards, still heavy. You know, it is not a universal concept.

This is the same type of work but now looking at hypertension. You also see this relationship. What is going on? I don't think the gene of these people have changed radically. If in fact it has changed, what has happened to the admixture rates, unless you can justify that the only type of genes that African Americans have incorporated from the European genes are all bad? If not, you can't explain it. This has to be the impact of current environment.

Now, this really drives the point home. This is the same group of people, Nigerians. As you move from the rural to the city, there's a universal concern. Blood pressure tends to increase with age, but the degree at which that increases with age is driven by the environment that that person lives in. This is rural, urban. As you move from the rural environment, you increase

your risk of just about all the cardiovascular diseases.

Going back to genes, this is the particular variant here that we studied in the angiotensinogen gene. Again, the angiotensinogen gene system is one of those really, really critical systems for us in terms of high blood pressure. The salt and water balance, actually. What you do see, when this variant 235T was identified in the population, there was high excitement, and we've been doing work in trying to understand the genetics of hypertension. Maybe we have again finally identified one of the very important variants in terms of hypertension, but what we noticed when this result came out, I ran to Nigeria right away to try to collect samples to see what is it that is going on because one of the conclusions of this paper was that because this is related to salt and water balance and given the history of the Middle Passage, that this may actually explain the differential distribution that we see in terms of hypertension rate between white and black in this country. So I wanted to know what is going on. If indeed that is true, then this should be overrepresented in the population of African Americans and that was indeed true, but what is not true is that what we see was not just African Americans. It was in all of the other older populations, the Asian population, and if you look at the Caribbean. What you do see is that it is the Europeans, the Caucasians here, that actually do stand out when you compare, so there is an evolutionary history message here, again it is gene. And our attempts to try to link this particular variant to hypertension in Nigerians and African Americans have been very, very difficult. But you do see again differential frequency of the gene. We went therefore to try to measure the products of this gene, which is angiotensinogen gene itself. What you do see is that when you compare cases and controls, you do see the differential distribution in the plasma level of the angiotensinogen gene, but when you compare the variant in these two, it is not significant, and the conclusion that is reached with that kind of finding is that this variant may not be important. I actually reached that conclusion myself, but what you do see here is that to actually find the difference that is between 90 and 92 for this to be significant, you need a very, very large number of people in this study. So I think sometimes

we rush to a conclusion because of, again, a complete lack of understanding of the picture.

I just wanted to end with a slide of my -- I have twin boys, and this was their 11-year birthday party just a few days ago, and to actually see how again we are all in the same boat and the environment that we find ourselves in is probably what is going to drive what we become and how we interact with each other, and that the African Diaspora really will inform us as we try to understand the variation and the impact of that variation on disease distribution, who we are, how we relate to each other, and that genetics is not a death sentence. If you are a Nigerian, and you have a susceptibility to malaria, and you are able to stay under that mosquito net for a very long time, you may never get malaria. Thank you.

DR. BURKE: Thank you very much. It is 12:20, and what I'm going to propose is that we take a break now and have as short a break as we can make it, 20 to 25 minutes max. So we will be reconvening at quarter of 1:00, and we'll ask Dr. Graves to speak with us at that point.

(Whereupon, at 12:20 p.m., the meeting was recessed for lunch, to reconvene at 12:45 p.m.)

AFTERNOON SESSION (12:50 p.m.)

DR. BURKE: Let's go ahead and start again. Dr. Graves?

DR. GRAVES: All right. I entitled this "The Emperor's New Clothes: Genetic Testing and the Social Construction of Race." You already know who I am. This is based on the discussion in Chapter 11 of my book, entitled "The Race and Disease Fallacy," which came out last year.

Now, we know that the mortality of African Americans has been pretty much double that of EuroAmericans across the 20th Century and that's from accumulation of all recorded biological sources of mortality collected by the U.S. Census. So what I have done here is shown the age-specific mortality patterns relative to the so-called white mortality at that age for the years 1963, 1980 and 1996. As you can see, these patterns have not changed across the latter portion of the 20th century. If you read my book, you'll know that these patterns were even worse at the beginning of the 19th Century and in the 18th Century during chattel slavery and so forth.

So the mystery becomes why have these mortality differentials persisted across modern times? My colleagues in the previous presentations have discussed how biomedical research and the biomedical research establishment has unjustifiably relied on genetic determinism or it has incorrectly understood the nature of human genetic variation and the social construction of racial categories. Very good historical examples of this are the Tuskegee syphilis experiment and the case of the disease pellagra. Pellagra, as you know, is a vitamin deficiency disease, yet Charles P. Davenport in the Eugenics Record Office at Cold Spring Harbor convinced the

American public that this disease was genetic and linked to congenital feeblemindedness. Between 1916 to 1941, 75,000 people would die, 55 percent of them described as non-white children from a disease which was entirely preventable by including leafy green vegetables in the diet.

Our research programs are still confused. The National Cancer Institute, the National Institute on Aging, utilized the term "special populations." First, we could describe these special populations as minorities, women and disabled. Then we asked what is biologically special about these groups. These terms confuse the social with the biological categories.

Now, since the previous speakers have already explained why there are no biological races in anatomically-modern humans, and in my presentation, I have attached an appendix to explain why there are no biological races in anatomically-modern humans, what I want to do is talk about the implications of that for medical research and genetic testing.

Now, one of the things we need to realize is that if we look at all phenotypic characters together, they demonstrate readily the fallacy of racial categories. Physical features that are used to define America's social races are discordant with our evolutionary history. In other words, if I use those physical features, I can draw groupings based upon physical features that do not match the genetic history of our species. Therefore, the idea then of using socially-defined categories as if they are surrogate for underlying genetic variation is simply false. Now, the reason this happens, and I'm sort of cut off here, is because diseases are also phenotypes, and they are determined by both genetic and environmental contributions. So the pattern of disease variation is going to be no different than any other phenotypic variation.

So what forces determine how genetic contributions to disease predisposition differ in various populations? Well, together, it's natural selection and genetic drift that are going to determine

disease frequency. Now, in populations of different geographic origin, these factors will have been by necessity different. Populations are homogenized by gene flow between them. The socially-defined races of North America have varying amounts of gene flow, as described by Dr. Rotimi's population figures in the last presentation.

Now, we can take examples of exactly how this worked. For example, if we look at what are considered monomorphic loci that have one allele at a frequency of greater than 99 percent, that's because variants at these loci are usually highly detrimental to individual fitness. Take the hemophilia A mutation which has a frequency of about 2 times 10 to the minus 4. Well, the gene is a large gene, and contains 26 exons, 186 kilobases. Mutations at this locus include large and small deletions or insertions. There are 78 large deletions and 223 point mutations known. Now, thus it is likely that unrelated families probably carry different hemophilia A mutants. Their frequencies are determined by mutation selection balance. That is, once the frequency gets extremely low, essentially chance events are going to determine the frequency of hemophilia A within any given local population group. Now, the severely-deleterious alleles thus, such as the one described here, are likely to vary in the socially-constructed races due to particular aspects of their population history simply by chance alone. Now, on the other hand, you have polymorphic loci with numerous alleles with no single allele having a frequency of greater than 99 percent. Phenylketonuria, Tay-Sachs, cystic fibrosis and sickle cell anemia have all been discussed here today. They vary between different groups, but the fact that they vary between different groups does not mean that we can use these to define races that are not essentially arbitrary. In other words, I could use some other characteristic and come up with completely new frequencies in these groups, such as whether I have whorls, whether you have whorls on your fingertips or whether you have loops in your fingertips. I could come up with new gene frequencies for these diseases in those groups that would be just as valid as whether I happen to be from any particular geographic region in the world.

Also, individuals carry genes of diverse geographic origins. So that for any individual in this room, we do not necessarily know where your particular allelic variant originated, depending again on one's social history. In the case of African Americans, admixture from Europeans is well known. These estimates differ on average between 20 to 30 percent European admixture, also about 10 percent American Indian, thus Asian admixture. Therefore, 40 percent probability of disease predisposition originating in either Asians or Europeans and these estimates again vary by local populations throughout the United States and the Caribbean.

Now, as America's ethnicities continue to intermarry, it's going to be even harder to associate social definitions of race with biological variation. A recent study showed that the interracial couples are far more frequent than interracial marriages. So we may be looking at statistical data of marriages that are orders of magnitude below interracial couples who are also producing offspring. The fact that they don't have a ring on their finger does not mean that they will not produce children. Amazing how that works.

Diseases of complex origin. Now, identifying genetic explanations requires the ability to control environments, and this is probably the most difficult point that needs to be understood when we begin to talk about genetic predisposition for complex disease. In fact, we haven't been studying it right for the most part and that's because there are things, like permissive mutations, environmental effects, and if we look at the overall phenotypic variants for a complex genetic trait, variants of that phenotype is determined by genetic sources, environmental sources, gene-by-environment interaction and also the covariants of genes and environment which I'm going to spend some amount of time on and why that is relevant to issues of genetic testing.

Now, I'm going to sort of skip through hypertension really quick because Dr. Rotimi has already talked about this, but essentially if hypertension rates are stratified by socioeconomic

status, the differential is located amongst African Americans in the higher socioeconomic categories. Seems contradictory but that's what the evidence suggests. That means that the hypertension difference, I think, results from a biological response to these social-cultural factors. So the social construction of race is real in the sense that it has biological implications. The fact that those groups are not biologically justified does not mean that we shouldn't study them because our social history has produced conditions under which people in those social-cultural groups suffer and they suffer drastically. So one way to deal with this would be to control racism, and I know that's a radical suggestion, but if we were to control racism, we might immediately reduce the hypertension differential. Yes?

DR. LLOYD-PURYEAR: Your first bullet, what do you mean, that African Americans in a higher socioeconomic status have a higher rate of hypertension?

DR. GRAVES: Yes. That's exactly what that means.

Now, there are a number of gene loci associated with increased risk, AGT and ACE, for example. Now, at angiotensin locus, there's a mutant called 235T which, at a position 235 in the protein tyrosine has been switched from methionine. In EuroAmericans, 235T is associated with an increased risk of hypertension. Now, as Dr. Rotimi pointed out, 235T is found at a frequency of 85 percent in African Americans. However, 235T is not associated with increased hypertension risk in Nigerians. Now, at ACE, there's a common alu insertion polymorphism that affects the activity of this enzyme. The D allele is characterized by the absence of these alu insertions and thus has higher enzymatic activity. Again, available evidence shows that enzymatic activity of the insertion insertion, insertion deletion and deletion deletion genotypes are similar in Nigerians, Jamaicans and in the United States amongst all populations. Yet the deletion genotype doesn't seem to be influenced by racial background. Again, we're talking about differences in the environment.

Now, Evans and Johnson in 2001, in their pharmacogenomic analysis do not utilize the term "race" at all in discussing it. What they talk about is the common gene, common disease hypothesis. Individuals from any socially-defined race may have a disease-predisposing allele. Now, the difficulty with this is that this assumes that the environmental influences on the gene's expression are the same in each group. However, can we assume that safely in the United States? I say no. No such equality of environments exist for socially-defined minority groups in America, and therefore the covariants of genes and environment, the term I was discussing in the overall phenotypic variant's equation for complex traits, that term is either positive or negative.

Now, for us to be able to determine or to isolate loci involved in this, we would want that term to be zero, but in fact, I argue that for socially-defined racial groups in America, that there are positive and negative covariances there. Therefore the common gene disease hypothesis would fail if the candidate gene consistently experienced different environments depending upon an individual's socially-defined race. For example, if one group were more likely to experience environmental or occupational toxicity, well, is there any evidence of that? Okay. Well, here's one, a GIS map showing racial composition of public housing sites within one mile of toxic waste sites. Okay. Fifty to 75 percent minority occupancy represents 533 sites, greater than 75 minority occupancy represents 2,628 sites or 53 percent of the total. Therefore, it would be useful to collect social science data concerning the exposure of groups to different environments. We drastically need this kind of data to determine whether genes are predisposing for disease or not or whether we're looking at environmental effects.

Now, one of the questions I was asked to prepare for this meeting was should population categories other than race and ethnicity be used? Well, I would argue that we probably have never seen genetically-based racial differences in most disease categories. I'm going to repeat that because that is probably the most radical thing that I have said in my entire presentation.

We probably have never seen genetically-based racial differences in most disease categories. Instead, we have observed underlying differences in the environments of the socially-constructed groups that influence genetic predispositions for disease. For example, poor communities often have elementary schools located by hazardous waste dumps, as this map shows. And if one race has been historically poorer than the other, then they would have had greater exposure to environmental toxins and so forth.

Now, the impacts of these environmental differences can be complex, and I think one of the earlier speakers mentioned this, also. For example, studies of malnutrition in rats show that maternal effects on adult health extend over several generations. We have already seen that differential stress exposure plays a role in predisposing some African Americans to hypertension. Offspring of alcoholic mothers show fluctuating asymmetry in their teeth and fluctuating asymmetry has been linked to lower IQ in college students. Numerous studies show that lasting adult pathology can result from stress in the maternal environment.

Now, there have been longstanding differentials in health and mortality between socially-defined racial groups in America. These differences are not predicted by the underlying genetic variation we see in humans. So in other words, if we were to look at the genetic distances alone and the amount of genetic overlap that we see between populations, we would not predict the huge differential in health, morbidity and mortality that we see in American populations. This is the elephant standing in the living room. I've been saying this for years. I started saying this way before the Genome Project. As a graduate student in Michigan in the early '80s, I was saying this. Of course, I was a graduate student and nobody was listening to me. Now, I have a book and now I'm here in front of you guys and hopefully somebody's going to take this message beyond this meeting. These differences are not predicted by the underlying genetic variation we see in humans. Yet research has focused on innate or genetic explanations. This research has been accomplished without adherence to proper genetic theory

or experimental design. What I mean by that is we cannot even begin to talk about isolating genetic variants in populations who have different environmental histories. Is an elementary component a proper complex genetic analysis design? We've been doing it in Drosophila through the entire 20th Century. Jandanski wrote about this. H.J. Mueller wrote about this. Morgan wrote about this. This is not new. If you don't control environments, then you cannot make proper estimates of genetic causality. That has never happened for the socially-constructed racial groups in the United States.

So conclusion. Once we realize the lack of concordance between biological and socially-defined races, then the disease and mortality differential becomes even more problematic. Well-intentioned researchers who insist that "special populations" need to be included in biomedical research designs need to be wary of how and why this is being done. I give an example of a couple of studies, particularly the famous NitroMed study. For example, the greatest amount of genetic variability in the human species can be found in Subsaharan Africans. It makes sense to include African Americans who have significant Western African ancestry in studies to examine genetic impacts of disease. In fact, if we were doing these studies right to begin with, we would have started with Western Africans and African Americans, instead of starting with Europeans, because the greatest amount of genetic variability in our species is found in those groups, instead of looking at subpopulations that by necessity because of their recency don't include all of the genetic variation, and there is an example of the social history of science determining who we look at and who we design our research paradigms for.

Now, we will also learn a great deal about how social and environmental factors influence genetic predisposition, but we will not see essentialistic racial difference. Plato died when Darwin wrote "The Origin of the Species." There isn't an essence of humanness. There isn't an essence of racial identity. We are people and populations with genetic variation and that

genetic variation overlaps all of the groups. So eventually, as Dr. Rotimi was saying, we want to be able to look at individuals, look at their individual genetic history and then see how that contributes to their potential for disease. So the remedies we design from the socially-constructed theory of race are radically different from the biological theory. The latter blames the victim for their illness. Why are you sick? There's something wrong with you. You've got some gene that makes you sick, and you know what, your race has got that gene and this other race doesn't. That's why you're sick. Instead of asking the other question, the former asks what does our society do that contributes differentially to the genetic predisposition of individuals due to their membership in a socially-defined racial group. Those are radically different questions which will require radically different types of solutions and a radically different moral resolve on the part of this nation to deal with this healthcare disparity. Okay. So that's my appendix. If you still think there are races in the human species, read through the appendix, and I'd be more than happy to answer any questions on that after. Thank you for your attention.

DR. BURKE: Thank you very much, Dr. Graves. Dr. Brooks?

DR. BROOKS: Well, I was asked to come here to discuss the haplotype map project kind of as an example of a scientific research project which actually involves identified populations. So in order actually to understand the use of this information, I actually have to back up and explain what the pieces are that go into this project. So I want to thank Drs. Mack, Rotimi and Graves because they've done some nice descriptions of a lot of the things involved in defining populations and genetic variation in humans, so that makes my talk more understandable. So what I'm going to do first is really discuss the science of the haplotype map and then at the end discuss some of the population parts of that.

So first off, what we're talking about for the haplotype map is a way to approach complex diseases, the diseases that are contributed to by single genes. The methods for finding the

genetic basis for those diseases is more or less in hand. The problem is the complex diseases that most of us are going to die of, I'm afraid, diabetes, heart disease, cancer, there's a lot of diseases that are affected in very complex ways. There's genetic contributions. There's environmental contributions. There's interactions of disease in the environment, and this is very complicated. So I want to make it very clear, building on a couple of the last talks, that in no way is the Genome Institute at all a genetic determinist. Clearly, these complex diseases have very strong environmental contributions. On the other hand, being the Genome Institute, our contribution to kind of trying to figure out the basis for these diseases can come through the genetic side. The basic agenda here is that by having some insight, by finding genes that contribute to these diseases, that gives you insight into the biological process of how the genes and the environment contribute to get the disease.

So the basic challenge is how do you find genes that contribute to complex diseases, and of course as pharmacogenomics, when I say disease, that's a shorthand for saying disease traits that aren't diseases, response to drugs, response to vaccines. So just as a definition of single nucleotide polymorphisms, what I'm showing here is a stretch of DNA. This is a stretch of DNA, one piece of DNA, call it the very left end of Chromosome 1, and here are chromosomes from three individuals that are that same stretch of DNA. As was discussed previously, 99.9 percent, most of the sites in the DNA are the same among all individuals. About one in 300 sites have variation in the population, but since you wouldn't be able to actually see this slide if I showed you a realistic frequency, all of the white bases are the same in all individuals, and what I have as the different colors here are bases where there's variation among individuals. So here, for instance, one chromosome in one individual at this particular site in DNA has a C, another individual has a T there, and so there's several of these shown here. So that's what a SNP is. Any questions on that?

Okay. So then, if you're trying to find genes that contribute to a disease, what you're really

trying to find are these variants that contribute to the disease, and these variants help you find the gene, and it's those variants that cause the differences in susceptibility among individuals to getting particular diseases.

So you can sort of think of two methods. If you're going to look at all SNPs in the genome, for instance, what you're really looking for is a SNP that that variant, that SNP allele, contributes to a disease, and it may well be in the gene. It may be something that's regulatory for that gene, but that's kind of basically what you're trying to find, is the gene and the variant that contributes to disease. Now, that's one way. The other thing to do is that you figure, okay, you're not necessarily going to find the exact gene there, but if you look at a lot of SNPs throughout the genome and since genes are inherited, SNPs are inherited on chromosomes, so they come in blocks, if you find something that's fairly near a gene that's contributing to a disease, that's also going to be very useful.

So the question then is which SNPs are associated with disease, and this is a very hard problem. There's about 10 to 30 million SNPs in the human genome, and genotyping is very expensive and not to mention some of the statistical issues. So going through all of these sites in order to figure out which of these variants are associated with disease is a very, very hard problem.

Now, it turns out recent studies are showing that the genetic variation is organized along chromosomes in a way that's actually very helpful. So in order to sort of explain how that way is helpful, again I have to do some definitions. So these are the same chromosomes, very left end of Chromosome 1, but now I'm talking about each chromosome here. There's a particular SNP allele. This one has CCGT, and then this chromosome has a different set of alleles, and this one has a third set. So each chromosome here in the particular genomic region is called a haplotype. So haplotype is the set of alleles. It's a type of chromosome and these have

frequencies in the population. So for instance, the top one is a frequency of 40 percent, then 30 percent, then 20 percent, and then there may be a handful of other haplotypes at a frequency that total about 10 percent. So is there any questions on that definition of haplotype?

Okay. Now, one more definition and then we'll get to a haplotype map. In a particular genome region, there may be a large number of variants, but in fact, in terms of SNPs, there may be a lot of SNPs in that region, but the number of common haplotypes, common being more than 5 percent in the population, is actually rather limited. There's only a handful, about four to five to six on average, in a population. And so the number of haplotypes is much, much smaller than it could be. It turns out there's just this handful. So if you're looking in a region, you're trying to identify which haplotypes an individual has, you only need to look at a very few number of SNPs. In this instance, the arrows show two SNPs I'm calling tag SNPs. Many SNPs could be used as tag SNPs. You have to choose something. So these are two that work. If you just look at these two SNPs, and the top one is AA, AC, or GC, if you just look at those two SNPs, by knowing the alleles of those SNPs, you then know which haplotype that chromosome is, and so what this means is that even though there may be a bunch of SNPs in this region, it only takes two SNPs for these three haplotypes in order to know the number of haplotypes.

Okay. So we're getting towards then what a haplotype map is. The genome turns out to be organized so that you have these blocks of haplotypes, that in a particular region of the genome, you'll have just a few common haplotypes that are just in these blocks. These are very highly-associated SNPs within the block, and then you go to the next region over, which also just has a handful of haplotypes, and going from one block to the other on chromosomes, you see some recombination because there's sort of one from Column A, one from Column B, one from Column C, and so this is the way that genetic variation is organized. It's not just every SNP for itself. It's not that there's completely randomness from SNP to SNP but you do get

these blocks. So the world didn't have to turn out this way, but this is the picture that's emerging of haplotypes are organized. So what this means then, if you want to use the structure of the genome, you don't have to look at every SNP in order to find out which SNPs are associated with some disease. What you can do is really try to find blocks that are associated, and in order to do that, you only have to look at a few SNPs that define each block. So for instance here, there's a couple of SNPs that define this block. There's one SNP for this one. There's two SNPs for this one. So there may be a lot more SNPs in the genome but in order to really capture this haplotype structure, you only have to look at a few.

So a haplotype map then is a map of these haplotype blocks. It's a few SNPs that define the common haplotypes. It's very roughly 400,000 SNPs total, that's as opposed to 10 to 30 million, and it's a resource for later association studies. So just looking at that again, it's the blocks and it's the SNPs that define those blocks.

Okay. So how do you actually use this to find genes that contribute to a disease? Well, so just to make it clear, haplotype map is a tool. It's going to be done sort of once, more or less, get a bunch of SNPs. Then those SNPs are going to be in databases as to which SNPs are and what the blocks are. Then any time anybody wants to do a study in order to find the genetic contribution to disease, so there's going to be zillions and zillions of these sorts of studies, and they can all use the haplotype map.

I mean, this is where some of the comments before. These are the studies that have to be done properly. You don't want to be confusing environmental differences with genetic differences, but when these studies are done, as I say, they have to be done very carefully, but the theory is you look at two groups of people, individuals with a disease and individuals without a disease, and if you think about these diseases, individuals who have the disease on average have a higher proportion of the environmental contributions to that disease and they have a higher

proportion of the genetic contributions to that disease. So if you're going through the whole genome, what you'll see is that you can compare the genome and individuals without and with a disease and look at the frequencies of the haplotypes in these blocks. So this is an example and just to make the bottom line easy, in this region, the frequencies of haplotypes is exactly the same in individuals with and without a disease. So there's no evidence that there's a genetic contribution from this region. On the other hand, in another region here, individuals with a disease, without a disease have a difference in frequency. The frequencies of these common haplotypes in individuals without the disease, those haplotypes are still there but they've changed in frequency and, in addition, in this example, there's a higher frequency of haplotype in an individual with a disease that's not even common in individuals without a disease. So what this identifies then is the candidate region. This is a region that's worth looking at. This isn't proof. What one now needs to do is go through in a much more careful way and figure out the genetic contribution, how that interacts with the environment, to see if there really is something real here and sort of get out the biological complexity. So the haplotype map is a tool to bring you to this stage. Much more detailed studies for any particular disease then is needed to sort of follow up on that.

Okay. So the recent results are that really most SNPs are in these haplotype blocks, that each block has a few common haplotypes. Now, talking about populations then, it turns out that the common haplotypes are pretty much in all populations. So as was discussed earlier, the frequencies of the haplotypes may differ among populations, but the common haplotypes are in all populations. There are some population differences in haplotypes. It's turning out that the boundaries of the blocks seem to be pretty similar among populations, except that African or African-derived, such as African American populations, or maybe a block in European or Asian ancestry individuals or populations are subdivided in the African or African-derived populations. But sort of aside from that, the blocks are very similar, but the frequency of the haplotypes differ.

So I'm going to go back to some points made earlier, and I kind of like to think of it in this way as what I call my circle diagram. And what this is, if you think about the total genetic variation in the world, that's the outside circle. The inner circles are the total amount of genetic variation within any group, and I use group very loosely. Group can be a town. It can be a country or larger group. The point is that most of the genetic variation in the world is found even in a small group, such as a town. So this is getting to the point about individual differences. Things like ABO blood groups. All populations have individuals that differ in their ABO blood group. The way a variation works is not that some groups have all A allele and some have all O allele. In fact, the variation is within the groups. So that's kind of a picture of the structure of human genetic variation.

Now, what does this mean for something like the haplotype map? You could get a huge amount of information just by looking at one population. You would find pretty much the common haplotypes. So you get a lot by looking at one population, but what you lose by looking at one population is the differences in frequencies. You know, this commonness comes, as was discussed before, because of our common evolutionary history, that humankind arose in Africa. Some Africans then walked to the rest of the world. So we share the genetic variation that was in the original group, but then, of course, along the way, mutations have occurred, so there's some new alleles. Founder effect sorts of things have changed the frequencies of haplotypes.

So in thinking about developing a haplotype map, and I should say that there was a meeting last July that many of you attended. Since then, there's been a couple of working groups, one on the methods for doing the experimental design, the sort of genotyping methods, the other to discuss the population and ELSI issues associated with this. And so as part of that and thinking about the populations, the rationale for including more than one population is that the part that's not in the middle is still important, too. So the part in the middle, by looking at different

groups, you get differences in frequencies of haplotypes. By looking kind of not in just one group, you also get some haplotypes that may not be common in other groups. So even though most of the haplotypes are common, there's still some others that are there and they're also important. You know, partly this was discussed, like the cytochrome P450 alleles.

So the way the haplotype map, the ELSI population groups has been discussing populations is really in terms of specific populations, that under this scenario, it's not like different groups are radically different from each other. So the point is to get a sampling of groups from different ancestral places, not that any particular group is essential and not that any group that we're talking about is well defined, but as sort of a sampling of sort of filling in the stuff around the edges and the frequency differences to get sort of some more populations. So the guidelines that we've been working with of when you sample a group, you try to make it as specific a group as possible. You don't talk about, say, all African Americans but African Americans in a particular place, and so this is partly to get around this feeling that any particular group kind of represent a huge bigger group and to recognize that group-to-group, there are still some differences, even if they're not large differences.

So Jean McEwen has been in charge of doing the ELSI side of things, of organizing the community engagements and the individual informed consent and the population stuff. She's going to be discussing sort of some related stuff, but I think during the discussion, Jean will be talking about that more, if you're interested.

DR. BURKE: Thanks very much. Dr. McEwen?

DR. McEWEN: I was asked to talk a little bit about some of the research that is currently being supported by the Ethical, Legal, and Social Implications Program at the NHGRI to look at the ELSI issues around this kind of research.

So actually, a lot of what we're doing at the moment really arose out of the most recent five-year plan for the Genome Institute that was published back in '98, and as you'll notice here, two of the five goals that were enunciated in that plan for the ELSI Program at the Genome Institute, one was examine the issues involving the completion of the human DNA sequence, and also to explore how socioeconomic factors, gender and concepts of race and ethnicity influence the use, understanding and interpretation of genetic information, the utilization of genetic services and the development of policy.

So sort of coming out of that set of recommendations, we issued back in the spring of '99 a Request for Applications to support research on studies of ethical, legal and social implications of research into human genetic variation, and so a lot of the studies that we're supporting right now came out of this initiative. In addition to the Genome Institute, three other institutes, Deafness, Environmental Health and also the National Institute of General Medical Sciences, were co-sponsors of this initiative, and we ended up funding about nine projects relating to these issues and formed a group that we're calling the Genetic Variation Consortium, which I'll talk a little bit about more in a bit, but essentially it's just a group of the principal investigators on these grants that meets together a couple of times a year to sort of discuss their research and share ideas.

But let me talk a little bit about some of the specific projects, what these nine funded projects are, because there's actually some pretty interesting work being done, although it's really premature yet to say what exactly is going to come out of some of the studies because they're just now really beginning to analyze their data. In another nine months or a year, we should start to actually see some of the results.

The first project that I want to talk about is Pamela Sankar at the University of Pennsylvania, actually in conjunction with Mildred Cho at Stanford University. They are doing a project that

looks at genetic stigmatization and really trying to sort of parse out what are the factors that go into making particular genetic diseases more or less stigmatizing than others and that may make genetic diseases in general perceived by some as more stigmatizing than non-genetic diseases. it the geneticness of the disease per se or is it in some cases the association of the disease with a particular racial or ethnic group that may account for the stigmatization, and they're looking at these questions in a number of different groups. For example, people who identify themselves as being members of particular racial or ethnic minorities versus those who do not, people who do or do not have genetic diseases and also looking at differences in perceptions among people who actually do genetic research and members of the lay public.

A second project in the consortium is Celeste Condit at the University of Georgia, who is doing work on communication issues around genetic variation and using focus groups and survey methodology. She's working with African Americans and European Americans to look at their understandings of the relationships between race and genetics. The end goal is to develop an actual measurement scale for assessing the extent of discriminatory impact of various types of specific communication messages about genetic variation. So how we talk about these concepts which will be extremely important, both in terms of helping to shape public dialogue and also in terms of helping researchers understand the impact of the findings from their studies as reported out in the journals and then obviously in the popular press as well.

A third study in the group is Bruce Elliott's study at the University of Minnesota, called "Ethnicity, Citizenship and Family: Identity After the Human Genome Project," and this is essentially a group that's gathering together an interdisciplinary group of scholars, ranging from philosophers and religious studies people to anthropologists, historians, sociologists and so forth, to actually look at the impact of genetic variation research in terms of people's conceptions of their own personal identity and authenticity, also in terms of how they view their identity in terms of their larger community and then at the other level, how they look at

their identity in terms of family and kinship relationships. So it's sort of these three levels of identity and how that may or may not be influenced by findings on genetic variation research.

Another project is Mark Rothstein at the University of Louisville, who is doing a very interesting study on pharmacogenomics and population groups, and this study actually has two parts. He's doing, first, sort of a fairly traditional legal analysis, looking at some of the legal issues that are likely to arise from increasing research in pharmacogenomics, particularly as it relates to drug development, for drugs targeted at particular racial or ethnic groups, and some of the issues that will arise in terms of recruitment of participants into these trials, other legal liability issues, issues around coverage mandates and sort of looking into the future, probably not-so-distant future with respect to certain drugs, in terms of the kinds of legal issues that we're likely to see coming up. The second part of his study involves a very large national survey of about 1,800 people, really designed to assess the current state of knowledge and public attitudes about pharmacogenomics research and more generally about attitudes toward genetic research that is focused on looking at differences between different racial or ethnic groups. I think he actually just recently began to sort through the data, but it will be interesting to see it as it comes out because he actually got a very high response rate to the survey. So I think that there will be some interesting findings.

Another project that we're supporting is Patricia Marshall at Case Western, "Informed Consent and Concepts of Race in Genetic Research," and Patty Marshall is working with Charles Rotimi and has been working with him in Nigeria in connection with his ongoing studies of genetic epidemiology studies on breast cancer and hypertension and also in conjunction with researchers in the Metropolitan Chicago area who are doing research on the same diseases. She's looking at differences between the two cultures and the way that people approach the informed consent process and also in the way that they conceptualize their understanding of the relationship again between race and genetics, you know, particularly in the context of these two

diseases.

The next project, Morris Foster at the University of Oklahoma, "African American Community Review of Genetic Research." This project builds on some of his earlier work with Native American communities. This time, he's working with three different populations or three different groups of African Americans within the Oklahoma City area, some in the urban Oklahoma City and then others sort of in the suburbs and others in sort of small all-black towns in the area around Oklahoma City, each of which has a very distinct history and also a different set of sort of social organizations, and so he's looking at ultimately trying to develop sort of a model protocol or set of protocols for engaging communities in genetics research projects that would be appropriate for these three very different types of populations with different histories and population sort of leadership structures.

A somewhat analogous project but focusing on Native American communities is Paul Spicer at the University of Colorado, who is doing work with five Native American tribes, two urban tribes and three rural, and again looking at processes not only for sort of engaging the communities but in fact for working with communities and going through the process of getting tribal consent which, as you know, in Native American communities is actually a legal requirement, and so he is talking with tribal leaders, tribal elders, members of Indian IRBs or tribal IRBs, where they exist, and with general tribal membership to try to get a sense of what the range of concerns is, looking at whether there are differences, significant differences between tribes, between rural and urban tribes and so forth. Again, the ultimate goal here is to develop some kind of a model protocol that could at least be a starting place for other tribes to think about when thinking about how to or whether to participate in this kind of research.

The last two projects are actually not regular research projects. They're actually more training and career development grants, but we decided to include them in the consortium nevertheless

because the people involved are actually doing research that's very related to these issues, and the first one is Sandra Lee at Stanford University, whose mentor is Barbara Koenig, and she is doing a project that I think is very relevant to what we're talking about here today, "The Ethics of Identifying Race in the New Genetics," and essentially this is an ethnographic study in which she's looking at the way that racial and ethnic categories are used by genetics researchers, actually doing interviews with some of the researchers involved, people who have been involved in setting up some of the cell repositories that involve samples from identified populations and so forth.

And finally, another career development grant that has a significant research component relevant to these issues is Linda Hunt at Michigan State, "Concepts of Race and Ethnicity in Genetics Research," and again she's looking at the way that racial and ethnic categories are used actually not only in research but also in the clinical practice setting.

So just to say a few words about the way that the Genetic Variation Consortium has worked. We've met so far about three times, and we try to meet about twice a year. The meetings, I think, so far have been fairly useful, both from the standpoint of giving people who are doing the research in this area an opportunity to get together and sort of exchange their preliminary findings and talk about common issues. We've also used it as an opportunity each time to bring in at least one or two people who are actually involved in and doing the research, genomics researchers -- Joseph Graves actually came to our last meeting and was useful there -- so that we can again promote sort of a bidirectional interchange between the sort of ELSI people and the people who are actually doing the research.

In terms of our plans for the near future, we just recently, a couple of months ago, issued a new RFA that follows up on the original one, "Studies of the ELSI Implications of Genetic Variation Research for Individuals and Diverse Racial and Ethnic Groups". Again, I don't have

time to go into the details, but I did bring copies of this for anyone who's interested to take a look at the kinds of issues that we're addressing. This time, we actually have 10 participating institutes across NIH which I think reflects the strong interest and growing interest of other institutes in this area and the real recognition that there's a whole host of problems here that are quickly going to be upon us, and we really need people that are looking at these in a rigorous way. At this time, we're expecting about $4.5 million available to fund these studies, and we think we can probably fund about 10 to 15 new projects, and so we'll be getting Letters of Intent in the next couple of weeks actually and the application deadline is July 10th. So again, if folks around the room may be interested or know of others who may have an interest in this area, I again encourage you to take a copy of the RFA and pass it around.

The last thing I want to mention briefly is plans to further explore some of these topics in a workshop specifically on race and genetics that we've tentatively scheduled for this coming August. This would be a workshop that would be actually part of the planning process for the Genome Institute's new five-year plan, and the idea, although it's in the very preliminary stages, is to draw together a fairly large number of both people who are doing genetic research, particularly involving identified racial or ethnic groups, and also people who are doing research on the ethical and legal and social implications and to really see if we can hammer out some kind of agreement about what we understand and what we don't understand and also to develop a research agenda for the next several years in this area. Our council just approved the concept for this conference a few days ago, amid much discussion and some concern that it's bound to be extremely controversial, but I think there was general agreement that these issues really have to be tackled head-on. So that's what we plan to do. So that's it, and if you have questions, I'll be happy to take them in the discussion.

DR. BURKE: Thank you very much. Our chairman has kindly given us permission to talk until 2:15, and we've heard lots of interesting stuff. So I just want to open the floor at this point

to any questions that committee members may have for the panel.

DR. PENCHASZADEH: I have a question for Dr. Brooks. Hi. Could you tell us exactly how and which groups are going to be studying what criteria? I don't think you addressed that.

DR. BROOKS: I should say, even though I'm going to put these up in a moment, they are not 100 percent set yet. The Population ELSI Group has been discussing this and it continues to discuss it, and we're talking with people who may be collecting these samples and doing the community engagement.

DR. BURKE: I'm not sure we have time to discuss that.

DR. BROOKS: There are two scales. One is large scale, looking over the entire genome. The other is smaller scale, looking over about 30 regions of the genome. Those can potentially become large scale depending on what's found. So what we're talking about for large scale is the CEPH samples, which is a Northern/Western European background, even though they come from Utah, the Arubian samples potentially, with Howard University participating there, possibly China, Japan possible. And then the smaller scale ones we're talking about, Jean, correct me, we've got Mexican American, African American, Chinese American, India American, Italian American, and possibly Kenyan and South African.

DR. McEWEN: And possibly East European as well.

DR. BURKE: Well, with no one else jumping in, I'd like to ask a question of Dr. Graves. I think you made a very provocative comment, a very provocative observation when you pointed out that one might see differences between populations in prevalence of disease and attribute them to genetic differences when in fact the difference might truly be a difference in

environment, where the genetic susceptibility is simply a small part of the story, if I'm understanding your point correctly. It seems to me, and I'm now pushing for things that might be important for us to understand in terms of making recommendations, it seems to me that one of the lessons there is that looking for genetic susceptibility to a particular disease condition should involve cases and controls from the same population and ideally the same general environmental circumstance. That is, it seems to me the lesson you're pointing us to is that we shouldn't be looking at white and black Americans and looking at genetic differences that seem to correlate with differences in diseases, but rather perhaps looking at a population of black Americans, some of whom have the disease in question and some of whom don't have the disease. Am I understanding you correctly?

DR. GRAVES: I was at Henry Ford Hospital last week in Detroit, and the exact same question came up in terms of how to do their epidemiological design, and what I said is what you need to be doing is precisely that, not just looking at so-called blacks because I don't use that term because it really doesn't describe what we're interested in, but you also need to look at whites. You also need to compare whites and blacks of the same general conditions and blacks and whites of the same general conditions, and I guarantee that for many things when we do that, what we're going to see is the underlying environmental association with genetic predisposition for alleles that are found in both groups. And people are not doing that because the working hypothesis has been this essentialistic idea of race, in which there's a black disease and there's a white disease. Blacks have hypertension, so we study blacks and hypertension.

DR. BURKE: Thank you.

DR. KOENIG: Thanks. My concern, as I've served on this Committee and have raised a number of times the issue of race and genetics, is really an ELSI concern, which is, how is the new genetics and genomic research going to affect our social understanding of race? That's a

sort of big "E" ELSI concern. It's not just an issue of individual discrimination, et cetera, and so it seems to me that we have two real policy challenges ahead of us. One is, as we begin to collect data, for example, about the postmarket surveillance of genetic tests, for example, should we make any recommendations about how to categorize data without giving in to this ritualized behavior of classification by traditional categories of race and ethnicity since we've heard over and over again that although they have incredible political salience, they have no biological meaning or they do only in particular context, for example, when you're studying racism, when there might be a biological effect of the racism.

So that's one issue, and the second real policy dilemma that we have is, as we start thinking about tests that may be labeled as specific to certain populations, as we've seen recently in certain drugs that are labeled as possibly more effective in certain populations, as we think of, for example, cystic fibrosis panels that may be more appropriate in populations with certain continental origin, how can we do that in a way, again to raise the same issue, how can we do that in a way without reifying the idea that race exists and having and making that a major social problem associated with the positives of genomics? That may have been completely inarticulate. I apologize if it was.

So it's those two issues. How can we collect the data, especially considering the DHHS guidelines on data collection, which we're subject, which is why we invited the early panelists, and then, also, how can we deal with targeted marketing and also regulating possibly direct-to-consumer marketing of genomics products? If the panel can sort of play with those two things?

DR. ROTIMI: Barbara, I think you ask a very difficult question, but I think it's one that we really need to start again trying to define how best to do the research. For example, the construction of the human haplotype map and its implication for future research. Lisa went into detail how we're trying to sample different populations. I think what is needed here is a

reeducation of the scientists and the public and that what we see in the human is a continuous distribution of variation and that different groups may fall on a different point of this continuum, but there's no way you can draw circles, a clear circle around these groups. You may find a Nigerian here, maybe 80 percent of Nigerians here, they may find 15 percent here and another 5 percent down the road. So there's no way you can draw a circle. So what is important is that realization, so that when we are sampling, we should try to sample the human population, and once you establish the human population, then I really at that point would question any scientist's justification for group identity.

So what is needed is an attempt to represent the variation that is out there, and once that is done, I will question the need for ethnic identity at that point, but if you are interested in an environmental impact on disease, then you need this because that's the cultural and practices that may have very serious relevance for disease. I use the example of alcohol, for example. In a typical community in Nigeria, where you have predominantly Muslims, you're going to have very few alcohol, whereas if you move to another population, you're not going to have. So if you're studying a disease that has implications for alcohol use, we need to know who is the Muslim, who is a Christian or who's the traditional worshiper in that context. So I think the problem is when you lay genetics on that cultural experience that we get into trouble.

DR. GRAVES: To give you another example, you mentioned targeted marketing of products, and I started off Chapter 11 in my book with a case in which Tums marketed the calcium content of their product to Asian and Caucasian women. They argued that you had an increased risk of osteoporosis, therefore you should take our product. And it makes perfect sense. If calcium supplements help you, then you should take it, but everyone has a risk of osteoporosis. So why would you target marketing to just those groups when in fact all humans have a risk of osteoporosis at later age? It makes zero sense.

DR. BURKE: Thank you.

DR. TUCKSON: Let me just also thank you all. What a stimulating panel. We maybe won't get to ask everybody questions, but this is tremendous. I guess what I'm sort of -- I always want to find a way and hope that we can get back specific things from you. I'm struck by what seems like a degree of heterogeneity in your conclusions, and so I only have two questions. First, I'm wondering where do you disagree, and strongly disagree, with each other. That would help me to understand better whether in fact there is a certain unanimity of consensus forming. Number 2, I found myself struck with Dr. Mack's presentation of the maps, and then reinforced by everybody, is that there is much data, there is so much variability, this all is so subtle, down to the whether it's C123S* in Malaysia, how will a genetic counselor ever have access to enough information to be able to use any of it in precision guiding any individual person from any individual state who is from any permutation of people at any particular moment in time to be able to know what to do? And so I conclude my question with is it therefore true that it is impossible and it doesn't matter? The counseling doesn't need to get down to that level of detail around whether you get a pharmacogenomic test for being a fast metabolizer of opium. At the end of the day, who knows? And it doesn't matter. Question.

DR. BURKE: Comment from the panel?

DR. TUCKSON: So two questions.

DR. MACK: Two questions. Oh, these are much easier than the last two, fortunately.

DR. TUCKSON: I'm not as smart as she is.

DR. MACK: Well, thinking about where we differ, I don't really think that we all differ very

much to an extensive degree. I think we're all coming from different perspectives and we're all thinking about using the data in different ways, but I think almost everyone up here has kind of spoken about hopes for a future where we look at an individual as an individual, instead of lumping together in any sort of classification scheme. I think that's something that we should all think about as an ultimate goal, is to do away with all of these classification schemes at some level. Unfortunately, there's 6 billion, probably on the order of 10, 15 billion individuals, to think about in this century, and I think that's part of the daunting task, and that's also part of the reason that it's such a confusing issue because there are so many people and there is so much variation. I can't speak for everyone else, but I think that that's the basis of the commonality in our arguments.

In terms of the second question, it's a lot more of an issue for each individual to decide for themselves. For pharmacogenomics, the thing that I'm concerned about is having an adverse drug reaction. I think it's something like 7 to 10 percent of patients in hospitals have adverse drug reactions, and this could be avoided with the proper test. The question is is it possible to have a proper test, based on all the variation? And that's something that I think we won't know for a while still. We'd have to do a genetic survey of the world. We'd have to look at all the variation without considering classification or grouping.

DR. CARTER-POKRAS: Yes. Actually, I heard a lot more commonalities than disagreement, and I kind of jotted down some of the areas where I thought we were in agreement. One is that it sounds like there's general agreement that race is a poor surrogate for genetic variation and biological variation, that we may see or observe higher frequencies of certain genes in certain populations, but that's not the same thing as saying that it's a good surrogate.

Also, the importance of environment in gene expression -- I heard that oftentimes – concerns about stereotyping and misuse of this information, and that where we'd like to go is

individualized medicine, and it sounded like we were in general agreement here, and I'm seeing a lot of nods across the room. So I heard more agreement than disagreement.

DR. TUCKSON: That's what I meant. I spoke so rapidly. That was my thesis as well, but what you just ended was where now you've got me right -- if you're going to have individualized medicine, I'm hearing a poor prognosis anytime soon to be able to have individualized medicine because we're just so far away from being able to make sense out of all this. Or am I misunderstanding?

DR. GRAVES: Yes, I think you're misunderstanding, because generally physicians have a panel of things they look for in diagnosis. And what the problem has been in the past is because they've thought that these things are essentialized to race, if an African American walks in with scleroderma, a doctor doesn't see it as scleroderma because they see the dark complexion of their skin and says, "Well, that can't be scleroderma, so I'm not going to send you for a scleroderma test." Now, I know that's true because I've had that happen in my own family. I've had several people, students, come in to me with various problems in their families, and physicians telling them that you don't have that disease because it's not a black disease. So physicians and genetic counselors need to be aware of the nature of human genetic variability and the overlap, and then they go through the normal process of elimination. If it's not that disease, then maybe we should test for this one. If it's not that one, we test for this one. But if you start out thinking that there are races and races have essential features and some races don't have this disease and other races do, then you miss the boat, and I think everybody here agrees that we can't use that kind of approach.

DR. TUCKSON: So -- I'm sorry. Put me in the line if there's time.

DR. McCABE: I'm going to follow up. Maybe something I've learned from Dr. Tuckson is to

now focus down a little bit more, and so, Dr. Mack, I think your vision of an individualized medicine is wonderful. We all talk about medicine becoming individually predictive and that's one of the real benefits of the genomic medicine, and you gave us some specific examples. I'm wondering if there are examples that you could think of that would have a high impact. If we look at the whole thing, it's too big for us to get our arms around. So where could we have major impact by developing some specific examples?

DR. MACK: Well, the first example that comes to mind is type I diabetes, where you have an extremely high correlation with a particular subset of HLA alleles, and there's a relatively easy way to test for your HLA type and you can determine the specific determination of risk. That is irrelevant with respect to race. In fact, I'm thinking about some data that we had on a study of diabetes in Mexican American populations, and we were able to determine the haplotype that particular diabetes alleles were on, and it's the sort of situation where you can give someone a kind of an individualized approach to their risk for a particular disease without really having to worry about other issues. So diabetes comes to mind, and there are a few other examples that we've touched on here, like cystic fibrosis, some of the beta-thalassemias, and sickle cell.

DR. McCABE: What about in pharmacogenomics?

DR. DESNICK: Well, that's where I think clearly we're going to have the advances because that's one that's easy and straightforward. We need to do a lot more research to understand allele frequencies, but I think if you consider that if every baby born had their genotypes for, let's just take one example, CYP2D6, every baby has ear infections and every baby's going to have decongestants and cough medicines, and there's probably one in 25 in this room or more frequent, depending on your background, who knows that when they take Sudafed, they get tingling and they get palpitations, and all you have to do is decrease your dose in half. But

babies can't tell you that, so the pediatrician's going to be able to know that because that information will be available, and that is not an issue that causes great ethical, legal, or social concerns because it crosses all barriers and it will be helpful to all babies. I think those are the ones that will come right away. In the meanwhile, I think we end up looking at groups -- you know, I thought it was very useful when it was pointed out that 86 percent of all the polymorphisms are public. Four percent are private. So when you look at the 3 million base pairs that are different between you and me, what you're really looking at is the variation that causes disease, and those are the ones that the SNP Project is going to focus on to find common disease, but I think what we're going to be able to do is to learn a whole lot more about how these things affect the general population, but at the moment, with limited resources and so forth, we're focused on more private populations and that's where our screening has been directed -- high-frequency disease, genes that are workable, counseling, and so forth – and I think at the moment, we're moving in that direction. Down the road, it's going to get personalized because everything's going to be mixed up.

DR. CARTER-POKRAS: Actually, there are two conditions that I can think of that would have a great impact. One is in the area of hypertension. When you were talking about pharmacogenetics. What came to me when we working together, Claudette and I, and working on the Office of Management and Budget's review of the Federal standards for racial and ethnic data, the director of Project RACE, which is a multiracial advocacy group, sent a pharmaceutical insert to me for a hypertensive drug, and she said, "You know, I've got multiracial children. When my children are grown, what level of this hypertensive med is this doctor going to give me?" Because it said if you're African American, then you essentially start the dosage at two or three times that of everybody else. So she was very concerned about that, the fact that the Food and Drug Administration has approved an African American-only clinical trial in regards to hypertensive drugs. This is an area that definitely we need some guidance.

So that's one thought. The other is the Deputy Assistant Secretary for Health Policy had mentioned to me the area of mental health. She's very concerned that we're going to learn a lot more about genetics and mental health conditions and that this has even greater concerns regarding stigmatization, and she feels like guidance is really needed in this area.

DR. McCABE: Yes, and that just points out one of the commonalties, and that is that race is a construct that is losing any relationship to anything that we're concerned about in the healthcare arena, certainly. And that even as we start talking about ethnocultural groups, we then are using artificial constructs there, and ultimately we will devolve down to the individual because it's difficult to really be predictive until we do that.

DR. BURKE: We have less than 10 minutes. We have actually about seven minutes. I don't think we have time for any other commentators. Please be brief, so that we can get everybody in.

DR. HUDSON: I, too, want to thank all the speakers for very clear and provocative presentations. I particularly want to thank Dr. Rotimi for highlighting some of the confusion and conflicting statements that are sort of circulating and swirling around us in the field of genetics and genetic studies. I did actually walk away with a little bit of confusion myself, and I feel like I periodically have a good grasp of this information and then I lose it, and then I get it again, and I lose it. Dr. Desnick, I heard you say that if the studies to try to identify the genetic contribution to breast cancer had been done in Jewish populations initially, that it would have sped up the identification of BRCA1 and BRCA2. And actually I agree with that statement, and then I heard Dr. Graves say that because of the genetic variability in African populations, that more genetic studies should have been done in African populations. Those two statements seem to be, at least on the surface, conflicting, and I was wondering if you could help me work through that.

DR. GRAVES: Okay. They're not really conflicting statements at all. What they have to do with is the way different types of populations can solve different problems. So first, attempting to identify the broad genetic variability in the human population, you would want to go to a population that has the broadest variability.

DR. HUDSON: Absolutely. Right.

DR. GRAVES: Now, specific genetic variants may have different phenotypes, may produce different phenotypes in the particular genetic backgrounds, as in the case of BRCA1 and BRCA2. Those genetic variants actually were not associated with increased early risk of breast cancer in a large study of English women, who have a different genetic background than Ashkenazi Jewish women. So his statement is correct. They were identified because of the specific genetic background of that population, and so they're not contradictory at all. What it is is we need to recognize what it is we are asking and what kind of population is appropriate for answering that kind of question.

DR. HUDSON: I think that's right. I think clarity and being able to say what we're seeking to find by specific studies in specific populations.

DR. DESNICK: When you're going to do a positional cloning project, homogeneity by descent is powerful.

DR. HUDSON: Is the key. Absolutely. I'm just pointing out that on the surface, those two statements, even to a sophisticated audience, can come across as confusing, and so we have a lot of work we need to do in order to communicate really effectively so that we make clear why some studies are appropriate in some populations and some are not, and I think we've got a lot of work to do here. I think the studies that Jean outlined are going to be really critical in that

regard.

DR. LLOYD-PURYEAR: I have a similar question, but I don't think it's duplicative, that you guys called for broad population mapping or engaging of populations very broadly in the mapping, but that many scientists, if I understand, who are involved in the HapMap Project think, and I may be characterizing this poorly, but that the sample from Utah – what's it called?

DR. BROOKS: CEPH.

DR. LLOYD-PURYEAR: CEPH. That that would be perfectly adequate to do the HapMap Project, that one doesn't really have to go out to all these other populations, because what we're talking about, if we're talking about common diseases, then we're talking about common diseases, we're talking about common mechanisms. I mean, it's similar to Kathy's question, and I think that's going to come up again. Can you address that? Because I think that's a basic difference.

DR. BURKE: And I apologize for this, but I just want to remind everybody, we have to be brief. We've got about three and a half minutes.

DR. BROOKS: Fine. I'll be very brief. I just want to point out, the haplotype map is a tool. It's just going to be a bunch of SNPs, and then there will be all sorts of studies, as I said, very carefully designed, comparing all different populations, environments, all that kinds of stuff. So don't confuse the HapMap Project as a tool development with the subsequent studies that will be used to associate variance in environment and disease.

DR. TUCKSON: Since in the interest of time maybe I'll have to ask for mine to be -- if I can impose on you to maybe send us something to this question, then I won't ask you to do it now,

and that is this. Two things. By the way, one, Dr. Bennett, if there's anything we can learn from your political experience – you don't have to answer now, but anything you can teach us politically. If we don't say race is all that -- you know, whatever you all got beat up from on the Census, teach us, so we'll know what to avoid or at least how to handle it politically, because you all got beat up.

DR. BENNETT: Yes.

DR. TUCKSON: Number 2 is how do we write advice to the American people in our booklet or report around what they should think about or protect themselves against when it comes to race and genetic testing? If it is Sudafed, does every American baby get pharmacogenomitized for Sudafed or only if it's marketed to you because you are an Ashkenazi Jew, you really want to get Sudafeded and the rest of you don't. Don't fall for that, dumb American. Deal with it like this, and here's what we're going to write in the booklet. We've got to write a booklet. It's got to have some stuff in it. Americans have got to get information because they've got to know how to make these decisions.

Number 2, similarly, the opposite is because of Dr. Desnick's presentation, it sounds like it's a really good thing for Ashkenazi Jews to know some stuff and that maybe everybody else doesn't need to know. You really do want to know what it is before you have a baby. It's very, very important. So here's a time where it is important, but it doesn't sound like it's going to be important for African Americans to ever have anything that's, above all, I want this genetic test. Gosh, darn, I've got to have it.

So I need you to help. That's what we've got to understand. Which times does it say because of what you are, you've got to have it, versus there ain't no time in which you ever want to be singled out because it's all a grab bag anyway?

DR. BURKE: I think what I'm hearing is a request for cogent examples, and again, in the interest of time, I would just ask humbly of the panel, if they have good cogent examples that will help us to craft educational messages, could you send them on to Sarah?

DR. DESNICK: I think the best response is that we have to educate the population about different diseases that they may be at risk for and let them make their own choices. I think that in the future people will get educated and we have to focus on educating them as much as we can, so that they are informed enough and educated enough that in the simplest way they can make choices about their reproductive and other futures.

DR. BURKE: Thanks.

DR. KOENIG: Following up on Reed, I'd like to ask Dr. Bennett and Dr. Carter if you could maybe start this process of helping us to avoid getting burned in the same way. Are there any guidelines that are absolutely needed for us to follow when we make suggestions about, as we're setting up a database with CDC for postmarket surveillance of genetic tests, what if we were to say, to try and deal with this important distinction about when race is important as a social construct, as opposed to when it's not useful as a marker for real biological or genetic variation, can we make those kinds of distinctions in the way we set up the database or will we be having problems with the minimal data set?

DR. BENNETT: I would encourage you to give serious thought to doing exactly that, making the distinction as to when race is in fact important for genetic reasons and when it is not important for genetic reasons, because what you've basically said since I've sat here is that as far as genetics is concerned, race doesn't matter, but you have to always remember in American society and you have to put things in the historical and cultural context in which they evolve. You also have to remember that you're dealing with individuals, and I would encourage

education. I would encourage training to your physicians not to make assumptions just because of a person's race, not to draw conclusions based on geographic concentration, because race in America is very geographically concentrated, and diseases are going to be very geographically concentrated because of the populations. So those are some things that I would encourage you include in your database. And I don't think that the Office of Management and Budget would in fact have any problems with that delineation in terms of when it should be considered and when it should not be considered.

DR. BURKE: Thanks very much. We'll let Judy make the last comment. We're out of time.

DR. LEWIS: I want to say that I really agree with Dr. Desnick around the idea that we have to do more and more of educating people and having people make decisions for themselves, rather than us making decisions for them. But the question that I have for the group is, as I chair our Access Working Group, looking at the fact that we've talked about a lot of variation, how much does access to care and access to services serve as an overlay to all of this and is that something that is incredibly critical? I think, more than anything, if you can't get there, it doesn't matter what we can give you when you get there, and any help that you all could give us in terms of figuring out ways to ensure that access isn't based on anything that is artificial would be really helpful.

DR. BURKE: And I just want to close by saying, obviously, we've barely begun a discussion, we continue to need your help greatly, and we hope that you'll be willing to continue discussion with us as we try and figure out what's the appropriate advice. Thank you very, very much for your time.

DR. McCABE: I also want to thank each member of the panel for your very important presentations to us. It really has helped to inform us, and we definitely would like any written

comments in response to Dr. Tuckson, and any other ideas that you have that have come out of this that could help us. Thank you very much.

With that, we will move on now to the public comment. I have two individuals who have been registered for public comment, Maria de Carvalho, representing the Oncology Nursing Society, and Katherine Schneider, president of the National Society of Genetic Counselors. So first we have Maria de Carvalho. If there is anyone else who wishes to speak from the public, please register. Please let Sarah Carr or the folks outside know. Otherwise, it will be these two individuals. We are running behind. I'd ask you to keep your remarks to three minutes or so, if you can. Thank you.

MS. DE CARVALHO: Thank you very much. I am representing the Oncology Nursing Society in giving commentary on informed consent for genetic testing and the role of advanced practice nurses in cancer genetic counseling.

The Oncology Nursing Society is the largest organization of healthcare professionals in oncology in the world with more than 29,000 registered nurses and other healthcare professionals dedicated to excellence in oncology care. We thank Chairman McCabe and the Secretary's Advisory Committee on Genetic Testing for the opportunity to testify today. We commend the SACGT for its thoughtful and timely consideration of all issues related to genetic testing and their continued exploration.

Genetic testing must be voluntary and conducted in conjunction with signed informed consent. ONS joins with the International Society of Nurses in Genetics, the American Society of Clinical Oncology, and the Task Force on Genetic Testing in advocating for informed consent for genetic testing. Standards should be set to specify the minimum information that must be provided to assure informed consent. Providing individuals with clear, concise, complete, and

standardized information is essential for informed decision making. In the interest of time, I will not read through the components of informed consent that ONS advocates, but direct you to our written testimony that includes these details.

Critical to the informed consent process is a dialogue between the patient and the providers in a joint endeavor to facilitate informed decision making and consent. This dialogue should occur at the level of language and comprehension of the competent patient and should be provided by a professional competent in both cancer genetics and oncology. There currently is no "tailor-made" professional to provide cancer genetic counseling services. The component of expertise in cancer care is as important as expertise in genetics with respect to cancer genetic counseling. ONS asserts that the provision of cancer genetic counseling is within the scope of oncology nursing practice. Since 1997, the Oncology Nursing Society has had an established position statement on the role of the oncology nurse in cancer genetic counseling. Healthcare providers who offer and order cancer predisposition genetic tests should have sufficient knowledge and competence in genetics, genetic testing, hereditary cancers, and cancer care to protect the well-being of their patients. ONS maintains that advanced practice nurses, such as those with master's preparation and those with specialized training in cancer genetics, are ideally suited for practice in counseling and education regarding cancer predisposition testing. Long-term management of patients at high risk for the development of cancer by those with an expertise in cancer prevention and management must be assured. Despite the use of advanced practice oncology nurses as part of the multidisciplinary team providing cancer genetic counseling services, certain insurers will not recognize oncology nurses as legitimate providers of such services. We continue to advocate that insurance carriers recognize nurses as competent providers of cancer genetic counseling. We encourage the Committee to propose the inclusion of nurses for medical provider recognition for reimbursement of genetic counseling services related to cancer predisposition testing.

We thank the Committee for the opportunity to provide commentary and look forward to future work which will assure that cancer predisposition genetic testing is accessible to those who need it and that those individuals are supported with the highest quality of counseling and professionalism. Thank you very much.

DR. McCABE: Thank you, Ms. de Carvalho.

DR. TUCKSON: Just one brief question. I want to understand, as we try to think about this issue across all the disciplines that -- by the way, I'm talking to you, but I can't – you know.

MS. DE CARVALHO: I understand that.

DR. TUCKSON: As we think about this across all the disciplines that want reimbursement for this, isn't, though, there a great variability in nursing education, even at the level of the oncology nurse, from school to school regarding these issues or is there uniformity and they all have certain numbers of courses that make this a consistent curriculum that provides a consistent expertise?

DR. McCABE: Judy?

DR. LEWIS: Maybe I can fill in a little bit of this in terms of nursing education, and my question to Maria was going to be on terms of a number of advanced practice nurses who are so credentialed, so maybe you can think about that while I'm saying this. But nurses, there are national certification exams that have standards, and that if you pass that and you become certified, like a certified oncology nurse or a certified nurse practitioner, then you have met standards that have been set for the profession and it's quite similar to board certification in the medical specialties. So I would argue that irrespective of the school you go to, the schools are

all credentialed, but it's the national certification exam that sets the standards for people who are competent to provide that level of care.

DR. TUCKSON: But is that in genetics?

DR. McCABE: Yes. That was what I was going to ask. Does the certification exam include genetics?

DR. LEWIS: Yes, and it would be certified as an oncology nurse, and then within that people would be appropriately credentialed, but the state, in terms of reimbursement, what they're looking for is that certification piece.

MS. DE CARVALHO: Yes. There are a variety of different kinds of certifications within nursing, and certainly within oncology nursing there is a basic certification and then there's an advanced practice certification, and actually I'm an advanced practice oncology nurse myself, and now, within genetics as well, we also have credentialing services within the International Society of Oncology Nurses. So we do have credentialing processes which do provide that there is certain expertise and certain expectations of oncology nurses or nurses in general that are able to provide this kind of care because of time within, that they have shown a certain expertise within the kinds of clients that they have seen, as well as with continuing education, as well as certification in terms of testing.

DR. TUCKSON: Well, Mr. Chairman, I think on this issue, I don't want to single out the one discipline, by the way. It's a generic question, but given that this is coming up over and over again around this reimbursement of genetic counseling, I think we're going to need, if we do not have now, some sort of a common template that says what should those who are being asked to pay for these services, how do you know who's qualified to provide the service and

how do you think through that, because everybody – first of all, not only in terms of providing it, but how should an informed patient or consumer make a choice about who and where they get their counseling?

DR. McCABE: Judy, brief comment, and then we're going to have to move on.

DR. LEWIS: I think it's very interesting that we ask these questions of the allied health professionals, but we don't necessarily ask them in terms of other communities. For example, I know that in order to prescribe drugs in Virginia, I have to have special certification and the pharmacopeia is limited and I can only prescribe certain schedule drugs, but in Virginia it's okay for a pediatrician to prescribe medication for a patient with Alzheimer's disease. So I think if we're going to do this, we need to do it for all disciplines and not just for the allied health professions.

DR. TUCKSON: I would say that across the board. I agree with you. I agree.

DR. McCABE: Thank you very much, Ms. de Carvalho.

MS. DE CARVALHO: Thank you very much.

DR. McCABE: The next presenter is Katherine Schneider, president of the National Society of Genetic Counselors.

MS. SCHNEIDER: I have planned comments. I also would like to just take one second and respond to the conversation that just happened. Representing the National Society of Genetic Counselors, we are very concerned about the lack of reimbursement for genetic counseling services and I think we need to spend more time fixing that, rather than singling out which

provider is best suited.

DR. TUCKSON: Okay.

MS. SCHNEIDER: I am currently president of NSGC, the National Society of Genetic Counselors, which represents nearly 2,000 genetic counselors in an array of medical specialties and is the leading voice, authority, and advocate for the genetic counseling profession. We commend SACGT on its accomplishments to date and appreciate the opportunity to comment on the committee's continuing activities. At this time, I would like to raise three points.

Point 1. Quality assurance measures for genetic tests should include genetic counseling. Patients and families have the right to expect that the correct genetic tests have been ordered, specimens have been sent to the appropriate laboratories, tests have been performed correctly, and test results have been interpreted accurately. While the majority of discussion yesterday focused on the importance of quality assurance measures for the laboratory analysis, it is equally important to ensure the high quality of the pre- and post-analytic phases of testing. As a quality assurance measure, this Committee should send a strong message advocating the importance of genetic counseling during the testing process. Genetic counseling is critical for assessing patients' risks, determining whether genetic testing is indicated, describing limitations and implications of testing, selecting appropriate laboratories, and interpreting the test results. In essence, genetic counseling is a key part of providing appropriate oversight for genetic testing. The subtle nuances of reduced penetrance and variable expressivity complicate the clinical implications of positive or negative test results and require providers who have a firm understanding of basic genetics. Genetics specialists are therefore the logical providers for being responsible for arranging complex genetic tests and discussing the clinical implications of test results for patients and their relatives. Concerns have been raised about the shortage of genetics professionals, and this issue must also be addressed, including strategies for educating non-genetics specialists and primary care providers regarding appropriate genetics referrals and

available genetics resources. Innovative strategies for provider education will need to be employed. For example, at the annual endocrinology meeting to be held in June, the American College of Medical Genetics, with assistance from NSGC, will be hosting a creative interactive program of genetics education and counseling.

Point 2. Clinical genetics research needs to be encouraged and supported. Patients found to carry specific germ-line mutations invariably ask their clinicians, "What does this result mean?" The only way to truly answer questions about genotype/phenotype correlations, as well as questions about appropriate management, is through large-scale cooperative research studies. NSGC strongly believes that such studies will provide valuable information for patients and families. Thus, genetic research projects should continue being encouraged and supported, including studies on the ethical, legal, and social implications of testing.

As a separate issue, clinical genetics researchers need clear guidance on how to protect each family member's right to privacy while being allowed to gather the medical information needed for family studies research. Pedigree and linkage analysis studies, cornerstones of clinical genetics research, are becoming increasingly difficult to undertake because of concerns about individual family members' rights to privacy. Yet these studies are critically important in our quest to characterize rare genetic syndromes and to provide optimal care to families. It was gratifying to read the draft documents on third parties and human subjects research prepared by the National Human Research Protections Advisory Committee and the NIH Office for Human Research Protections. Members of NSGC with expertise in clinical research are available as a resource to help with further discussion and resolution of this issue. And, of course, having sufficient privacy protections in place on a state and Federal level is also important.

Point 3. Race and ethnicity in genetic research and testing. As we have heard in today's discussion, the distinction of race and ethnicity in the field of genomics is debatable. However,

in clinical genetics studies, the use of diverse populations is critical. Ethnicity may influence the rates of detection of specific strong gene mutations and the severity of phenotypes, such as in the case of cystic fibrosis, and the use of diverse populations is also important in research projects studying attitudes, knowledge, and behaviors around the use of genetic test information. The successful recruitment of non-white populations into clinical genetic research studies will have two potential benefits. One, study conclusions will more accurately reflect the rich ethnic diversity within the United States, and two, inclusion in such studies may pave the way for an improved dialogue between the genetics community and various ethnic groups. Some ethnic groups' past experiences with genetic research have made them suspicious and reluctant to participate in genetic studies. It is important, therefore, for researchers to be sensitive to these past experiences and recognize potential barriers to participation. Successful recruitment of diverse populations will depend on having researchers who are familiar with the views of ethnically diverse groups, including alternative views on health, illness, the role of medical providers, and even the decision-making process. Thus, SACGT should include issues of diversity training in educational efforts targeted to both researchers and clinicians.

In closing, the National Society of Genetic Counselors enthusiastically supports the efforts of your Committee. Thank you for your time.

DR. McCABE: Thank you. Any questions or comments for Ms. Schneider?

DR. McCABE: If not, thank you. Our next topic is discussion of FDA's progress in the development of premarket review of genetic tests. We heard yesterday that Dr. Gutman really can't tell us a whole lot, that it's under legal review, and so I would just like to go on the record stating that SACGT requests that FDA expedite the review of our oversight recommendation or, in the absence of the ability to expedite the process, then provide SACGT with a more complete explanation of what the issues and barriers are, and we would appreciate having that

as soon as possible and definitely before the next meeting, Steve. So, thank you, and we understand that you're merely here sitting at the table, that you're not the problem with this.

DR. McCABE: But thank you for taking that message back to FDA for us. Any other comments on that before we move on?

(No response.)

DR. McCABE: We're going to briefly discuss the expected topics at the May 14-15 meeting and see if there's any input on those topics from the members of the Committee, and then we're going to ask Kathy Hudson -- maybe, Kathy, while we're booting up over here, you could give us some discussion of what's happened on the Hill.

DR. HUDSON: Sure. I'd be happy to. Yesterday, there was a hearing of the Health, Education, Labor, and Pensions Committee in the Senate on genetic discrimination, and it was a really positive hearing from my perspective. It was standing room only in the hearing room. A significant number of senators were present at the hearing. Senator Hillary Clinton chaired in Senator Kennedy's absence. Senator Jeffords was there, Senator Gregg, and Senator Enzi.

I think the importance of this particular hearing was that since June, when the President made his radio address on genetic discrimination, there really has been no clarity in terms of what the Administration would support with respect to genetic anti-discrimination in health insurance and employment. We knew that the administration was against it, but we didn't know what the specifics were, and what happened at the hearing yesterday was that the chairwoman of the Equal Employment Opportunities Commission and the Assistant Secretary from the Department of Health and Human Services, Bobby Jindal, both testified and articulated, I think very clearly, where the Administration will support legislation, and they made six basic points

which I think are fairly consistent with the recommendations that the Secretary's Advisory Committee has made. So we'll sort of see where we go from here. This is the first time I think that across the board everyone was sort of singing from the same song sheet, so I think there's some renewed optimism, although we have been charged with saying that before.

DR. McCABE: Thank you very much, Kathy, and maybe if you can keep us apprised. If things are happening that we ought to know about, you could let Sarah know and she can get it out to everyone. Thank you.

So the sheet in front of you is up on the screen. Obviously, we're going to begin the May meeting -- just to remind everyone, it's May 13 to 15 at the Hyatt Regency in Maryland. The first day will be devoted to the policy conference on *Genetic Testing and Public Policy: Preparing Health Professionals*. So we need to definitely review what has happened at that May 13th meeting. The next topic would be review of the Access Work Group's paper on the need for changes in reimbursement policy for genetic counseling and education. That came up here today, and certainly seemed to have a consensus that reimbursement is important, that that drives policy. Does anybody have any objection with that being on the agenda?

(No response.)

DR. McCABE: Reporting out of the Rare Disease Work Group's white paper and recommendations regarding education of laboratories on CLIA certification requirements. That's a follow-up to the November meeting and to this meeting, so that would seem to make sense.

Discussion of the public comments on the SACGT's information brochure, *Some Basic Questions and Answers About Genetic Testing*. And that will be going out for public comment

very soon, so there would be time to get that in. We could have those summarized. Discussion of the proposal for the HHS strategic plan for genetic technologies and, if warranted, an HHS agency coordinating committee, and we talked about the positives and negatives of a coordinating committee here, but it seems like that would be appropriate for follow-up.

Report from the Data Work Group on case studies on the continuum of the development and successful application of a genetic test that we talked about yesterday. You think that's doable between now and then?

DR. BURKE: We will certainly have something to report.

DR. McCABE: And Sarah added one that's on the screen and not on my sheet, a follow-up on data on race and ethnicity issue. That certainly sparked a lot of discussion. Yes, Wylie?

DR. BURKE: Obviously, we're nowhere near done talking about this. I think we're still just beginning to get our arms around it. I wanted to ask whether it would be helpful to think about inviting our panelists back to be part of that conversation. I felt like there were lots of questions people wanted to ask and even answers they wanted to give that we weren't quite done with.

DR. McCABE: Anyone have any objection to that?

(No response.)

DR. McCABE: Certainly, the panelists were extremely informative and it would be good if they could be a part of that discussion to the extent possible.

DR. PENCHASZADEH: I certainly endorse that, but probably there should be a second stage in that. You know, perhaps analyze particular studies or case examples that would give more meat to discussion, because otherwise we're keeping the generalities of the gene environment and so on.

DR. BURKE: But a sense I had, and you guys should tell me what you think, is that we were all feeling a little muzzled. In other words, I'm sure there is lots of specific additional information we'd like to have. I'm wondering if maybe the next phase of it is more open-ended discussion where we get to clarify and maybe then clarify what data will be most useful to us.

DR. LEWIS: I'm wondering if maybe, rather than in a forum such as this -- and it may not be possible to do in May. We may need to wait to August -- if we have one of those half-day roundtables where we can have more of a working type of opportunity with both the people who presented today and some of the people who have worked with the Access Group to start informing some of the issues, so that we have even more of a diverse group than we had today. But I think the framework -- when you give people 15 minutes to present, it's really hard. So we never end up with enough time for discussion. So if we could have more of a free-flowing discussion with some goals and objectives maybe a half day before our meeting -- and I know we're booked before our May meeting, but that's why I was thinking maybe in August to do it, so it has time to do justice to it.

DR. McCABE: Yes, except I would agree with Wylie. I don't know what we would ask for in such a meeting at this time. I think that it would be helpful to invite the panelists back, have a longer discussion than we were able to have today built on what we learned today, and then use that to decide should we go to a roundtable discussion in August.

DR. BURKE: Get how to focus it.

DR. LEWIS: Okay. I think both would be good.

DR. BURKE: Yes.

DR. CHARACHE: Well, along those lines, I'm just wondering if we can frame up, and perhaps send to Sarah, some of the questions we have. I mean, one of the challenges is going to be to relate this body of information to our charge and to the various working groups' material that's being prepared. Again, I agree. This should be more free-flowing, but if we can have some concepts outlined, it may be helpful.

DR. McCABE: Okay. So send your ideas and your questions to Sarah, she'll circulate those, we will work on them by e-mail, narrow them down, and help focus the discussion.

DR. BURKE: It sounds to me, Pat, like what you're saying, and I strongly endorse it, is we need to keep our attention focused on what's an appropriate role for SACGT. How does this translate into ways in which advice from this Committee could be helpful?

DR. CHARACHE: That's exactly what I'm saying, because I can see lots of perspectives in which we have to decide how we're going to use this data.

DR. McCABE: Thank you. Then final issue, Number 8 on the screen and Number 7 on your sheet, is a roundtable on the history of the development and implementation of the CF population screening guidelines. These were the ones described from NIH, ACOG, and ACMG, and the laboratory and education counseling components. It'll be another loaded session, a loaded two days, but all important topics. Any of these that people feel are not important and we should prioritize to a later meeting?

(No response.)

DR. McCABE: We'll try and see if we can get them in?

(No response.)

DR. McCABE: Okay. Good. Sarah will work her magic and get them all into the two days' agenda. I want to thank Sarah and Susanne Haga and Suzanne Goodwin again for organizing the meeting. Have a safe trip home and we'll see you in May in Baltimore.

(Whereupon, at 2:48 p.m., the meeting was adjourned.)