SECRETARY'S ADVISORY COMMITTEE ON GENETIC TESTING

Eighth Meeting

Thursday,
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Conference Room 6C-10
Building 31
31 Center Drive
National Institutes of Health
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 (9:12 a.m.)

DR. McCABE: Good morning, everyone. Good morning, Pat. Welcome to the 8th meeting of the Secretary's Advisory Committee on Genetic Testing. The public was notified about this meeting through an announcement in the Federal Register on January 26th and a posting on the SACGT's Website. We appreciate the public's interest in our work and welcome hearing from members of the public in attendance during the comment period this afternoon and tomorrow morning. There is a sign-up sheet on the table outside for individuals interested in providing public comment.

Before we begin, I want to introduce a new member of the Committee, Dr. Irene Stith-Coleman. Dr. Stith-Coleman is currently senior public health advisor to the Assistant Secretary for Health, and she is here today for Dr. Greg Koski, director of the Department's Office for Human Research Protections. Dr. Koski was recently appointed to serve on SACGT, along with the six other non-voting agency members, and Dr. Stith-Coleman is serving as Dr. Koski's alternate today.

Although our principal focus is on genetic tests that are already in clinical or public health use, we have made some recommendations about genetic testing research, and we clearly have an interest in addressing genetic testing issues that arise during the research phase. The addition of OHRP to our roster will provide us with expert technical and policy information on the protection of human research participants, and will ensure coordination of mutual areas of interest between SACGT

and OHRP.

Dr. Stith-Coleman will also be attending the meeting tomorrow of the Work Group on Informed Consent and IRBs, and wearing her other hat, she will be presenting to the Access Work Group on the Department's health disparities issue.

Dr. Stith-Coleman, welcome, and thank you for being here and for your participation in our work group activities.

SACGT received a positive response from former Secretary Shalala to the recommendations we made in our report on enhancing the oversight of genetic tests. A copy of the Secretary's letter is at Tab 2 in your briefing book. We are very pleased that Dr. Bill Raub, Acting Assistant Secretary for Planning and Evaluation, is here this morning to review the Secretary's response with us and address any questions we may have about the Department's current plans for implementing this program of enhanced oversight.

In light of the significant role that we recommended for FDA in enhanced oversight, we will be hearing from Dr. David Feigal this morning about FDA's plans for establishing innovative review processes for genetic tests. We will be updated at a later meeting on other agency activities, such as CDC's data collection initiatives.

After Dr. Raub's and Dr. Feigal's presentations, and before we move on to the additional work of the meeting, we are going to hear a presentation from Dr. Francis Collins on the initial analysis of the human genome sequence. As I'm sure you all know, this week marked another extraordinary milestone in the human genome

project with the publication of the sequence and initial analysis, and we are delighted that Dr. Collins has agreed to review some of the more significant and surprising findings with us today.

After Dr. Collins' presentation, we will begin our discussion of the classification methodology. We will spend most of today's meeting on that topic, with some time set aside for public comments and an update from Dr. Pat Charache on the activities of CLIAC. Tomorrow we will focus on finalizing the proposed genetic test information template for health professionals. We have abbreviated the length of our full Committee meeting by two hours on both days to take time for four work group meetings, and we will be hearing progress reports from these work groups tomorrow.

I also want to report that since our last meeting I briefed FDA, AHRQ and OHRP about our oversight recommendations and future plans. These were very productive meetings, and I hope they were useful to the agencies as well in enhancing awareness of our priorities and the future directions as a Committee.

At our meeting in November, we agreed to take two actions: first, to express concern to the Secretary about gene patenting and certain licensing practices, and the need for additional assessment of the impact of these practices on access, cost, and quality of genetic tests; second, we agreed to recommend that the National Human Research Protections Advisory Committee, NHRPAC, conduct a review of current federal policy regarding the regulatory requirements for informed consent of family members of primary research participants. Copies of correspondence on these two

issues are included in Tab 5 of your briefing books.

Before we turn to Sarah for her important reminder about ethics rules, I have one final item to mention, a conflict of interest disclosure. On January 1, 2001, I assumed the presidency of the American College of Medical Genetics. I have been authorized by HHS ethics officials to participate in all matters that are of general interest to ACMG. However, federal law prohibits me from participating personally and substantially in specific matters affecting ACMG. Should a specific matter affecting ACMG come before us, I will recuse myself and I will ask Dr. Wylie Burke to stand in for me as chair.

This concludes my opening remarks, and now Sarah will review the rules that govern all of our conduct during the Committee meeting.

Sarah?

MS. CARR: Thank you.

These rules are very familiar to you. I always remind you of them, and I appreciate the time that you let me do that. I only will mention one today, and that's on conflict of interest.

Before each meeting of the Committee, you are asked to provide us with information about your personal, professional and financial interests. This information is used as the basis for reassessing real or potential conflicts of interest, or even the appearance of such conflicts that could compromise your ability to be objective in giving advice during meetings of this Committee.

If you are found to have conflicts, waivers can be granted because the need for your advice outweighs the potential for a conflict of interest created by your interests. Most of you have been granted waivers for general matters. If a specific issue comes up during a meeting that could affect your interest specifically, you have to excuse yourself from the room and from participating in the discussion.

If you have any questions about the rules of conduct or conflict of interest, please see me or our committee management officers, Ms. Claudia Goad and Ms. Mary Nuss. They'd be happy to help. We're all happy to help answer any questions you have.

DR. McCABE: Thank you, Sarah.

Again, thank you to Sarah and her staff for all the work that they carry out for the SACGT.

At this time, I want to welcome Dr. Raub back to the Committee. In addition to serving as Acting Assistant Secretary for Planning and Evaluation and being science advisor to the Secretary, Dr. Raub chairs the HHS Interagency Working Group on Genetic Testing, which is composed of agency representatives and officials in the Office of the Secretary. The working group formulated SACGT's original oversight charge and was responsible for reviewing our recommendations.

In other words, Dr. Raub is substantially involved in the continuum of policy development for the Department in this area, and we are very pleased that he could be here today to discuss Secretary Shalala's response to our report and the current

status of the Department's plan to implement a program of enhanced oversight of genetic tests.

Dr. Raub, thank you for coming, and welcome.

DR. RAUB: Thank you, Dr. McCabe.

If I may, I'll use the podium, and I have a few view graphs. As a sign of my generation, I haven't quite learned to trust PowerPoint, but I have moved beyond the stone tablets.

It's a pleasure to be here. As I was saying to Dr. McCabe before, there's a sense of closure of one phase and moving on to another here, a satisfaction we don't often get on some complex topics. We've come through I think a very exciting and a very important period where some important challenges and issues got articulated. This group addressed them in a very disciplined and forthright way, and it has given the Department the opportunity in turn to respond to your recommendations in a way that I keep thinking will move this ball down the field.

As indicated by this view graph here, you all know this intellectually, but I always find the graphic helps. Genetic testing is what we euphemistically refer to as a cross-cutting issue. That means it doesn't live happily or comfortably in any one of the agencies, even though every one of the agencies involved here has a substantial role in it and it's an integral part of each agency's mission.

For things to happen for the collective of the Department, it means a continuing and effective interaction among the representatives of these agencies,

keeping in mind all the time the mission and restraints and resource limits under which they work, but also stepping back and understanding the needs and opportunities that their colleagues face, and the challenge that the Department overall faces. Today I express my gratitude to the members who served on this group, my colleague, Lily Engstrom, who has been our anchor in the Office of the Secretary, and the privilege of being able to work with this group, and the expectation of further continued productive interactions with them.

As this group considered the recommendations of the earlier task force, sponsored by the genome program, and looked at various strategic directions, it seemed in principle that we had three extant legal authorities within which we could do a lot if we could find a way to do it in a coordinated way. I recall in an early briefing for then-Secretary Shalala saying, "Our strategic approach, Madam Secretary, is that we'll all hold hands and step into the traffic together."

In many ways, the charge that came to the SACGT was an embodiment of that, and from my perspective, and I know Secretary Shalala's and others', you all responded beautifully by not buying that automatically but by keeping that in mind and coming back with a framework that takes advantage of those extant authorities and gives us a way to move within them; but again, with your emphasis on doing it collectively and collaboratively.

As we move to implement the recommendations from the Committee, we see three overarching principles guiding this. One is, to the extent feasible, to apply

systematically the methodology for classification that you've been addressing and that we look forward to continuing to mature as you consider it. Second, to give renewed emphasis to the requirement for informed consent for research associated with the development of genetic tests where individually identifiable human subjects for samples are involved.

Third, as we address our approach to oversight, following your lead to cover both the home brews and the genetic test kits. I hasten to say that cover them doesn't necessarily mean to do it in one-size-fits-all, do it uniformly, but rather we also will be mindful of your challenge to us to be imaginative, to be creative, to let the circumstances shape our approaches.

On the second bullet here, as just one small but important example of how the interaction of these pieces comes into play, as protocols come before institutional review boards, there is an easy and straightforward opportunity to ask for assurance that the CLIA certification is in place for the laboratory in which this work is based. If that happens not to be the case, there is a relatively straightforward process triggered to get the CLIA certification. We see this IRB process as one additional help in promoting the compliance with the CLIA activities, and that's especially true with a number of the relatively small academic-based laboratories, many of whom don't necessarily know that they really should be certified by CLIA, and here's an opportunity, if we design the system and the timing right, to help promote that compliance.

Starting with the Health Care Financing Administration, and this is

spelled out in Secretary Shalala's letter, HCFA will be moving to identify and register all laboratories providing genetic test results to patients and/or providers, in keeping with its responsibilities. Further, it will move to develop new surveyor guidelines with respect to these methodologies, and training surveyors in what is a new modality for many.

Further, there will be the conduct of educational efforts, in collaboration with the CDC, FDA, and most importantly, outside accrediting organizations and professional societies. Last but not least, developing, again with CDC, new CLIA regulations as needed for the expanded oversight of genetic testing laboratories.

Much of what has strengthened this effort, in my judgment, has been the effective partnerships between public and private entities, and we see here just another instance where it is much in the interest of the Department, and we believe the society at large, for that style to continue.

For the Food and Drug Administration, plans to require manufacturers to register with FDA and to list their tests, the foundation of moving to the type of expanded and tailored oversight that this group has recommended. Working with professional organizations -- the CDC, HCFA and others -- with respect to the development of the premarket data templates and the standards. Investigating the feasibility of using the classification methodology, as recommended and as evolving under the tutelage of this group. And last, but again not least, developing process for

the premarket review of tests and ensuring their accurate labeling. Here is where the challenge for creativity and tailoring very much comes into play.

For the Centers for Disease Control and Prevention, the development of voluntary integrated systems for the collection and dissemination of data on genetic tests. This involves the development and the refinement of appropriate standard templates for data collection, the creation of a pilot database, the collection, dissemination and analysis of information on the analytical and clinical validity and clinical utility of a broad range of genetic tests.

I've had the privilege of working with Dr. Khoury and his colleagues as they have nurtured this idea along, an extremely difficult challenge. The group, as many of you know, chose to focus in two areas initially, one on cystic fibrosis, and the other on hemochromatosis, taking advantage deliberately in the one instance of a fair body of activity in commerce with respect to testing, and in the other not only an important genetic disorder but the prospect of a major study and data collection effort funded by the National Heart, Lung and Blood Institute.

I think many would say these two are not the typical ideal example in the sense that most of the world won't have the advantages as that proceeds, but it gives a base on which some of the fundamental ideas about what kinds of information about the tests ought to be collected, gives some reality check, but also helps to steer what kinds of actions should occur in the future. I very much compliment Dr. Khoury and his colleagues for their persistence and taking on a very challenging task. It's one that this

group has discussed before, and I'm sure we'll discuss it again as this plays out.

That's it. Okay, thank you. I'll have the lights down, please.

Looking at this from my perspective as somebody who makes his living as a strategic planner, it seems the challenges going forward here for us, given the recommendations you've given us and the positive response from Secretary Shalala, is at each time along the way, have we got the right vector direction for this. And if we have, have we got the right objectives, and have we got those objectives sequenced in the right way? If so, are we going about all this at about the right pace?

Some of you will recall that a little over a year ago, Representative Morella held a hearing on genetic testing. Dr. Watson, Dr. Collins and I were among the witnesses. The general thrust of that hearing, as I recall it, was sort of how are we doing? It wasn't an oversight hearing, it wasn't a budget hearing. It was more a look at the state of play, and each of us gave our own perspective. I think each of us in our own way signalled where we weren't completely happy with some things, where we saw more that needed to be done, but by and large we also felt some satisfaction about the progress.

One of the Congressional staff later summarized that hearing as saying, yes, that's about right, that overall, things seemed to be moving the way they should and about the way they should with about the right degree of discipline.

That was comforting then. It shouldn't lull us into comfort now that we've got it right. So I think a continuing challenge for our staff group and for this

Committee, together and individually, will be asking ourselves from time to time that set of questions, being sure that this extraordinarily important but also very difficult effort will stay on track.

Also, from the perspective of a planner who tries to get the things implemented, there are some things we need to keep in mind. I mentioned before that our agencies involved have different missions, different traditions, different requirements upon them, and different priorities. So there is very little in the natural set of forces that bring this together. On the contrary, most of the natural forces will tend to pull these elements apart. So a continuing challenge for our internal group and for us interacting with you will be to be sure that the collective view and the interactions continue to come into play.

An analogous thing holds with the Congress, especially as we seek the resources that this will require. For good reason, the practice of the Congressional appropriations committees is to take one agency at a time, and often even one component of one agency at a time. Most of our agencies represented here are under what is in shorthand called the Labor HHS Appropriations Committee -- CDC, HCFA, NIH, HRSA, AHRQ, and the Office of the Secretary. But even there, the hearings will be on different days, different members will have particular interests in different components, and we have a special challenge to get across the integrated view of this so the committee members, in assessing budget requests, can understand some of the interactions.

With our colleagues at FDA, it's even harder, because the FDA appropriations flow through the agriculture committees, another set of considerations in a very different context. The Congress has its own good reasons for doing it that way, and I'm not complaining about it, but it's the fact that we need to work harder at getting across the larger representation here.

I also don't offer this as an advance set of excuses as to why we might fail on some of this, but rather it's the reality that has to be faced, why things are usually harder than they seem to be, and certainly they're always harder than I think they're going to be when it starts. But it's that kind of consideration we will put ourselves to.

Let me close with answering the question you haven't asked but I expect is on your minds: Will things be different with a new administration? If I told you I knew for certain, I'd be lying. We're about 10 days in and counting. We have a vigorous new Secretary who says he's passionate about research, and he certainly evinces that in his interactions with many of us. He's very straightforward, very hands-on in the issues, and he's clearly intent on being a vigorous and activist promoter and manager of the programs in the Department.

With respect to genetic testing, the challenge we faced in the last administration was how do we protect patients and promote public health while fostering the technology, fostering its development both publicly and privately, fostering its validation, and fostering its appropriate use and incorporation into medicine. In the last administration, it never was a question of either/or, and I feel confident that with

Secretary Thompson it will not be a matter of either/or either. His style will be: "Give me both."

I think the challenge will fall to the agencies to be sure that we keep our eye firmly on both of those issues, and as we shape budgets, as we shape strategies, make sure that every step of the way we're paying attention to the patient and public health issues, but we're also paying attention to fostering this extraordinary technology that the genome project and other parts of the biomedical research community have put at our disposal.

I'll be glad to respond as best I can to comments or questions that you might have.

DR. McCABE: Again, thank you very much, Dr. Raub, for coming this morning.

Are there questions for Dr. Raub?

Yes, Reed?

DR. TUCKSON: I couldn't help but notice several times in the letter, and re-emphasized in your presentation, about the term "to the extent feasible," "to explore the feasibility of." Is there a message that we are getting from HHS in those words? Are you telling us that you are concerned that the classifications that we have offered are cumbersome, too bureaucratic, too difficult? Are you saying you want us to be sure that something does not happen? What's underneath these words?

DR. RAUB: Good question. If we thought any of those things, I

think we're obliged to tell you, and we're not. That is, we're not saying that, not that we're not telling you that.

I think it's more the caution that many of us have learned over the years, that things often have ramifications that we don't expect. Let me give you one example. In addressing the issues of both home brews and packaged kits, a number of members of the industry not working in the genetic testing arena have legitimately raised the question what does it mean for other kinds of home brews? What will actions in Area A mean for actions in Area B, C, and D? They don't have to be the same, but we better think of the question and have a rational approach to it. At least today I'm not so confident that we would know every one of those ramifications until we begin to explore it.

In another area, my colleagues and I are actively involved in the preparedness for bioterrorism. One of the themes in preparing for bioterrorism is to do more with rapid diagnostic devices. Some of those are home brews. Some of those are, in the jargon of the military, forward deployed into some major certified public health laboratories. That forward deployment usually takes the form of a kit. We don't have any commercial manufacturers for those kits, and are not likely to have any. So these will be government efforts, not commercial, but in the strict reading of FDA statutes and regulations, manufacturing, and finding ways to ensure that we can meet the letter and spirit of those requirements in that area in a way that's consistent with what we do in genetic testing is a particular challenge.

More than once, where I thought we had something solved, one of the legal counsels from one of our agencies said I hate to tell you this, but there are six court precedents on a related issue that affect how we implement this statute. So we have to take those things into account. So I hope you would read no more than from the "as feasible" than some experienced staff who have got the scars from previous efforts and wanting to ensure that we don't promise you something we can't deliver. But clearly, if there were a fundamental dissatisfaction in any way with what this group is recommending, I think integrity and our working with you requires that we be forthright about it.

DR. TUCKSON: And a real quick second one, in terms of not knowing what's going to be happening with the new Administration and so forth, there are a lot of things on people's plates. Is there any need for us to send any specific or particular letter to the new Secretary, and particularly to whoever is going to be the ASH under this new arrangement now that Dr. Satcher will probably be doing a more limited role, although an important role as the Surgeon General, to keep our issue in front of them? Or is it not necessary at this point?

DR. RAUB: My view is it's not necessary, but it's desirable. We have a Secretary who likes to be involved. With all due respect to our staff, he likes to hear other perspectives. I think whenever this group feels that the time is appropriate from its point of view to make its interests and priorities and concerns known, I feel confident saying he would welcome having that.

DR. McCABE: Ann?

MS. BOLDT: I was trying to recall what we had said in terms of the postmarket data collection, that laboratories should do that. For the CDC, you talk about a voluntary system. Could you address why it's voluntary versus more of a mandatory type of thing?

DR. RAUB: My colleagues may want to respond to this as well. The initial step here is recognizing that going beyond voluntary means, by definition, regulatory actions, more likely regulatory actions by FDA rather than CDC. So rather than load another one onto the plate of FDA, and not having fully explored the voluntary efforts that are underway and that have been discussed previously by this Committee, strategically that seemed to be the place to start.

Muin may want to speak to that more, or David.

DR. KHOURY: No, I think you summarized it nicely. I mean, that's where we want to start.

DR. McCABE: Yes, Pat?

DR. CHARACHE: I'm wondering if there are some efforts being made to consider the added resources required to meet the recommendations which have been made. I'm thinking particularly of HCFA, if it has to go in and register and review a couple of thousand academic laboratories, and their only funds come from the labs they review. We don't want to burden these small research facilities with that kind of funding, and also FDA which, clearly, if they get into the home brew area, is going to

need resources.

DR. RAUB: Much of the caution in Secretary Shalala's letter is around the uncertainty about resources, just how much and just how fast. Not only was that caution on her part not committing a successor, but even if we were in the middle of her term, you probably would have heard the same set of cautions.

In a nutshell, every agency head is faced with a set of choices. We're now in the middle of a budget development process for fiscal year 2002. It should be early in April, if the schedule holds, that the first budget of the new Administration will be manifest. As part of that drill, as in previous years, each agency has a mark in terms of a top-line number that the President will go forward with. There are likely to be, as in the past, various emphases, or even earmarks, associated with that in terms of things that are priorities for the Administration. Within that set of choices, each agency head must find a way to get the right set of priorities to go, recognizing that not everything desirable will go.

Even NIH could spend more money intelligently than it has, and that's true multiple times over for a number of the other agencies that have had much more constricted budgets.

A challenge for our staff group, those more so than me, but those in the agencies who know best what the challenges are and what these issues are, is getting those repeatedly in front of the leadership of the agency to be sure those tradeoffs can be made. Again, I'd be lying to you if I said, oh, no problem, the resources will be there. I

like to think that the clarity of your recommendations and the credibility of your recommendations give us a quality of argument that we wouldn't have had without it, and we'd be foolish if we didn't try to use it in every place that we could.

DR. McCABE: Barbara?

DR. KOENIG: Thank you very much for your very helpful report. At the beginning you mentioned that three principles would guide your implementation in the Department of our report, and the second principle that you mentioned was the issue of informed consent for research with identifiable subjects, populations, tissue, whatever. I'm wondering if at this point you could say something about the Department's response to other efforts to guide you on the informed consent issue and human subjects protection in general -- for example, from NBAC -- that would guide us over this two days as we begin to think more specifically about informed consent issues for genetic testing.

DR. RAUB: Are you referring in particular to the NBAC report on human biological materials?

DR. KOENIG: Right, exactly.

DR. RAUB: In a parallel effort anchored in my office, with a major role from my colleague Lily Engstrom, and Carol Greene, who is also here, an interagency working group has gone through and addressed every facet of the NBAC recommendations. We're now close to a final version of that, of a consensus view within the technical staff in the Department, and we're planning to submit that to the

agency heads for their review and action, and we hope within a matter of a couple of months, realistically, to come back not only to NBAC, to whom we owe a response, but to the world in general saying this is how the Department of Health and Human Services collectively views the recommendations of NBAC.

As in a similar NBAC report on individuals with impaired decisionmaking, much of our action recommendations focused on the office that's involved in the protection of human research subjects, and I expect that coming out of this report will be particular things to be added to the already substantial agenda for Dr. Koski and his colleagues. But again, we feel as part of our accountability that we owe it to NBAC and we owe it to the taxpaying public to have a thoughtful and definitive, and I would hope value added, response to it, being candid where we either can't do something, being candid where we may see the world differently, but also where things can and should move forward, being able to make clear what practical, tangible steps the Department can take, much in the spirit of Secretary Shalala's response to you.

And just as we look to you to hold our feet to the fire, I think NBAC will hold our feet to the fire, too.

DR. McCABE: I had one question. In your comments, especially regarding item 2, the comment about the identified authorities in the law regarding rare diseases. One of the intents in our recommendations had to do with not federally-funded individuals carrying out research. I just wondered if you could comment on that and had any thoughts on how the Department might proceed.

DR. RAUB: Some of my colleagues may want to comment here too. But to begin, to the extent that we have funding from one of our agencies involved, then the common rule is in play, and part of our challenge there is to be sure that all of the IRBs understand that some of these issues around genetic tests are and always have been part of that mandate.

Even if we don't have public funding in it, if it is part of the development process for something that is subject to FDA regulation, then there is the analogous set of FDA regulations that look an awful lot like the common rule that come into play.

Where it's neither, by definition it is now out of reach of either the common rule or the FDA. I don't know enough about the CLIA statute to know whether a particular laboratory might nevertheless be subject to some of that coverage, and I would ask for help from some of my colleagues here on that score. But those are the kinds of issues that we need to work through.

DR. McCABE: This was more in the research phase, before it would become a CLIA. I'm recognizing the dilemma that you've just outlined to us, and I was wondering if this had been addressed in the discussions between the agencies.

DR. RAUB: This larger issue of the reach probably will be driven not by genetic testing but rather by the generic question of protections for human research subjects. As you know, many people, including many of the NBAC members, feel strongly that all research, irrespective of source of funding, should be so covered. Some

in the Congress have thought statutory change to effect that. That may come up in the new Congress. But I think that will be the driver, and our obligation will be to ensure that as that moves, that genetic testing is dealt with in the most appropriate way within it.

DR. McCABE: Thank you.

Other questions for Dr. Raub?

(No response.)

DR. McCABE: If not, thank you very much again for coming.

DR. RAUB: Thank you. It was a pleasure, and thank you for all of the contributions of this group.

DR. McCABE: We appreciate the trans-agency efforts that have been occurring to address the SACGT's recommendations on enhancing oversight of genetic tests. We know that efforts are also taking place within each of the relevant agencies. We've been particularly interested in the FDA's efforts to respond to the challenge we laid down for them. We know from Dr. Steve Gutman's presentation at our meeting in November that FDA has been working hard, in collaboration with industry and professional laboratory groups, to think through the agency's regulatory options and to formulate out of the box ideas.

Now we will turn to our colleague, Dr. David Feigal, director of the FDA's Center for Devices and Radiological Health, to hear more about FDA's plans and progress. Then we'll also hear from Dr. Gutman, who has an addendum to Dr. Feigal's

presentation.

Dr. Feigal?

DR. FEIGAL: Stand by for technical difficulties. I think I've got it.

DR. McCABE: We're pleased with your courage with PowerPoint.

DR. FEIGAL: You know, after a long string of it always working, I've had a couple of failures recently.

DR. RAUB: I just said to Pat that I rest my case.

(Laughter.)

DR. McCABE: Well, I was commenting as an aside to Sarah that it's actually Sarah and the presentations for this Committee that have gotten me into PowerPoint. But I always carry my slides or overheads along with me.

DR. FEIGAL: Yes, belt and suspenders. We can put the diskette on the overhead over there.

(Laughter.)

DR. FEIGAL: Let me begin a little bit and talk a little bit about the process. What we have been doing at FDA is actually trying to reach out to as many stakeholders in different formats to begin talking about these ideas, to begin looking at different ways that we can solve problems, and a framework for really identifying mechanisms to begin to bring some regulatory framework to genetic tests.

The process has started by looking at the most fundamental part of device regulation, the part that's required of all devices, even the ones that are exempt

from premarket review, and that's the process of registering facilities and listing the products that are made available.

So this will be a process that we view as one that will be phased in, and part of the process of registering and listing will also be deciding what the classification of the tests will be as they arrive, and we'll talk a little bit more about how that will happen and discuss that, but it's a fundamental part. As we presented in the past, one of the fundamental philosophies of device regulation is the fact that it should be risk based, that you should take into account the risk of the information from the product of the setting that it's used, and that you should scale the regulatory requirements accordingly.

I think a large part of the collaborative effort will be in the third bullet, the development of review templates and standards. There are some areas of device regulation that are so successful that standards can completely replace the application process. For example, a non-motorized wheelchair. If you take a series of interlocking standards that describe how a well manufactured non-motorized wheelchair works, all you have to do to notify us to come on to the market is that you are conforming to those 12 standards. In this kind of a framework, then that conformance assessment would probably be done with a combination of the CLIA process and perhaps the FDA inspection process.

But the use of templates and standards, we need to look at them in a way that streamlines the process and deals with the issue of having a large number of

tests that may be using similar methodologies or similar technologies and not requiring that repetitive things be demonstrated for all of those.

We will be facing, at some point, a bolus of work, and even with new resources, that bolus of work will be larger than the resources at hand. The way that we have approached that in the past has been to phase in the process on a risk basis, to call for certain kinds of applications at certain times, and when we look at the treatment of the older tests, the tests that have been out there, there will be some type of strategy that will need to be developed, and we'll have to discuss that.

That can be a very long process. In 1976, they said that we should take the high-risk devices, the ones that would currently require a PMA if they were to come on the market, and call for PMAs. That process actually is almost done, but it still continues. There are products at the end of the list that are still having to call for PMAs.

Then a final part is to design and tailor to the field of genetic testing what type of premarket review and controls there are for brand new tests, the tests that aren't even on the horizon yet.

We've given some careful thought to the SACGT scrutiny level, and the options here I think are still in evolution. I think it would be safe to say that we're trying to find a way to regulate the majority of these tests in a 510(k) framework in the setting of looking at substantial equivalents. Some of these tests don't have any approved predicate device on the market, but there's a process that was given to us in the FDA Modernization Act that allows us to take products directly into the 510(k)

framework even if they're novel. Within 510(k), there is a spectrum of controls.

We're not at a point yet where we can really get down to the specifics to say exactly what controls go where, but needless to say, at the lower level of scrutiny, we would see the process being much more abbreviated and directed and focused. At the high level of scrutiny, we would probably treat that the same way that we treat most other in vitro diagnostics.

So if you come back to what's going to be required of all genetic tests, which is a level that a genetic test manufacturer might want to start at -- that says registration laboratory, but it's supposed to say listing. No, I'm sorry, that's right. Registration of the laboratory, listing of the genetic tests, and medical device reporting to the FDA.

The third part is a very important one. This is when the laboratory realizes that it has a test that has a problem, and it may actually result in the recall of a test. The current situation with home brew is that this is one of the areas that falls between the cracks. So the fairly well publicized recall of the Tay-Sachs testing by one of the laboratories that offers that as a home brew, there was no requirement under the current framework for them to report the fact that they were having a problem with that test and what the remedy was to the FDA. So as important as the registration and listing, it will also be having an organized system for determining what are problems with the test and when should they be reported.

Let me say a couple of words about the regulatory process and what

that will look like. We will need to craft a Proposed Rule to require premarket submissions of the home brew applications to FDA. In that Proposed Rule, we will propose the time frames of how we will deal with the old tests, when new tests will have certain requirements. Typically in a phased-in fashion for developing new regulations -- and regulations are requirements, they're not optional things, they're not guidances, they're things which will be required -- we typically announce that we're going to do it with a time frame, take comments on that time frame, and then finally announce it, and then there's still the time frame for implementation.

So there will be a period of time when many of our efforts, in fact most of our efforts will need to be voluntary. Actually, I think this is an opportunity, because it will be before the rule is final, so it will be an opportunity to consider whether some of the voluntary mechanisms work so well that some of the things in the Proposed Rule may not be necessary.

By the time of the Proposed Rule, we'll need to have a classification proposal worked out. This will be heavily influenced by the scrutiny levels that this Committee has worked on. We will also identify the elements needed by type of application if we are proposing broad categories, and exactly what will need to be in them.

So when a rule is proposed -- and that's sometimes a long process to propose a rule. There are requirements under the law to assess the economic impact of the changed rule, the effect on paperwork. The Department gets involved, the Office of

Management and Budget gets involved before the rule is even proposed. Then there will be a comment period, and then the comments need to be addressed, and then usually a final rule can take place at that point, although it's not unusual to re-propose a rule if, during that time period when the rule is proposed, you learn that you want to do things in a different way.

So we will have this rulemaking period of proposing the rule that will probably last about one to three years. Two to three years is sort of typical for a rule which requires a fair amount of back and forth but is one that is going to move forward. That's sort of the time frame that we have for the voluntary programs. During this time period I think we would propose that this is a time when we vigorously work to develop standards. The standards -- I've just given an example of two areas, of the analytic methods and the patient counseling as just examples; and that we build strong collaborative links between the Public Health Service agencies, professional societies, laboratory manufacturing communities, the patient communities, and others.

What I'll do in closing, and then actually ask Steve Gutman to walk through a mock-up of an example with a specific test, is how are genetic tests reviewed template, what such a template might look like, and what type of information we're thinking of asking for. Name of the test; intended use of the test, what does it measure; indications for use -- for example, what is the disease or the condition that it's testing; and the purpose of the test, is this something which is diagnostic, prenatal, presymptomatic. These are just examples. These are obviously factors that have been

talked about in this Committee that are factors that determine the scrutiny level, as well as target population.

We need to have information about the category of the method that's being used to do the genetic testing, and some description of methodology. This is an area that we could have expanded this section greatly, but it's also an area that, instead of great detail in this area, if there are certain standards that can be met, this could be a section of an application where it could say we do the following method by the following recognized standard, and that would be your documentation.

We propose in the review template seeing examples of the test results as they would actually be reported out; information about the analytic validity and how that's determined; control specimens, the number and types of specimens, what's known about the sensitivity, specificity, accuracy. How the test results are confirmed and the statistical methods would be ways of assessing the analytic validity.

Quality control procedures that are used to assure that the test is CLIA-compliant and is manufactured and produced in a way that gives quality results. Clinical validity when it's available, and this will often be literature based, and there may be some issues that are specific to specific test methodologies. There also will be tests that we'll have done studies and will have results and summaries to give us information about the validity.

How is the test to be clinically interpreted by those who order the test? What do the report templates look like? What kind of information is used for risk

assessment calculations? Then finally, we'd like to have information about the technical and sometimes the biological limitations of the test. The test may perform very well, but there may be facts about the biology of a particular genetic condition that are complex and that the test can't get around.

Then finally, the hardest thing usually to know for many new tests is clinical utility and how that's known.

So having presented the outline, at this point what I'd like to do is ask Steve if he would come and take Fragile X trinucleotide repeat assay as a specific example and show concretely how this would happen.

DR. McCABE: Dr. Gutman, if it would be possible, maybe after your presentations, to make your PowerPoint available to us, I think it would be helpful.

DR. FEIGAL: Sure. We'd be happy to do that.

DR. GUTMAN: Thanks.

DR. McCABE: And I'll just draw everyone's attention to the draft that was passed around this morning. It should be at each of your desks. It had to do with the presentation, the Fragile X nucleotide repeat assay.

DR. GUTMAN: Yes, and we will make that available to the public as well if they are interested parties.

Although we're not as organized or as well-heeled as the CDC genetics form, FDA has been sponsoring a parallel activity directed at a variety of regulatory issues and directed at how professional groups can interact and help us do our

work or the general work that's been put on the Department's plate as a result of this Committee's activities. We at FDA call this the Professional IVD Roundtable, and we're actually fortunate to have two liaisons who are in the room today. Pat Charache representing the American Society of Microbiology on that committee, and Susanne Haga who has represented the program on that committee.

The Association of Molecular Pathologists has, for the last couple of meetings, taken the lead, but nobody has been not invited to the table. We have representatives of the College of American Pathologists, the American Society of Clinical Pathologists, the American Association of Clinical Chemists, the American Society of Microbiology, the American College of Medical Genetics, and I've probably forgotten a couple of others who have attended at least one or more of the meetings.

Although we have certainly talked about a wide variety of issues from the private sector and how can they help, certainly a central focus has been on the expansion of this wonderful SACGT template that Wylie is responsible for. We have been looking for common ground on this template, looking at expanding this template so it certainly would be useable for FDA, and perhaps parts of it might be user-friendly for HCFA, and that it might actually in some way plug into the program that Muin has planned, so that he can put the icing on the cake, or maybe the cake on the icing as this model moves forward.

It actually has been a privilege for me to be an interactive member of a subcommittee that's developed this template. The chair of the subcommittee was

Deborah Leonard, who is ex-president of the AMP, and I can assure you that there was no regulation here. The interaction on the expansion of this template was pure science, and it was clear to me it was a labor of love.

So I'm going to walk through an example. Two of my colleagues at FDA, Maria Chan and Refina Carlos, said, well, what if we were to actually get a submission for Fragile X and how might it play with regard to this template? So they plugged into it. Some of this is based on their lab experience, some of this is based on literature, and some of this, frankly, is made up, and I'm going to walk you through a Fragile X example. I suspect that further refinement is probably needed and we would appreciate comments personally to me, or they can go to Joe Hackett or Peter Maxim if anybody wants to take the time to look at the use of the template for this example.

But to be perfectly candid, we think it's a neat starting point, and it's been a useful exercise. As a starting point, there are four identifiers. These identifiers so intrigued and interested the subgroup working on this and the committee as a whole, that we suggested that FDA, if they were ever able to progress to registration and listing, maybe the first four items could be snuck into the registration and listing so that the menu of tests, in fact, would include some key things to nail down the test.

Those key things might be the name of the test. In this case, the name might be Fragile X Trinucleotide Repeat Assay. That might include the indications for use that David just presented to you. I'm so hung up that I have a special slide for it. That might include the method category, in this case Southern blot hybridization. We

could as easily have picked PCR. We could have been more avant garde and picked a protein marker for Fragile X. We picked southern blot hybridization. Then the methodologies and expansion of that southern blot hybridization for determinations of trinucleotide repeat expansion in the untranslated portion of exon 1 of the FMR1 gene.

As I said, I was pretty hung up about indications for use. Certainly in the subcommittee deliberations of FDA, which loves indications for use, expressed that love and that interest and probably expanded this section. You have to realize that part of our labeling regulations, 809.10(b), is in fact indications for use, and that the indications for use determines the classification of the product for us, it determines the review mechanisms to be applied, and it determines whether the product is a 510(k) or a PMA, and whether a 510(k) or a PMA, the indications for use will establish the groundwork for the threshold that we'll be aiming at to try and establish appropriate performance and labeling for a test.

As David has already walked you through, we look at indications for use as having three separate, distinct, but very important parts. The first is the conditions for test use, and Refina and Maria suggested that, in this case, those conditions might be individuals with mental retardation of unknown etiology; development delay or autism, especially if they have any physical or behavioral characteristics of Fragile X; or a family history of Fragile X syndrome; or male or female relatives with undiagnosed mental retardation. Then they added the disclaimer that for individuals with mental retardation of unknown etiology, this test should be

performed as part of a comprehensive genetic evaluation.

The purpose or uses of the test. In this case, you'll note that they were concerned with the types of alleles, whether you're dealing with a normal or a full mutation, they suggest that perhaps it would be relevant to have information on the association or link or parallel between repeat size mosaicism and the mutation itself, and they actually suggest that there might be information on the sex-dependent prevalence of the syndrome.

Then last but certainly not least is the target population. Again, they define that rather carefully and suggest that a possibility might be any child, male or female, with delay of speech, language, or motor development of unknown etiology should be considered for Fragile X testing, especially in the presence of family history of mental retardation, a consistent physical and behavioral phenotype, and absence of structural abnormalities of the brain or other birth defects. They actually reference that. So that would be part of the indications for use, part of the first four identifiers.

If we really had our cake and icing too, we would actually put that all in the registration database. I can't guarantee we'd do that. We'd just like to do that.

Representing the fact that this was a laboratory-based analytical group, they went wild on methodology and picked all the things that we would know and love about a methodology. It plays out well, in my opinion, for trinucleotide repeats, so they were interested in the specimen type. In this case, it would be whole blood. They were interested in specimen handling. In this case, you've got to keep it at

2 to 8 degrees, and it's only good for about five days. They were interested in the DNA extraction method. If you bothered to look, they actually specifically suggested that extraction method be outlined.

They were interested in DNA storage. They knew you ought to keep it real cold. They actually didn't know how long you could keep it and still be safe, so they put an X. They were interested in a description of the method. If you look, there was a certain precision to the description method, which ranged from a description of the digestion of leukocytes all the way through to a statement of the source of the restriction enzymes. They thought all of that might be relevant in review.

They wanted an outline of the expected results, which would include things like the description of size and band patterns to be seen and classification of those in the report, and then the technical interpretation itself and the fact that those band patterns would result in the reporting of a normal, the reporting of a gray zone, the reporting of a premutation, and/or the reporting of a full mutation.

Analytical validation. As you surely noticed when David put up his slides, it got a little bit expanded in our template. We decided there were three parts to analytical validation. We sort of cheated because that wasn't exactly I think what everybody had in mind. We actually wanted to see the test results, and we thought whoever is reviewing it, whether it's us or a designated body or CAP or CLIA or HCFA or somebody else, they ought to actually get a couple of Southern blots of each example and get at lease a sense of the quality of the work being performed in that lab. So,

frankly, if it were going to be mailed in to us, we would want them to mail some Southern blots or pictures of Southern blots along with the application.

The analytical validation was true to the whole sense of SACGT, and we used the same definitions for sensitivity and specificity. We threw in precision and repeatability, and we discussed, although maybe we don't have enough insight into this disease, we discussed the fact that for our common review process, we're always interested in interfering substances and issues that flow at the surface. It might be a learning curve for us in applying that part of the template to this part of the knowledge base of tests.

Then we snuck in QC and QA, because our laboratorians were so fanatic. They thought that it's important to know what's being run for positive and negative and method control, and it's important to know whether there is proficiency testing or some other kind of QA process being put into place.

Then last but not least, the mandate from this Committee is the most problematic and the most challenging, the one that we all need the most help with, which is the clinical validation. We sort of lumped together clinical validation, clinical interpretation, assay limitations. You have to realize that we are absolutely obsessive, at the FDA at least, about assay limitations. Then the one we're going to leave for Muin, which is clinical utility.

Under "Clinical Validation," again we stood pretty true to form to what the Committee wanted. We made these numbers up. This is all modeled. We

didn't actually do a meta-analysis or a review of the literature, but we plugged in here the fact that we probably want some sense of the clinical sensitivity or specificity. Again, if FDA is going to have a spectrum in review light, if a test came along that didn't have sensitivity and specificity, we are not at all convinced we would not allow it onto the market with simply information about agreement. If we thought it was biologically plausible or it's going to be useful. But obviously, we took the high road here. For Fragile X, it probably would not be unreasonable to get estimates of clinical sensitivity and specificity.

Refina and Maria snuck predictive value in. I have to tell you as a caveat that we tend to eschew predictive values in our applications because we understand that predictive value is so heavily prevalence driven. We often will instead suggest modeling so that people will understand that the predictive value will be different in different populations, and we'd be curious to get a sense of what kinds of predictive values we should be including as part of this template, or talking to HCFA or CDC or others about actually describing.

Clinical interpretation. We wanted a test report, and we think whoever does this review ought to look at a test report so they actually see what information is available to the physician, the health care provider, the patient who might actually be seeing results. It was recommended -- not a very powerful or malignant recommendation -- that it follow the NCCLS standard test report format.

We threw in assay limitations. For this particular assay, that might be

the premutation status for mutations of 50 to 100 in size may be missed. It might be that a partial enzymatic digestion could actually mimic and produce a false-positive appearance of a Fragile X, and/or it might be that a point mutation can't be detected. Those all might be assay limitations of interest to someone ordering the test.

On clinical utility, you'll see from this template that Maria and Refina did try to put the context in and put a powerful disclaimer that genetic counseling might be in order given the incredible complexity of this mutation and this disease state.

Our hope is that this -- actually, I should point out that we've done this at FDA with Fragile X. We have partners in crime. At least three of the professional groups have representatives who are doing the same thing with a variety of other genetic diseases, again to get a broader experience with how this might work. It's our hope that this will lead to guidance, to standards, to perhaps a fill-in-the-blank approach for whoever gets the pleasure or bane of this review activity, that it provides a ground for enriching future review and the oversight process for all three of the agencies that might be involved, and that it be a first step in standardizing the information content for this complex set of diseases.

Thank you.

DR. McCABE: Thank you very much.

Questions for Dr. Feigal and Dr. Gutman?

Elliott, then Kate.

MR. HILLBACK: I would like to commend you folks. I think this is

a great start. A lot of interesting things here. I think the key question, however, is still how do you deal with a couple of the boxes, Steve, that you sort of raised the issues, such as the clinical validity box? What's going to go in it and how much has to be there before a test is out there?

I don't know how much conversation you had about that in your meeting, but I'd love to get a flavor of what the conversation was like.

DR. GUTMAN: Well, I think, certainly from the review staff standpoint, but I actually think the professional groups we interacted with would probably concur, and I hope SACGT would concur, the deal here is really truth in labeling. We have a problem for a test as old as hemoglobin establishing performance standards and thresholds. We don't have any problem at all in quality controlling data and making sure it's properly represented, and we also, when we see something that stinks, we can recognize it and try to block it.

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

MS. BEARDSLEY: Yes, I'd like to echo what Elliott said about the way you put this together. It makes sense. I'd also like to say that I'm really glad to see that you have medical device reporting up there as a really early thing to do.

My question is I wanted to ask particularly whether you've had a chance to give any thought to FDA's manufacturing requirements and whether you've thought about if CLIA in some way would substitute for the requirements of the quality systems regulations.

DR. FEIGAL: That certainly has been part of the active discussion because we know that many of the laboratory services, even some large commercial ones that CLIA spends some time inspecting, are not set up with the FDA manufacturing GMP requirements and quality system requirements in mind. So I think the challenge to us is to distill down what the fundamental requirements are to assure that a product is well made and to see how much of that can be covered by CLIA, and if there are areas that we still have concerns, to find a way that's not burdensome to address that.

But we have to acknowledge the fact that this is a different manufacturing setting by its very nature, and also give some credit for the fact that this isn't someone who is trying to manufacture a kit that's robust enough to ship for other people to use. They are, in fact, using it themselves and have some levels of controls. I think the whole issue that we've had some discussion on and Elliott has provided me some papers on, I think we should acknowledge -- sometimes I actually try to find another phrase than "home brew" because it is a little bit pejorative. There probably are settings where a home brew gives more control and a higher quality result than some of the kits that are made commercially available.

I think Elliott just passed out.

(Laughter.)

DR. FEIGAL: But we need to figure out what it is that makes that happen, versus the settings where they're just a little bit too loose and uncontrolled and

don't have reliable results.

DR. McCABE: I have Victor, Muin, Barbara, and Wylie.

Victor?

DR. PENCHASZADEH: I think the Fragile X example is an excellent example, in part because it's one of the most currently used molecular genetic testing these days, but also because it raises a number of issues regarding some of the criteria for scrutiny that we discussed. In the first place, the question of rare versus non-rare disease. Here, if you go by the range of prevalence rates in males, it might fall into the rare category or into the non-rare category depending on if you take the lower range or the higher range of the 1.6 per thousand or 2.5 per thousand -- or 10,000. I'm sorry.

The other issue is the intended use of the test, because here -- and as far as level of scrutiny is concerned, actually what is being required or will be required of manufacturers of tests, because this is only one of the possible intended uses of the test. Probably in practice -- well, it's one of the most common uses, but you're not talking here about, for instance, using it for the detection of carriers, eventual use, because some people have even proposed this for population screening for carrier women who are not mentally retarded, and certainly for prenatal diagnosis.

So my question is how would that affect -- you did all this template assuming that this is a test that would be used for individuals with a phenotype; that is, mental retardation, et cetera. In those cases, obviously, the correlation between finding an expanded trinucleotide may have a more predictive value regarding that particular

individual than in a normal individual. How about if anyone decides or any jurisdiction decides to do newborn screening of males for the mutation? How would you deal with the scrutiny or how would you deal with the predictive value that probably would be completely unknown?

DR. FEIGAL: I think you raise a really key question. The reason that this example started with a very focused indication for use and followed from that is because the indication and the intended use does in fact determine, as Steve pointed out, the classification and the scrutiny level and the risk level. So, in fact, even if you had a test that had already been approved at a low scrutiny level, for example, in one setting, if you used it in another setting, it might require a higher level of documentation and review and data collection in order to get that indication in use.

This is already common practice. For example, to give you a mechanical example, a stent to relieve biliary obstruction from biliary cancer is well established and requires very little data. That same stent, without any physical change at all, for use in the carotid artery, to open the carotid artery, requires clinical trials, because we don't know what the risk/benefit is there, and we have the issues of emboli and all sorts of issues that don't exist for the biliary.

So even though that's physically exactly the same device, you're just moving it, different studies and different levels of scrutiny. The one indication is a 510(k), and in the other case it's actually a PMA-type indication. Same manufacturer, same device, same quality. So with the clinical indication, I think one of the basic

principles of truth in labeling, as Steve mentioned, is that you get to say what you know. There are some things where, if you don't know some things, you haven't got anything to say. So that's sort of the principle.

But I think the framework that we borrowed heavily from all of the interactions with this group and with the professional groups actually allows us a way to deal with that.

DR. PENCHASZADEH: And a follow-up question. Who determines the intended use? Is it the manufacturer or the reality that the test can be used for different purposes?

DR. FEIGAL: From our standpoint, it's what the manufacturer claims and what they promote and what their advertising is. There have been times when we have asserted that a physician who has advertised an off-label use and is creating a new use, in fact, has to come in and show evidence for that. But typically, if physicians or the clinical community uses a product for some use other than the manufacturer intends, that's not the manufacturer's responsibility and we don't review that.

But there are examples where we've done problem-solving to deal with that. For example, LASIK eye surgery developed as an off-label use with different kinds of approved equipment, and it was actually being studied by groups of ophthalmologists who had large patient experiences, and we actually worked with them to bring in the data so that we could actually write labeling based on experience for the manufacturers whose equipment they were using to get those indications approved.

So there are times when there gets to be a widespread use when we'll actually target and go after that. But a lot of the debate in Congress really has to do with how do you keep FDA out of the practice of medicine, and that will be some of the debate around this. This will not be an unchallenged assertion, that FDA should start regulating home-brewed tests. There will be those who say this is the practice of clinical pathology medicine and is not something that FDA has jurisdiction over.

From our perspective, it's the practice of clinical pathology with a medical device, and that moves it back into our jurisdiction. But you've asked questions that are right on the edge of those debates.

DR. McCABE: Muin?

DR. KHOURY: I, too, would like to commend the FDA for its wonderful work. I just wanted to have a chance to give you what's going on on the CDC side, since I won't have a chance to do it later on.

DR. McCABE: Can you get closer to the microphone, please?

DR. KHOURY: I'll get closer.

I think the template that SACGT developed has been really a driving force for a lot of the activities. As you all know, we have funded a model project to begin the collection of data, especially on the postmarket side, and we also use the same template. You'll all be glad to know that the cystic fibrosis work has almost been done. We used this template with the help of the Foundation for Blood Research and really looked at some of the same questions that were raised here.

Actually, there were many more questions, a total of 42 for which data need to be collected. The focus is obviously different on the postmarket side, because some of the empty boxes that will come to the premarket phase will have begun to be filled. For example, on the analytic validity and proficiency testing, there is the whole CAP/ACMG surveys that will provide valuable data. So in due time, I think what we want to do is put these two templates together.

That becomes sort of a seamless process from the premarket to the postmarket phase where, at any given point in time -- and I'm using Elliott's favorite word here -- we tell the world what we know and what we don't know, and it comes back to truth in advertising for the premarket phase, and then also at the postmarket phase what actually has gone on since that initial review process has appeared.

So we're really looking forward to working with the FDA and the other groups to make this a whole seamless and smooth process using the same definitions of terms, using the same templates and methods for collecting data.

DR. McCABE: Thank you.

Barbara?

DR. KOENIG: My question follows up a little bit from Victor's and gets into some of the complexities of the potential intended uses of Fragile X. My understanding of this, and I'm sure the pediatricians will immediately correct me if I get it wrong, but that there's enormous variability in the expressivity of Fragile X. Is that the case in terms of how it really correlates with retardation? I have always, in the

Fragile X situation, been particularly concerned about individuals who get labeled as retarded in a genetic sense who would not have been otherwise, and what the consequences for them would be. That's leaving aside the issue that it may help with case finding or whatever. So it's not really a simple issue.

So what I'm wondering is what -- I'm trying to imagine what the label -- assuming this all goes through for the intended use of diagnosis, would the label then say something like, "Not recommended for use in population screening"? What I'm imagining is what if a medical consultant to an elite private school gets the idea, well, wouldn't it be a great idea to just get blood from everybody who is applying to our school and we'll find a way of eliminating a category of kids who may not be quick enough, or they decide that they're going to base a screening program on physical characteristics which may be misleading?

I mean, I know that that seems perhaps far-fetched, but I know that there have been school-based screening programs for Fragile X that are questionable. So I'm just wondering how will this play out in terms of the labeling, if you can mention that.

DR. FEIGAL: Well, I think this is an area that we need to continue to explore and work with, because we'll be dealing with not just one application. As I recall from a slide from about a year ago, there were 85 laboratories offering Fragile X testing. So presumably there will be multiple people wanting to offer this service.

I think that if it's possible to develop some disease-specific consensus

on guidelines for the use of the test in different populations, that's one thing that you implied, the appropriateness. The other is the guidance for the individual practitioner. Montana has been often cited as someone who gets a result in Montana and doesn't have a nearby genetic counselor to kind of walk through and say, gee, now what do I do with this result?

I think that there are ways that we can look at developing standard sections that can be proposed, and a way of approaching this would be to say here's an acceptable section of the genetic counseling and the population use of this test, for this specific test that comes from -- and whatever group that we're all working with. If a manufacturer wants to modify that and so forth, then they have to explain why or the reason they think they should handle it a little bit differently.

But this is a little bit new ground for FDA, because much of the time the assumption is that the professional labeling to the clinical laboratorian is what's needed. If you go over to the drug side, you will see sections of patient instructions or patient information that's very abbreviated. We haven't done that as often for devices, but it can be done, and those are relevant sections for genetic tests, and it's one of the reasons that I think we need to have the richness and collaboration that Steve described on the clinical pathology side. We need to have that also on the human protection side, on the genetic counseling side.

Particularly as we look at some of the indications that are going to be commonly used, we should identify those first and start working through those

templates, say what would a template look like if you were going to provide something. We talk about putting it in the labeling. The labeling should really just be thought of as a product monograph for the physician who gets the result back. We could think of templates as a communication vehicle for the ordering clinician to tell them what they need to know about this test and how they should interpret it and what should be presented.

We should think about it from the standpoint of is there an information sheet that should be provided to the patient or to the family, given that there will be settings where people are able to order these themselves, either directly or they will talk a physician into saying I want this test, will you order it for me. There will be times when the interest will be driven from the patient's point of view or from the personal point of view, and we'll need to think about how do we communicate information from that standpoint.

Although our presentation started maybe more heavily with the laboratory and the quality on that side, I think, as we pointed out, as we work to set up templates and standards, the human side of it with the counseling is a very real part of it too.

DR. McCABE: Steve used the term "registration database." Is that a labeling?

DR. FEIGAL: I think you were referring to our database of the firms that are registered with us. It's actually a public database, although it's stored on

equipment that makes it almost inaccessible even to us. That will be remedied.

DR. McCABE: Okay.

Wylie?

DR. BURKE: I wanted to join with others in saying how appreciative I am of this effort and how good this template example looks. I particularly appreciate the expansion of our general category of purpose into clearly defined intended use and indications for use.

I think we know, we've always known, that the issue of off-label use is in front of us and is going to be there forever. I think it's really important for us to be clear about what we can accomplish at the premarket/labeling stage versus what has to come in the development of clinical practice standards. I don't think we should be hung up on the fact that off-label use will certainly occur for many tests, but I think we can protect consumers and providers the best by ensuring accurate labeling. If accurate labeling occurs, it's very clear when off-label use occurs.

I think the truth in labeling, as Steve referred to it, at the level of detail that we're discussing in this kind of report helps considerably in clarifying and making everybody know when a line has been crossed and when things therefore need to be looked at very carefully.

In that context, it does seem to me that this example illustrates how important it is to clarify two things: what needs to be in the clinical validity and clinical utility boxes; that is, being very clear to test offerors what kind of information is

expected to be there, including the statement that we don't have any information of that sort when that's an appropriate thing to say. In other words, a list doesn't mean they have to have answers to every question. They either have to have an answer to the question or they have to acknowledge that there is no answer.

It may be that this kind of thinking has important implications for how the test results are reported. In other words, I think this has already been brought up, that test results probably should be more than just a laboratory result and perhaps should capture what was in the original label to begin with under a purposes of test validity and utility.

DR. McCABE: Any comment?

DR. FEIGAL: I think you've touched on a lot of different issues. The one that I guess I'd like to illustrate by another example which was an experiment of ours may give us some ideas of how to deal with the issue of what's known. That's the big question, how do you know it.

About a month and a half ago, we put up a LASIK eye surgery Website for consumers. The reason we did this is because consumers usually make the decision before they see a doctor, and then they go in and there's a relatively short period of time that you have with the health professional. You may get to see their video and so forth. They typically only own one type of laser and offer a specific type of surgery.

So we looked at it from the consumers point of view, and the Website

begins with telling you what a typical health provider would tell you about LASIK, but it allows the consumer to go in and be an informed consumer and have a whole series of questions a step ahead that they may want to ask.

You then can click down and see a list of the approved lasers and what they're approved for. All of them are there together on a single table. You can click down and drill down and you can actually get down to the summary basis for approval which describes how large the studies were, what the side effects were in the studies, how long the follow-up was. You can do that by specific indication. You can also click over to the labeling at the time of approval, and you can even see the approval order to see if there were any limitations or postmarketing requirements, and you can click over and hyperlink over to the manufacturers' patient information sites, if they have them.

What interested us was in the first month of use there were 80,000 downloads. That's more than twice the number of correspondences we have with manufacturers in a year. So there's a tremendous amount of hunger on the public side to know about what are the things that they have, what's known about them, how were they studied, what exactly is the labeling, and the response to this has been very favorable. There were concerns that the health professionals would say, "You're giving my patients advice for me," and we did get a small amount of that. But most of them, in fact -- we worked with the Academy of Ophthalmology and other groups involved in retinal surgery, and it's been very positively received.

It would be very interesting to think of a similar site that would link the FDA regulatory side with the NIH research side and with other things that would provide this kind of layered information that allows people, whether a health professional or an educated lay person, or a not very educated lay person, to really learn about the products that they're using. I think the era of health professionals making decisions for their patients is long gone. We're experimenting with these efforts in other areas, and hopefully what we learn there will help the quality of what we do in genetic testing as well.

DR. McCABE: I think that's a very important point, because we think of labeling as package insert flat text labeling, and in the example here where you chose Southern blotting, it would be very easy to see where you could have taken your LASIK example and used the alternative methodologies drilled down on them to look at what the different advantages and disadvantages might be.

If we could briefly have comments or questions from Elliott, Pat Charache and Kate before we take our break.

MR. HILLBACK: Thank you. I sort of wanted to pick up on Victor's question, but I thought Wylie answered a lot of it. If you go back to Wylie's committee that talked about these various templates, we always assumed that there would be multiple intended uses, or could be multiple intended uses, and that each would require some different information. Maybe a lot would be the same, but some would be different. I think that's how we would apply it.

I then would like to second Wylie's comment about off-label. I think what we're going to see as life goes on is we'll have lots of intended uses, we'll have some of what we would call appropriate off-label uses, meaning pushing the envelope, because that's how we push the envelope, that we learn by trying things, we try them in a careful way, and then there are going to be a few stupid attempts. And this, Barbara, is not to comment on you but on that attempt that you talked about. I would consider a school educator trying to test for Fragile X to be stupid, and I don't know of a lab that would do it. It's not anywhere within the range of even off-label use.

I think that's where, as we move this forward, we're going to have to separate ourselves into dealing with intended use as the primary focus, finding a way to manage off-label use in a careful way but not stop it, and make sure that people are educated at the other end, not the labs but at the other end, not to request stupid uses of this technology. I think that's where we need to go.

DR. McCABE: Pat Charache?

DR. CHARACHE: I can be brief because Wylie covered the four things I had on my list, but I would add there's a very significant value in this template in providing it to IRBs to guide those who are beginning to develop a test so they know ahead of time how they're going to be evaluated.

The clinical validity issue I would also emphasize, that if you want to use the literature, I think that's highly appropriate for clinical validity. You just have to show that your laboratory gets the same answer on your patient population that you're

using it on. I don't think that's too much to ask because that's the only way you can interpret results. So I wouldn't downgrade that.

On the labeling, I would emphasize that the physician who orders the test never sees it. It's in the laboratory. So the only way they will have the information that's in the labeling is to require that key pieces of it be provided in the report. I'm emphasizing this because that's been interpreted as the practice of medicine. So we have to address this very specifically if we want certain components of the label to be included in the report for the information of the physician, such as the limitations of the test and in what populations it should be applied.

DR. McCABE: Thank you.

Kate?

MS. BEARDSLEY: I just wanted to ask a question about what I think of as standard of review, but I guess another way to say it would be how do you know if you have enough information to let a test go on the market? I mean, assume you have what Steve has put together here on Fragile X. Are you thinking of a system in which, if the labeling has the right information in it and it's truthful, the test would go on the market? Or are you thinking of a system in which you would make some sort of decision about whether it's safe and effective? I think substantial equivalents is not a very useful concept. Or is it sort of more like you know it when you see it?

DR. FEIGAL: Well, the other dimension that I think I would add that's related to safe and effective is risk/benefit. A lot of times when we are focusing

on so many things that deal with the accuracy of the information, we don't take that next step to say what's the benefit of having the information, what's the risk of having it in this setting. Some of the concerns about some of the off-label uses were actually concerns about the risks from the information in that setting, where the information would actually be harmful rather than helpful.

You may have caught when Steve presented something, he used a double negative, so I had to translate it, that there probably are settings where it's appropriate to allow a test on the market and say all we know is that it detects this gene, and there's some biologic plausibility to be interested in this information. The logic would be if the benefit of knowing preliminary information in the clinical community outweighs risk, then that's reasonable to do. If there's no known benefit from the information, then even if it's accurate and reliable information, traditionally we've been very conservative about saying, well, just because you can measure something reproducibly doesn't mean that there's any reason for it to be out there. There's no benefit, so there can only be risks in the equation.

I think this will depend on what we're after in different settings. The complexity is that I think it will vary even within a single gene, depending on the setting in which it's used. But I think that's the framework that we would put that in. If there appeared to be great benefit for measuring something, then that would be the setting where it would be reasonable to market the test appropriately, saying all we know at this point is that this measures something.

MS. BEARDSLEY: So am I understanding that we're really talking about clinical risk/benefit, except if there's some other reason to let it go? Is that right?

DR. FEIGAL: Well, it's always clinical risk/benefit, but what did you mean by some other reason?

MS. BEARDSLEY: Well, I thought you said that in some cases, even if the test had no clinical risk or benefit, it might be useful just to have the information.

DR. FEIGAL: Yes, if it was plausible. Then someone would make the case to us that even though we don't have the clinical correlation yet, this gene is so highly likely to be useful, this test should be approved already. That would be the case that would have to be made. Maybe it could be made from the literature, maybe it could be made from some basic biology.

There are other things that you just can't know without doing some clinical research. For example, pharmacogenomics. How would you know if there's an interaction between a diagnostic result that predicts clinical response to a drug unless you actually pair those two up and do the studies to establish that? But then there are other settings where there's a disease condition, there's a breakthrough, something Francis is involved with perhaps that creates intense interest in that target, and there appears to be a way of treating that condition if you could diagnose it early. That might be the kind of setting where you'd say just knowing that information is probably enough to put it out there early, even if the clinical work isn't done yet.

It's back to that principle -- there's sort of the two principles. You get

to say what you know, and you have to know enough that it's reasonable to want to do the test.

DR. McCABE: Thank you very much.

I want to thank the FDA also for beginning to translate the recommendations of the SACGT into very concrete templates and giving us good examples of how to do that. That's been very helpful, I think, at least in our thinking.

At this time, we're going to take a break. We will resume at 11:00. The members of the Committee are invited to Conference Room 9, and there's a cafeteria on the first floor of the A Wing of this building for others.

Please, we will resume at 11:00 so that we can hear Francis' presentation.

(Recess.)

DR. McCABE: This week, less than a year after the momentous announcement of the completion of the initial sequencing assembly of the human genome, the two groups working on the human genome sequence reached another monumental achievement, the publication of the human genome sequence in the journals Nature and Science. Along with the sequences, the authors have provided a comprehensive analysis of their initial findings, some of which have been very surprising.

Dr. Francis Collins is the director of the NHGRI, but he also has served as the leader of the International Sequencing Consortium. This has been no

small undertaking. The Consortium involves seven countries, 20 institutions, and over 1,000 scientists. Francis has provided vision, leadership, and inspiration, and I've heard that inspiration termed a quick kick in various parts of the anatomy, as well as at times a little bit of tough love. So we appreciate Francis' leadership to this enormously talented group.

Francis, on behalf of the whole Committee, let me congratulate you and the entire team on this outstanding achievement. We appreciate your willingness to present some of the team's findings to us this morning. Thank you very much.

DR. COLLINS: Thank you, Ed.

It is an absolute delight to have a chance to talk to you briefly this morning about what we've learned in this first reading of our own instruction book. Today is the day where a series of papers are officially being published in Nature, and tomorrow another series in Science. There was an embargo which was intended to be released on Monday, actually got released a little early thanks to some leakage of the information. But, oh well.

Knowing the timing was going to turn out this way, it just seemed like a wonderful occasion for this Committee, which has so much of an important role to play in terms of how this all affects the practice of medicine, which is, after all, the point. It seemed like it would be fun to have a brief discussion of some of the surprises that have emerged from this analysis over the course of the past seven or eight months. That's my goal here, to put some of those in front of you.

This cartoon, which you can't quite see the bottom of, the caption actually is, "Johnny probably won't be able to come out and play for some time yet. He's working on this genome map thing." Well, Johnny can finally come out and play because not only have we gotten 90 percent of the sequencing in public databases, which we were able to announce last June, but we've spent an intense time over the course of the last seven months trying to figure out what it means, and we learned a host of things, although I think it's fair to say it will be the full-time activity of thousands, if not tens of thousands, of scientists over the course of the coming decades to really sort all of this out.

Of course, what happened in the course of the genome project in the last three or four years is probably fairly well known to you, the speeding up of the effort to get the sequence in hand from an original goal of 2005 to much sooner than that. We did, by the good graces of this very hard-working group which Ed has alluded to, which was in fact a very international group as well. These are the genome center directors and other senior staff from the 20 centers that did most of this work when they met about a year ago in England.

These folks, I must say, put aside many of the other circumstances that would normally drive scientific efforts of this sort in order to work together as a team. Yes, we had some moments when things got a little bit in need of tough love, but everybody was so attached to the goal here, the importance of getting the sequence of the human genome done right and into public databases as quickly as possible, that we

got through those episodes relatively smoothly.

By March of 1999 we had done 15 percent of the work, and this is when the ramp-up really started, the full-scale sequencing of the human genome, initiated just about at this moment, with the goal of trying to have coverage in at least draft sequence of most of the genome over the course of the next year and a half. As you know, by last June that goal was achieved with this kind of coverage. I'll tell you that since June sequencing has continued, because we want to turn all of these chromosomes red, we want to have everybody finished in the same status as 21 and 22.

In fact, just recently we crossed the 1 billion base-pair mark for finished sequence. So that's about a third of the genome in highly accurate, no gaps, finished, archival form that we won't have to go back and clean up.

The remainder of the genome, about 94 percent of the sequence, is now in hand. There are still small gaps that we have not recovered in various cloning vectors, and those will undoubtedly be vexing to get to. But I think it's fair to say that we will have finished a highly accurate sequence of all the clonable parts of the genome in two years, or perhaps a little less. We're aiming for that April 25th, 2003, 50th anniversary of the double helix deadline to try to be sure we have the sequence finished.

Nonetheless, having this degree of coverage has enabled an analysis of most of the major features of the genome, for which this draft sequence is actually extremely useful. Over the course of these past seven or eight months, a group of computational biologists and other experts have been meeting in an intense, free-

flowing form. This is a photograph from one of our meetings. This one was actually on the weekend of the American Society of Human Genetics meeting, when we all met in a conference room at the University of Pennsylvania and spent two and a half days of very intense effort with these folks and a lot of high-end computing in the room, trying to figure out what we could learn from these 3 billion letters.

I must say, this group, the analysis group, constituted by about four dozen of the world's leading computational biologists, was enormous fun to work with. It's because of their energy and creativity that I think we got as far as we did in analyzing what we can learn from the genome at first pass. All of those folks who, when you read this paper, are listed along with the other 242 authors in a footnote to a paper obviously put their efforts into this without necessarily expecting much in the way of individual credit, but nobody seemed to have a problem with that because of the importance of the task, and the sheer joy scientifically of being able to band together with some of your brightest colleagues and tackle something of this magnitude.

What have we done here? First of all, let me say that it was a big task to put the sequence together into an assembly that was the best possible representation of the human genome from one tip to the other of each chromosome. That assembly task was tackled both by the NCBI and also by a group at Santa Cruz led by David Housler, but particularly informed by the remarkable work of a graduate student, Jim Kent, who turned out to be a critical part of this whole enterprise because of his amazing ability to come up with great ideas and program them at lightning speed. People have

now wondered is it really Jim Kent or Clark Kent that we were working with here because of the things that he accomplished.

So one of the things that you want to do once you've done that assembly is to see whether it's right, and what you're looking at here is chromosome 2. Plotted across the bottom here is the sequence that we've determined by putting all the pieces that have been cloned, these individual back clones together, and then assembling the chromosome. Then we're comparing that to what the map should have looked like for four kinds of maps that had been previously derived at reasonable spacings.

This was the first view of that when we looked at it, and you can see it looks pretty good here if things are along the diagonal, the way they're supposed to be, for each of these maps. There's a scattering of points that don't seem to be in the right place. Virtually all of those turn out to be problems with the previous maps.

But you'll notice there are two segments here that seem to suddenly flip and go the wrong way, and that's an absolute clue to the fact that the assembly of the sequence has made a mistake there and it got that segment turned around wrong, and that one too. When you go back and look at the data, you can actually identify how that was put together wrong and then corrected. So this is the version that then ends up on the Web for the investigators to use.

The contiguity of the sequence is actually pretty good. If you're an average nucleotide sitting in the genome and you look to your left and look to your right, there are 82,000 base pairs of continuous, highly accurate, no-gap sequence on the

fragment you're sitting on. So that's a pretty decent draft, considering that most genes are considerably smaller than that. Actually, the contiguity is even better than that. If you want to ask, well, are you sitting on a region of the genome where you know the orientation of the pieces, it's actually about 8 million base pairs that's the size of those kinds of contigs.

So while it is a draft, it is certainly further advanced in its analysis and its assembly than we had expected it would be at this point.

Now, once you get the genome in front of you, you can start to look at it, and it's quite a challenge to figure out how to visualize it. So laid out there on the table for all of you to look at is chromosome 1 in a form that we assembled with the able assistance of both computational biologists and graphic artists. They put the whole genome into this format. Behind me here, in a fashion I'm sure you cannot see, is the whole genome, and this is actually in that copy of Nature. The scale here is 3.8 megabases per centimeter. This is chromosome 1, and you go from chromosome 1 down to 11, and then X is here and Y is there, and you start up again with 12, all the way down to 22, so that they all kind of fit on the poster. Probably we should have supplied magnifying glasses with this issue of the journal, because you have to look pretty closely to read what's there.

On the table you can see a blow-up of what just chromosome 1 would look like, obviously at a much larger scale. What's on there are a whole host of features that tell you that the landscape of the genome is very lumpy. So this is sort of

interesting lesson number 1. If you imagine the human genome as sort of a random collection of genes here and there that had no particular constraints on their degree of heterogeneity as far as their neighborhoods, that's just not right. The degree of heterogeneity is certainly much greater than we had expected to find.

There are crowded urban areas where there are genes packed in much too densely, you would think, for their own good. There are great deserts where, for hundreds of thousands of base pairs, in some instances 5 or 6 million base pairs, you may find only a single gene, or maybe two, sort of like a desert with only a few residents within it. Not only the gene density but other aspects of the genome vary profoundly in terms of the GC content, in terms of where the repeats are, and those are all described in some detail in this paper.

You can cut the lights back down again.

I just wanted to point out with this particular representation how variable the gene density is. This is just three chromosomes. This is 17, 18 and 19. Look at 19 here. These tracks that you see there in various colors, all packed together, are our means of predicting whether a gene is present or not, and there are four different ways of predicting, and they're all demonstrated, and they correlate pretty well, but they're not perfect. I should tell you that our ability to predict genes is still imperfect because the computation methods aren't as good as the cell is in finding these things.

Look at chromosome 19. It's just absolutely chock-a-block with genes. There's hardly a place there where there's not a gene packed right on top of

another. Chromosome 18, on the other hand, is much more dispersed, many fewer genes. By the way, we've labeled on here all of the genes that have names. So across the genome, that's about 10,000 of the genes that are actually on this diagram. All the ones that are associated with a human disease are in red, and at this level you probably can't see them. But if you looked at the one on the table, you could see better.

Chromosome 17 is much more like 19, very gene dense. When I showed this diagram that you see up here to Alan Guttmacher the other day, he said, you know, you can just look at this and see which trisomies are likely to be viable in the human. It's absolutely true. Chromosomes 13, 18, and 21 are relatively gene poor. You could imagine, therefore, that if it was going to be viable to have a human trisomy, it would probably be those three chromosomes, and that's exactly the answer, in fact, which is an interesting correlation I hadn't thought of.

This is chromosome 11, a slightly larger blow-up so you can see some of the features of what's possible to see here. This is the scale across the top in megabases. So we're looking at the short arm of chromosome 11 here. This is the centimere, this gray block here. Again, you can see great variations in gene density. Notice that this track here is the chromosome banding pattern. In fact, the dark band --

MS. BARR: This is Pat on the phone. Can you fax me those materials? I can't see anything.

DR. COLLINS: Oh, goodness. I'm sorry.

DR. CHARACHE: We don't have them to fax right now.

MS. BARR: So he didn't have any there. They're just at the table?

DR. CHARACHE: No, they're not at the table.

MS. BARR: Oh, it's just on the slides?

DR. CHARACHE: Yes, it's just on the slides.

MS. BARR: All right. I'll try and listen very closely. Sorry for interrupting.

DR. COLLINS: I'm sorry, Pat. I should have thought more carefully about this. We'll be sure to send them to you, but I don't have them ready to stick into the machine right at this moment. Apologies.

MS. BARR: I'll imagine. That's fine. Bye-bye.

DR. COLLINS: Notice on this diagram, this is the track here which is the banding pattern. When you get to a dark band -- and, actually, this dark band is this dark band right there that you see on the actual cytogenetic picture of the chromosome -- the gene density just drops right off. Likewise with this dark band, which is that one. The gene density drops right off. So the correlation, which we suspected before, but now we really have the data across the genome, between banding pattern and gene density is really quite significantly profound.

So I guess lesson number 1 is the genome is a very lumpy place. It's rather like the wild west here, where you have sharp mountain ranges and deserts and lush valleys. It's not at all like the prairies of Iowa, where everything looks about the same. That degree of heterogeneity is fascinating and somewhat unpredictable.

Sorry, Jim. The prairies of Iowa are lovely places in their own right.

(Laughter.)

DR. COLLINS: Here is shock number 2, and this is the one that I think has gotten the most attention in the press, that we don't have nearly as many genes as we thought we did. This is the gene count for the organisms, the eukaryotes, for which we now have essentially complete genome sequences and you can make the count fairly accurately. I think we all would have guessed that humans would come out substantially larger in the gene count department than some of these other things, like yeast, worms, fly, and the mustard weed.

But, in fact, our best estimate -- and it correlates very closely with folks at Celera who have made their own estimate based on their sequence -- is that the total number of human genes is about 31,000 to 32,000, vastly less than the predictions that most people have been attached to for the last several years of about 100,000 genes, making us not look very impressive on this scale, which some have taken as a bit of an affront to human pride. But, oh well, the data is the data.

Now, that also suggests there must be some way to recover from this because we are, after all, biologically fairly complex organisms with a lot of things that we have to do. So how do we accomplish that?

Well, one of the things we've noted by having the whole genome in front of us is that alternative splicing, which allows our genes to make several proteins, is a bit of a rescue in this situation, in that the average human gene can make three

proteins, whereas the average yeast gene makes one and the average worm gene makes about 1.3. So if you want to convert this diagram from genes to proteins, you start to feel somewhat better about yourself. Here we are able to make some 93,000 proteins compared to yeast and worm.

Another observation, and maybe this is surprise number 3, is that when you look at the proteins, you don't find that humans -- and in this case we're probably not only representing ourselves but all of vertebrates, because we don't have other vertebrates to look at -- you don't find that vertebrates have invented a lot of brand-new motifs to put into their proteins. There are some, but only about 7 percent of the protein domains, the motifs, the folds that do something, appear in humans, and you don't find them elsewhere.

What you do find is that vertebrates, in this case humans, have figured out how to cobble them together in complex ways, so that a human protein can do more with what it's got, perhaps, than its counterpart in worm reply. We are capable of multi-tasking. If the worm gene makes a Model T, we make a Mercedes. We have more features attached to that particular protein than a simpler organism might, and that might also help us with this complexity issue.

Here's an example of how you can see those extra domains sort of cobbling on together. This is a bit of a complicated slide, and I'm not going to ask you to look at all of it. Just look perhaps at this one on the bottom. Here you have a particular gene that's involved in development, the trithorax gene. The Drosophila

version of that protein has all of these domains, each of which is colored in a different color and made into a different shape. In going from the Drosophila version to the human version of that, you have the same core here, but you've tacked on to the amino terminal end a bunch of other domains that make it potentially capable of doing other things.

We find over and over again examples of that, where the human counterpart has acquired additional domains that presumably allow that protein to function in more complex ways.

Other interesting lessons. If you look to see, of our proteins, how are they similar to others, about 40 percent of the proteins that we predict don't seem to have a counterpart to anything. They're not on this slide. The ones that do have a counterpart to something you can see are in various ways connected to other kinds of genomes, either vertebrates only or potentially larger and larger numbers of other types of organisms.

The reason I point this out, though, is actually this little 1 percent. It's actually just slightly less than 1 percent. About some 250 of our proteins do not have a homologue in worms, flies, yeast, or plants, but they do in bacteria, a fairly obvious homologue. When we first saw those we thought, uh-oh, we've contaminated our database, we've got sequences in here that aren't really human after all. But guess what? They are, because you can go back and prove that using PCR.

These appear to be sequences that have arrived in the human genome

by what would be called horizontal transfer, somehow getting across the usual barriers that we think prevent such DNA transfer from bacteria to us, and landing in our genome. Now, this didn't happen last week. I don't want anyone to feel a concern here that they're under assault by their own flora. These are probably things that have happened back tens or even hundreds of millions of years ago, in the ancestor of vertebrates or mammals.

But interestingly, these 300 genes are not really there causing us trouble. They're there helping us. On that list of those genes are quite a number of genes that you would immediately recognize as being pretty darn important for human biology, including monoamine oxidase, for instance. Apparently, those were acquired by us perhaps by a viral vector transfer, or who knows? But somehow getting into our germ line, being treated as a symbiotic positive event by the original ancestor, and carried along to this day. So not all of our genome ascends in the usual vertical way that we consider ourselves more traditionally to have arrived at, but there's also this possibility of horizontal transfer.

That's been seen, of course, in bacteria, and even a bit in worms and yeast, but it has not been suspected by anybody, as far as I know, to be possible for a vertebrate. So that's quite a big surprise.

The repeats. This is a complicated slide. The repeats occupy 50 percent of our genome, and there are various types, and the table sort of gives you a diagram of what they look like and how big they are, and how many of them we have.

The lines and the signs together make up almost half of our genome, these two types, and I just want to tell you one quick vignette about the signs, because the bottom line here is that the junk maybe isn't the junk after all.

The signs are the most abundant element. You have 1.5 million of these guys. They're commonly called Alu repeats in your genome. They're short, about 100 to 300 base pairs in length, and all together they take up about 13 percent of your DNA. They have been considered by almost everybody as cell fish DNA that copied itself over and over again, got into the genome, and we just couldn't get rid of it. We couldn't figure out how to clean our house, and so we've carried it along for all this time.

But having the whole genome in front of you allows you to do some very interesting things in terms of the analysis of these sequences, because you can date them. They're not all born at once. They're born over the course of hundreds of millions of years, and because they are born from a consistent donor sequence, over the course of time as that sequence diverges from the original, you can figure out which particular element landed when, and you can begin to look at their distribution.

One of the big debates and puzzles about these is that these signs, as they're called, tend to occur in the gene-rich regions, and that is sort of odd. You'd think if you were putting junk somewhere, you wouldn't put it in the living room. You'd put it up in the attic or down in the basement. Yet these elements seem to be very much in the living room.

The assumption had been that they must have some mechanism for selectively landing there, and somehow we tolerate that. Well, it turns out that's not right. Again, a bit of a complicated slide, but let me explain it to you. This is the toughest slide I've got and it will be smooth sailing after this.

What you're looking at here on the X axis is the density of G and C, and you can also think of that as the density of genes. There are more genes in the GC-rich regions than the GC-poor regions. The dark bands are down here, the light bands are up in this region. What we're plotting here are various of these signs, Alus, depending on their ages.

The youngest ones, AluY, which has been around for less than a million years -- these have come along since our divergence from chimpanzees. If you look at their distribution, they are more abundant in the gene-poor areas, and then they fade out into the gene-rich areas. That's telling you that their actual landing pattern is that they land in the places where there aren't very many genes.

But look what happens as you look at older and older and older cohorts of these repeats. Gradually, as you get to the older and older ones, they are much more abundant where the genes are.

The obvious conclusion from that, and one that we think is pretty well substantiated, is that they're being retained selectively in the areas where the genes are most densely located, that there is a drive here to clean out the basement and the attic, but to keep the guys in the living room that happen to be there, where the party is going

on, where all the rest of the genes are primarily located. The strong suggestion would be that they're there helping us. Otherwise they would be swept out, as they apparently are being swept out down here in the gene-poor areas.

This is quite a stunning result, that this category of repeats, the most common one in the genome, is not just there as an irritant to the molecular biologists and as an example of selfish DNA. It actually has a biological function that we have yet to understand, and this opens a whole new area of research for people to begin to pursue.

So again, I think this proves the wisdom of having decided not just to look at the coding regions of genes but to look at the whole thing, including the repeats, because some of the most interesting things we learned come from the repeats. They're a fossil record of our genome. You can look at the genome back 800 million years to where some of these repeats first landed there. It's like looking at geological strata in terms of evolution. But in all of our DNA, that information resides there. That's pretty surprising and pretty profound.

One of the things that we had fun doing was to put together this image which is on the cover of Nature that's being published today. Again, I think this is the image we wanted to convey about what this was all about. It was about DNA, but it's actually much more about people. This is an image which is created essentially as a mosaic. Every one of the little blocks in there is the face of an individual from somewhere in the world, and it's a very diverse group. Of course, the backgrounds have

been carefully chosen so that when you put it all together, you create the obvious familiar double helix of the DNA strand.

Just for fun, in this image we hid away a picture of Watson and Crick, and another one of Mendel. So when you get your copy of Nature, I'll challenge all of you to play "Where's Waldo?" here and see if you can locate these figures.

(Laughter.)

DR. COLLINS: There are rumors that there may be some other recognizable figures in there too, but I don't know if that's true.

Again, all of this data has been placed on the Internet every 24 hours since the effort began. So all the sequence has been accessible all the way along. One of the very exciting places to go and look at it is this particular browser, which is at UC-Santa Cruz, put up by this remarkable Jim Kent. This particular site is the one that displays the current assembly of the genome sequence which is in the paper, but also gives you a wide variety of other looks at the data, depending on which tracks you want to turn on or off. There are other such sites available, one from the EBI and one from NCBI that are also worth looking at.

One of the fun things about writing this paper was that I don't think I can remember writing a paper before where you were able to cite in the discussion of the paper published examples where the data in your paper have already been used by other people to make progress. So in the paper we listed more than 30 disease genes that have been identified by access to the public sequence over the course of the past

several years, including these, and these as well, and many more that I couldn't fit on the slide.

I think the point here -- and particularly this is relevant to SACGT -- is that the acceleration that we had hoped for in terms of this sequence availability in terms of uncovering genes responsible for disease has already started happening, and of course will happen even more rapidly now with the wide availability of the information.

I also did a little survey to see how the sequence has been used to uncover new drug targets, and there are three examples on this slide, but I could have put up many more. We found quite a few others simply by doing surveys through the sequence using computational methods of molecules that were previously undiscovered, genes that would probably be very nice targets for things like asthma and heart disease. So one can expect to see lots and lots of those consequences coming along.

Where do we go from here? Well, clearly, we need to finish the human sequence. It's nice to have this draft, it's a wonderful draft, but we want to be sure to fill all those gaps in. As I said, we'll be doing that over the next couple of years, and do not fear, we're not going to lose our momentum here and leave the sequence in anything less than the best possible form.

We need to take this index of genes and proteins, these 31,000 or so, and refine that as the methods get better to identify what's really a gene and make sure that we have the right list. The same with the proteins.

We need, now that we have the whole sequence in front of us, to

come up with better ways of identifying the regulatory regions that turn genes on and off. There are a lot of exciting things going on in that area.

We need to sequence additional large genomes because they will greatly illuminate how the human genome works. Actually, we are within about a month of having 95 percent of the sequence of the laboratory mouse in public databases as well, thanks to a consortium that has recently formed between NIH and several companies to speed up that enterprise, with the Wellcome Trust also a significant part of that.

The catalogue of human variation. I didn't have time to talk about it, but also in this same issue of Nature is a paper describing the identification of 1.4 million single-nucleotide polymorphisms by the SNPs Consortium. If you go to the public databases and look at all sources of such SNPs, it's now up to about 3 million that are publicly accessible, and obviously that is going to greatly speed up the uncovering of the genetic contributions to common diseases like diabetes and heart disease and mental illness, and hence the work of this Committee will become even more critically important if we're going to make sure that those discoveries find their way into clinical applications in well-validated ways.

Of course, now that we have this sequence, it is even more important than ever to push hard on the methods that we have to understand how these genes work, not just by themselves but interacting with each other, and there's a great deal of activity in that way. So this is the end of the beginning for the genome project, with a

great many more things yet to come.

Let me just say personally for me, as a final note, it has been an enormous privilege to lead this international effort. The intensity of the effort has been unbelievable at times. The outcome, though, is truly gratifying to see, and the way in which it is going to influence research I think we still don't fully grasp, but I suspect it's going to be quite profound.

I'm happy that we were able this week to make these announcements jointly with the scientists at Celera, who had assembled their own draft and published a rather similar paper in Science. It's gratifying that most of the major conclusions between the two groups about what is in the sequence seem to be quite similar, so you essentially have a validation of the outcome immediately by the fact that there are two such analyses.

We're going to have a workshop in April to look at the differences in the way that the assembly was done, the whole genome shotgun method versus the map-based method, but I think it's already fair to say that the map-based approach turned out to be pretty critical both for our own efforts and for Celera's efforts in that they needed to use all of the public data in order to get their own assembly to work in the way that they'd hoped for. So it turns out to be, I think, quite a nice outcome from all perspectives, and a good day for science.

Finally, the last quote. This paper in Nature is distinguished in several ways. It's the longest paper they've ever published. It also is written in a fashion

that intends to try to be accessible to the average graduate student and doesn't get into too many jargon details. At least we tried to avoid that. And it ends with a quote from "The Four Quartets" which I'm quite fond of and which seems to be a good way of putting where we are right now.

"We must never cease from exploration. The end of all exploring, which is not now but some future time down the road, will be to arrive where we began and to know the place for the first time," the place in this instance being ourselves.

So thank you all very much for the chance to tell you about all of this.

(Applause.)

DR. McCABE: Again, thank you very much, Francis, and congratulations to you and to the entire community. As a tribute to the accessibility, I can tell you that my graduate students were all carrying it around this week and wading their way through these papers, very interested and really being a part of this historical occasion. So thank you.

We can have some brief questions before we move on for Dr. Collins.

Yes, Muin?

DR. KHOURY: Again, congratulations, Francis. I'm sure some smart computational biologist has thought about what I'm going to say here. I'm not dismayed by the fact that the number of genes seems to be lower than expected, but really who we are as humans is not determined by the number of genes but the combination of genes. Let me give you an example.

If you have only 10 genes, each with a biallelic system, you have 1,000 combinations. If you have 20 genes, you have a million combinations. So the difference between 30,000 genes and 15,000 genes is really not 15,000, but 2 to the power of 15,000, at least. I don't know if that has entered into your discussion.

DR. COLLINS: It has a little bit, and I appreciate your comment because there has I think been some misunderstanding this week in the press about what this gene count means as far as the conclusions that we might draw about how human biology works, and there have been many stories I think in part encouraged by Craig Venter, who seems to also have taken this view, that having a smaller number of genes means that environment is more important than we thought it was.

I suppose environment may be more important than we thought it was in many circumstances, but I don't think the gene count really sheds any light on that particular conclusion, because even with 30,000 genes -- and you make the point quite nicely -- the opportunity here for an enormous amount of hereditary impact on virtually anything is still vastly in excess of anything that we can even contemplate.

So I don't think it changes the nature/nurture equation in any meaningful way. It does mean that our genes must be, on an individual basis, a little more clever than we thought, and I guess it means, if you're a gene hunter, that your hunting may now be a little easier because you don't have quite as many genes to hunt through. But when you find the gene you're looking for, it's going to take you longer to figure out what it means.

DR. McCABE: Right now at the Huntington Museum in Pasadena, they have the manuscript collection there, and they've put together a wonderful manuscript collection on astronomy. In one of the cases, it sort of documents the change from Aristotle, Ptolemy, to Copernicus, where we went from this egocentric view of the solar system to our current view, the more Copernican view. It's just interesting because I saw that just as all of this was breaking, and I'm hoping that this moves us a little bit away from the somewhat egocentric view of evolution that we've had and puts us more in the perspective that we are much more similar to other life on this planet than I think we have considered in the past, and hopefully will bring us into more balance with that as well.

Reed?

DR. TUCKSON: Actually, to this very point of how similar we are not only to other life forms, but how similar we are as a human race, you said there's more work to be done, obviously, on understanding variation. Can you clarify a little bit about what we now know about how similar or how different we are, and the meaning of those differences?

DR. COLLINS: Yes, and some of this is described in much greater detail in that paper on the SNP discovery process. I think the numbers held up pretty closely to what we've been saying based on a less full set of data, that we are, regardless of which two individuals you're comparing -- 99.9 percent is about the right number. If you look at a chromosome of mine and a chromosome of yours, and it wouldn't matter

which one of you I picked, I think they said every 1,200 base pairs on the average you would find a difference of a single letter. So that's slightly less than 0.1 percent, but awfully close to that.

It also seems that that variation -- because they did with a number of these look to see where the variation occurred -- most of it seems to be ancient, most of it seems to be therefore shared amongst all groups that you look at, although the frequency of the alleles may be skewed one way or the other, depending on which population you happen to choose. But most of the variation, at least 90 percent of it, appears to have preexisted in our common founder pool some 100,000 years or so ago.

Interestingly, a little bit of data that's coming out suggests that there may have been a very tight bottleneck in the European population as recently as 10,000 or 15,000 years ago, which may mean that when you go looking for disequilibrium between sites, that you find more of it in northern European populations than some of the theoretical models would have predicted, and that may be good news for those who are trying to track down disease genes, because that disequilibrium is helpful, although I'm not sure that it's completely certain that that's right.

So I think basically it validates the point that's been increasingly loudly made, and appropriately so, that the study of human variation further underlines the fact just how similar we all are, and how the assumption that somehow genetics and genetic science would be found to starkly underlay differences between ethnicity and race really was a false assumption. Those labels are largely social and cultural, and the

differences that one perceives between such groups are mostly skin deep, and if we're going to come to grips with all of the complexities of ethnicity and race, we shouldn't make it worse by implying that it has a scientific underpinning that really doesn't exist.

DR. McCABE: Thank you again, Francis. We really appreciate your making this presentation to us. Again, congratulations.

Now we will turn to our first major task of this meeting, which is to complete the formulation of our proposed genetic test classification methodology. You will recall from our meeting in November that we agreed to revise the initial framework we had developed in August due to concerns that had arisen about the feasibility of using test volume as one of the classification criteria.

In the course of our discussion in November, other concerns about the proposed framework emerged, and by the end of the day we had modified our approach in some significant ways. We agreed, however, that we should take additional time to gather broader input and commentary on our revised approach.

I'm going to turn now to Dr. Burke, who will give us an overview of the proposal that emerged from that November meeting. Then we will ask Dr. Khoury about a further analysis of this version of the methodology where it was applied to a number of additional genetic tests currently in use. Then we will ask Dr. Haga to provide a summary of the public comments received, and then open it for discussion.

Our goal is to consider and address the comments and concerns raised, and then to reach agreement on a framework that we can recommend to the

Secretary. This is a critical element of enhanced oversight, and we need to complete this aspect of our oversight charge.

Dr. Burke?

DR. BURKE: Thanks.

I'm just going to spend a few minutes basically taking us back to where we were when we left the test classification scheme at our last meeting. So the scheme that we ended up with is shown here, and what Susanne will do in a few minutes is review public comment on this scheme. Let me walk through it and make just a few comments about what I think are going to be key points that will come up in our discussion.

We said that the first step that had to be evaluated was the analytic validity of the test.

DR. McCABE: Could you try to focus that a little bit, Wylie? Some people are having a hard time seeing it.

DR. LEWIS: Or make it a little bigger. It's so small, it's impossible to see from back here. That's better.

DR. BURKE: That's better? Okay.

When a test is proposed for use, the first question is does it have analytic validity, yes or no? I think this is not a controversial step. I think there are issues of methodology -- that is, how you determine it, what kinds of standards you set -- but I think there's broad agreement that this is the right thing to do.

We then said is it going to be used for population screening, yes or no? And if the answer is yes, it goes to Level II. If the answer is no, it goes to the next question, which is is it rare or not? And we provided a definition for rare, a proposed definition. If the answer is yes, it goes to Level I, and if the answer is no, it goes again to Level II, everything else going to Level II.

I think there are three things I want to just comment on really for the purpose of laying stuff out that I think will come up in our discussion and that is reflected in the public comments on this. The first is that we started out our discussions talking about high and low scrutiny and ended up moving to Level I and Level II because we were a little uncomfortable with making too broad an implication for high and low scrutiny. I think we're going to have to go back and think about that again.

The points that we made were even though we're saying rare diseases go to Level I scrutiny, it doesn't mean we're not scrutinizing tests that have to do with rare diseases. We certainly want them to meet high standards, as we want all tests to do. So I think we really have to ask ourselves how different the review process is for this Level I and Level II and what kind of outcome we want from these processes.

The other I think unintended inconsistency that we've created and that comes out very importantly in some of the public comments is that early on, when we were still using high and low scrutiny terminology, we had a discussion about informed consent which suggested that a high scrutiny test would be one where there was a requirement or an expectation of formal documentation of informed consent.

Obviously, all tests are used under informed consent, but the question of what kind of formal procedures and written documentation might you need -- now that we have this simplified scheme, I would suggest that we probably aren't meaning to say that every test that falls under Level II scrutiny requires formal written documentation of informed consent, or at least I would propose that that's something that we have to come back to under this simplified scheme.

The other issues that came out in comments and that we'll talk about more are that some of the things we dropped to make a classified scheme were of concern. We're going to hear the public comments coming back with, "What about intended use? What about predictive value? What about social or medical risks associated with a test?" The issue there, twofold, is I didn't see other really dramatically different issues coming up, so I think our discussions have captured probably most of the important issues that need to be discussed, but we probably need to have some revisiting of why it is that we felt those issues needed to be dropped from a test classification scheme.

I would propose that that discussion is probably going to center around what is reasonable to expect from premarket review versus what might constitute clinical practice standards. I think that's been implicit in a lot of our discussion, but I suspect that we may need to go over that again and perhaps achieve some additional clarity on that.

So, basically, that's the scheme. I think the next in order we're going

to go to is Muin now.

DR. McCABE: Yes. Muin, if you could give us some of your examples, please?

DR. KHOURY: You all have in your folder -- sorry we didn't get it to you sooner -- a fairly detailed analysis of the gene test database which is online, both the PowerPoint presentation I'm going to make, plus some narrative. I'm going to pass around to you the data. This is the full 751 analysis. I didn't want to kill too many trees, but you can flip through it. I know this is not a monumental task like the Human Genome Project, but you'll see a lot of empty boxes in the analysis of this data set.

Before I start, I'd like to give credit to a lot of people here. This really was a joint effort between our office and the Division of Laboratory Systems, represented here by Joe Boone and his staff from CDC. There was a team of clinicians, epidemiologists, molecular geneticists, and genetic counselors that took a look at the existing database with the idea of trying to see where we are. I made an initial presentation to you all back in November, and this is sort of the final results of this which are going to be presented at the American College of Medical Genetics meeting coming up in March, as well as being put in a paper for the peer-reviewed literature.

How are we doing with technology here? I can see it, but they can't see it.

Maybe you can follow, or maybe I should have done like Bill Raub did, going through the transparencies.

DR. McCABE: We've got your handout here, so we can follow along.

DR. KHOURY: Okay. I don't want to lose too much time.

The second handout says the evaluation of this suggested algorithm, but we had two other ulterior motives here. The first one is to evaluate the public health impact of genetic tests today. People ask me all the time if there are genetic tests for asthma or diabetes on the market, and for the common chronic diseases. As we did this work, this is the evaluation of the algorithm, but the two hidden agendas is, one, evaluating the public health impact of genetic testing today as a snapshot in time; but the more important long-range is as we begin to look at ways to collect data in the postmarket phase, we have to prioritize.

So regardless of what SACGT comes up with, what you will see here is our attempt to prioritize the genetic tests that would seem to have the largest public health impact and will therefore commend our attention with respect to data collection analysis and dissemination.

Obviously, we fixed the gene test database back in November, and the gene test database, as you all know, from the University of Washington, is a rapidly moving target. So this database today is different from when we fixed it back in November. There were 751 diseases/conditions that are listed on the database, and they are put under the rubric of genetic tests, although this is a bit of a misnomer, as you will see. We compiled the data on these genes, their prevalence, their inheritance, and the purpose and intended use of testing, and we used the SACGT algorithm.

Here's a snapshot of the results for you quickly. Of the 751 conditions, roughly half of them, a bit less than that, are listed there under research only, and 423 for clinical use. If you apply the SACGT algorithm, you end up with 55, or 7 percent of the total, under Level II. Now, there is a caveat there because you can add to that list another 20 from the research only category, that these were conditions, if used for clinical purposes today, 20 of the 328 will fall under Level II. So overall, if you want to think about it, 75 out of the 751, which is about 10 percent, fall under Level II. I hope that's clear.

The categorization of what that is. Obviously, the biggest groups are the newborn screening-type groups, and you have a whole list of what they are; other population screening, like Canavan and some of the thalassemias; and then the biggest chunk was the prevalence, more than 1 in 2,000, or more than 1 in 10,000, and these are listed here.

Now, as we did this work, there was a lot of uncovering of many of the issues that you will hear about in the public comments very soon. We summarized them here briefly under eight bullets. The first one is that this initial classification does not capture the complexities of clinical validity and clinical utility. So there are many issues there that are really part of the review process. When you think about hemochromatosis and other conditions, if you want an initial screening situation that will essentially accomplish some of your review, you can't have it. You have to funnel those tests into the two parts and then do the more in-depth evaluation.

The number 2 bullet is really the most important one. The intended use of the test will drive the classification. A simple example is cystic fibrosis. If you're going to use it for diagnosis, perhaps for someone who is affected with failure to thrive, that's one level of classification. If you want to use it for newborn screening, that's another level. If you wanted to use it to diagnose people with chronic sinusitis, that's a different intended use. All of this will be driven by that.

Number 3, there are many tests there where one test could be used for multiple conditions. The ApoE is a good example of that, whether you can use it for some of the rare hyperlipidemias and also for Alzheimer's disease.

Number 4 is a very important one, because as we began to do the work, there is limited prevalence data. So if you want to use the incidence or prevalence frequency, and many of the public comments related to that, where is the data? I know the CDC and other groups have some limited data on some of these things. The world of newborn screening is obviously easier than others. But for most of these, you have to rely on what's published, and what's published is essentially incomplete or not optimal.

But the second part of this bullet is the problematic cutoff of 1 in 2,000 and 1 in 10,000. I picked that up immediately after our meeting. Actually, I went home back in November and I think I sent a message back to Wylie saying this won't work, and let me tell you briefly why this won't work. The problem with incidence versus prevalence is that you have two measures of incidence. One is the incidence rate at any given point in time, like the yearly number of new cases, and the other measure of

incidence is what we call cumulative incidence over a lifetime. So breast cancer in women cumulatively is a 1-in-10 condition, whereas yearly incidence rates are very low.

So if you use 1 in 10,000 as a cumulative incidence rate, which I think this is what my intention was, then at any given point in time the prevalence will never be higher than 1 in 10,000. Take things like encephaly. I mean, if it's 1 in 10,000, everyone dies, then the prevalence is always less than that. That's also reflected by a few of the public comments which will be discussed.

The regulation of non-U.S. labs. There were some of these gene test entries where non-U.S. lab offerings might affect U.S. citizens. So I'm not sure how, regulatory-wise, this is going to be handled. Obviously, as many people have found out, there are conditions that have unique ELSI concentrations, like Huntington's and others, that are deemed to be rare.

Finally, the distinction between research and clinical is not always apparent. There are the same tests that are listed for both clinical and research.

Pharmacogenomics is one that I thought about very deeply because it bothered me for a while, and then when I read some of the public comments I felt more at ease. It doesn't fit in any one of these categorizations, especially around rare versus common. If you're trying to measure the outcome if you give a drug, that could be a rare occurrence, but you could give that genetic test to a lot of people, like the ALL test and the 6MP.

This is sort of our CDC recommendations to this Committee, so take

them or leave them. Put them together with the public comment, that is there is an algorithm that could be used for initial screening for classification, it should strictly be applied for each intended use or setting of a test, and I thought that was implicit in what we discussed earlier, but sometimes it gets lost somewhere.

Use one cutoff level to define rare versus common. There was some discussion from the public comments about the 200,000 or 1 in 10,000. We can come back to that a little bit later.

Until proven otherwise, classify pharmacogenomic tests as Level II. I have a specific reason for that, because pharmacogenomics affects the practice of medicine, affects the way you're giving people drugs. You can either withhold important treatments or leave some untoward side effects if you're not careful.

Further explore and define those ELSI issues for some rare disorders and pharmacogenomic tests as well, because for every rule you come up with, there are always exceptions. This initial analysis showed many of the exceptions.

Now, in terms of the current law, it's 10 percent or less. But as I see the field of genetic testing moving forward, pharmacogenomics is going to grow bigger. The field for common diseases is going to go higher over the next few years. So while the initial load right now, today, is not that bad, 10 years from now or five years from now we have to continuously reexamine the issues of classification. It all boils down to what Level II means and what Level I means, and that's a subject for discussion that Wylie alluded to earlier.

So this concludes my brief presentation here. If you have any specific questions or you want to move to the public comments --

DR. McCABE: Why don't we move on to Dr. Haga, and then we'll open the entire set of presentations for discussion.

DR. HAGA: Muin took a lot of my words, so I'll try not to be redundant. I'll leave this up for a few minutes while I'm going over some of the general stuff.

The Federal Register was put out on December 7th for public comment on this classification scheme that was revised on November 3rd. We also sent a request for comments to all those who commented on the oversight recommendations, and we posted a request for comments up on our Website. We received 34 comments from a mixed bag of industry, academics, professional organizations and private citizens.

I just wanted to begin with a few of the overarching concerns and then delve into the specifics of the three criterion up here.

For starters, the definition of a genetic test. Again, we have a number of comments that were asking to exclude tests for somatic mutations, to make exclusions for pharmacogenetics, tests for infectious diseases, tests for tumor biology and cancer progression, that these types of tests don't really go well with the classification methodology as it is currently designed.

There's a recommendation to adopt a medically precise definition of

genetic tests limited to inherited diseases only, and to use a crisp and refined definition of clinical research when recommending FDA review of all tests, and that tests used only for research purposes should be exempt from FDA review.

Some of the broader general comments on the classification methodology. I thought the bottom line was that while the classification scheme is simple, which may be its strength or its weakness depending on your viewpoint, the scheme must contain enough detail to permit differentiation between the types of genetic tests that are of greatest concern. So does the classification scheme capture the test of greatest concern?

One commenter stated that the current approach is so narrowly constructed that it does not differentiate between those tests that are of higher and lower risk, that it is impractical to include all genetic tests under one oversight approach due to the wide variation in technologies and tests. Rather, it would be more cost effective to focus on tests in the areas of concern. An underlying problem is that all tests under SACGT's definition are not amenable to review of this type.

The proposed criteria do not capture the tests which the Committee has identified as its key concerns, tests which are predictive and tests which have ethical, legal, social and medical issues related to them; and there is a need to clarify whether the two proposed levels are substituting for FDA's established three-class system for devices.

To move on to the criterion of analytical validity, again the comments

were generally supportive of this criterion. The demonstration of analytical validity is paramount to any testing protocol. All tests should be analytically valid. There were some comments that CLIA already addresses analytical validity, that it's more important to focus on clinical validity. If analytical validity is a criterion, why isn't clinical validity?

Specifically in the Federal Register, we asked whether a threshold should be set for which tests that have no analytical validity or fall below a certain cutoff point would be rejected and other tests would move on through the classification scheme. The commenters that commented on this were basically split. Those that did want to see a threshold defined recommended that we look at established tests that are commonly used to define a standard cutoff. There may be some flexibility needed for extremely rare disorders. A cutoff should be defined by a panel of genetic testing laboratory experts in collaboration with clinicians.

Those that felt that a cutoff should not be defined stated that a test of analytical validity could change over time. A cutoff should not be set because there are too many methods with inherently different analytical capabilities. The thresholds would need to be threshold specific. A specific threshold or minimum should not be set but should be determined in consideration of the assay or disease. It is impossible to develop a threshold standard that could be applied across the board to all tests.

A recommendation that FDA or another commissioned group should establish specific criteria for judging analytical validity for any particular test but not set

a threshold. Another commenter stated that we should adopt the Institute of Medicine's recommendations, as close to zero error as possible and not specifically define a threshold, and that analytical validity of certain types of tests, such as chromosomal analysis, will depend on subjective features such as resolution and morphology that are often variable. Again, CLIA would be the most appropriate body to look at analytical validity.

Any threshold would be arbitrary. Setting standards could be a slippery slope. Specifically how could this work with panel tests or multiplexing tests. Individual tests could have poor sensitivity and specificity, but when grouped together could yield a higher, more accurate results. If results are used to make life-changing decisions, nothing less than 100 percent would be acceptable.

Moving on to the next criterion of population screening, again a mixed bag of comments. I think overall people were supportive of this criterion, but there were a number of concerns that were raised. One felt that population screening should not be a primary determinant in regulatory review. Not sure that all population screening tests deserve an automatic Level II review. Disagree with the criterion because, 1, all tests carry the potential obligation of population screening; and 2, this criterion, while assessing the magnitude of harm, does not assess underlying issues of showing accuracy, disclosure of potential limitations or benefits, and ensuring appropriate clinical applications.

The classification of test scrutiny based on the number of individuals

being tested is inappropriate. We need to further define how population screening will be utilized for determining scrutiny level. Tests that begin as diagnostic and are later used for population screening, would this trigger another FDA review at a higher level?

One commenter specifically focused on newborn screening. Pending clarification of what Level II review entails, they stated there may be little to be gained from subjecting newborn population screening assays that are developed, reviewed and evaluated by state public health labs to Level II based solely on the criterion. The intended criteria of such applications require further clarification and recognition of the already rigorous internal procedures in place. For other tests that are not included in state newborn screening programs but are targeted to the newborn population, Level II may be appropriate.

There are a number of comments on our definition of population, which I'll put up for you to look at. Seven commenters felt that the definition was appropriate. Others didn't. There's a need to more clearly define population. It may be more likely that the population being considered is normal rather than one defined by a particular phenotype. A cluster of individuals who have a family history of disease is omitted from the definition. The definition makes it difficult to differentiate screening from testing. Even in small, high-risk groups, the tests could be considered screening under the proposed definition.

Defining a group or a population of similarly characterized individuals seems inconsistent with the definition for rare, and an example was given

that a group of pregnant women who show abnormalities on ultrasound consistent with trisomy 18 have confirmatory genetic testing. A confirmatory test could receive Level I review since trisomy 18 is rare, but the test applied to this population could receive Level II.

Another concern was that newborn screening for hearing loss could be considered population screening, and therefore receive a Level II review, but what about genetic testing for all those that have a positive hearing loss detected in newborn screening?

Definition seems to suggest that more than a thousand individuals will be tested, or does it refer to the size of the population in which screening is intended for regardless of whether a thousand individuals in the population are actually tested?

Quickly moving through to rare diseases, a number of comments again felt the definition was acceptable and that the division between rare and common seemed reasonable. Again, a number of concerns about this rare/common dichotomy. Rare disease tests should be treated like any other test. There's a suggestion to collapse the rare/non-rare dichotomy and have review levels based on the outcomes for a person's test. The use of rare diseases in determining review level is not considered appropriate. Disease frequency is not an absolute and may create situations in which different sources lead to different data, and disease frequency may not be available for each genetic test.

While the number of individuals to be tested may be small, the

consequences of erroneous results are no less devastating. How do you know a disease is rare unless population screening has been done? Multiplexing a genetic test may be less amenable to disease frequency criterion. It's not only the size of the population to whom the test is applied that causes concern, more important is what we know and what we don't know.

There were a few comments related to prevalence versus penetrance. How would you accommodate penetrance, first of all? In some cases, this would appear to contradict prevalence on the basis for review. If prevalence trumps penetrance of a particular gene, were more than one acting alone or in concert with other factors to cause disease, this may be helpful. It's not the fact that a disease is common but that the mutation may have less than high penetrance that raises concern.

Other comments. The rationale for automatically relegating rare diseases to Level I is flawed both scientifically and ethically. It equates Mendelian diseases with rare diseases. Rather it should be viewed as a continuum, with Mendelian and other rare diseases on one end of a continuum of complexity and heterogeneity of expression rather than as distinct from other, more common diseases.

The suggestion for a higher level of review for common diseases or conditions may be appropriate at the population level, but it breaks down on the individual level, particularly when complexity, heterogeneity and problems of analytical validity, clinical validity and clinical utility may at least be as great for rare as for common diseases.

The suggestion to grant premarket approval for tests for rare diseases to allow these tests to be available while data is being collected. Another comment stated that the issue is not the rarity of the disease. It is inappropriate to use frequency of disease as a criterion because the argument could be made to favor high-level scrutiny for rare diseases as well as for common diseases. The medical and social consequences of false-positive and false-negative results must receive priority consideration. Tests for rare diseases can have a high impact for a few individuals.

Lastly for this one, don't believe prevalence is a useful criterion. The indication for testing will determine the amount of testing. For many conditions, the indications may be general or non-specific, and testing will be much more frequent than is reflected by prevalence or incidence values.

Concerns regarding the definition. Again, it's a 1 in 10,000 prevalence or a 1 in 2,000 incidence that we've put out. One commenter stated that the cutoff numbers for incidence and prevalence are not substantiated and raise a number of questions. For multifactorial disorders such as breast cancer, do incidence and prevalence figures include all cases of breast cancer, the percent of cases estimated to be caused by genetic mutations in toto, or is it the percent of cases thought to be related to the specific mutation being tested? For disorders occurring primarily in one sex, do the incidence and prevalence figures include both sexes or only the most affected sex?

A recommendation to use the definition from the Orphan Drug Act, fewer than 200,000 Americans, and a couple of comments suggesting that all federal

laws and regulations should define prevalence according to the same standards for consistency. Another commenter stated that there are already multiple definitions of a rare disease, and SACGT has created two more which are not equivalent. They write that diseases due to genotypes that occur in less than 1 in 10,000, the incidence value, will never achieve a prevalence as high as 1 in 2,000 unless those without the disease die at younger ages than those with the disease.

A couple of commenters state that there's a need for clarification on whether carriers of alleles for autosomal or X-linked recessive disorders are included in this definition. We should explicitly include the carriers or set a cut point for carrier frequency above which a test cannot be considered a rare disease if used to detect carriers. Rare disease can't be defined in a simple formula. While both prevalence and incidence should be incorporated, the presence of carriers should also be factored into any definition of rare disease.

A question of how will SACGT address the variations between disease frequency and race and ethnicity. Cystic fibrosis could be classified as rare depending on which prevalence data from what population are used.

Those were the specific comments relating to the three proposed criteria. There were a number of other potential criteria that were suggested for us to consider. These should be in your blue folders. Again, I think as Muin said, there's nothing really new here that most of us haven't been already over. Predictive value, tests that have a low predictive value should get a higher level of review. Social

stigmatization predictive tests should get a higher level of review. Tests for behavioral disorders, higher level of review.

Invasiveness of testing. The most suggestive one was the purpose of the test or intended use. There were a number of people who commented why this should not be used as a criterion, as well as those who felt it should be. Some reasons why it shouldn't be considered is that all tests should receive the same standard of care. If this was a criterion, there would be different standards of quality based on how the information was intended to be used. Given the multiple uses of tests, support not using this as a criterion. May be impractical from a laboratory standpoint. The assay is the same for all intended uses.

Other criterion were sensitivity, specificity, genetic heterogeneity, penetrance, pharmacogenetic testing, complexity of test, difficulty of test interpretation, burden of disease, pattern of inheritance, late onset disorders, availability of proven treatments or prevention, clinical utility, prenatal testing, disease incidence or progression, availability and strength of confirmatory procedures, and the reliability of clinical corroboration.

We also asked in the Federal Register what criteria would raise tests that were for rare disease, which would be at Level I, to Level II. Again, many of the similar criterion I just went over. Testing of healthy individuals, prenatal testing, commercial attractiveness of a test -- that was a bit different -- carrier screening of ill-defined populations, risk of adverse effects, population screening, risky medical

interventions, implications for family members, absence of medical intervention, burden of disease, and complexity of tests, including interpretation of results.

Some specific examples that were given were Parkinson's disease, cancer predisposition testing, and Huntington's disease.

The last group of comments focused more on informed consent and genetic counseling, not on the classification scheme. Specifically, some would like to see a standard set of minimum information given to patients, recommend establishing a panel to work with SACGT to develop criteria to determine the level of education and counseling for certain tests, assurances of informed consent must be obtained in order to assure patient autonomy in decisionmaking.

A group of these commenters, four specifically -- Wylie mentioned this -- looked at our oversight recommendations for genetic counseling and documented informed consent for all tests of high scrutiny, and in looking at the classification for scrutiny, those would be tests for non-rare diseases and population-based screening tests.

Specifically, this group of commenters were focused on population-based screening tests for somatic mutations and raised a number of concerns, that implementing our oversight recommendations for required genetic counseling and documented informed consent would create marked increase in clinical workload for an unclear benefit; that it may decrease the use of such tests by physicians who do not have the time to get written informed consent and perform genetic counseling; and believe

that the customary consent and discussion process between the patient and physician ordering any standard laboratory test would be sufficient for these types of tests.

They asked the Committee to re-address these recommendations in light of the proposed classification methodology and remove them for the testing of somatic mutations.

Last, I just wanted to give credit to some of the really well-thought-out comments and some of their suggestions for re-drawing the proposed classification model of ours. Pharmacogenetics, it's already been said that the classification scrutiny isn't applicable to this type of testing. The commenters say that it should require clinical test results from at least one well-controlled clinical study that demonstrates the validity of the test to predict the desired outcome, and then they broke it down into tests for new chemical entities and tests for previously marketed products. They would receive the same level of review and suggested that it receive a Level II review.

Commenter 24, tests that should be reviewed by FDA, broke it down into three specific areas: tests that analyze targets that have a penetrance of 90 percent or less; population screening tests; and new tests for which there are no standards to guide test introduction decisions.

A suggestion to put predictive value following analytical validity. Another suggested putting intended use prior to analytical validity. On the bottom, it's inserting pattern of inheritance between the criterion of population screening and rare.

Level I tests should be tests for disorders for which treatment or

preventive strategies are available. Level II tests should be all predictive tests, except for those for which treatment or prevention modalities are available.

Another commenter broke it down between previously approved tests and new tests. For the new test part, basically the same criteria, population screening. They used FDA's three-tier level class instead of our two. Population screening would get the highest scrutiny. Tests with severe clinical or social consequences of false, invalid or misrepresented tests would get high scrutiny. Rare tests would get Level II scrutiny. Non-rare tests would get a Level III scrutiny.

Two other commenters really went to town and rewrote our classification scrutiny. But if you look at them, they use a lot of the same criterion. They just drew it differently or used FDA's standard three-tier system. This one started again with proven analytical validity. The next question is the test intended to predict disease or risk of disease in asymptomatic individuals, and if yes, it would get a Class 3 level of review. If no, it goes on to the next criterion of is the condition rare. If it is a rare disease, it would be exempt from FDA regulation, that CLIA regulations would apply, and that ASR regulations would apply.

If the test is not rare, it goes on to the next one. Are there significant medical risks associated with the test? If yes, it asks another question: Is the test for an inherited condition? If yes, it would get a Class 3 review. If the test is not for an inherited condition, it would get a Class 2 review.

This is my last one. Again, very similar, except potential use is

inserted, as it was in the last one. It starts with, baseline, the test has to demonstrate adequate analytical validity before it goes anywhere. The next is clinical validity. If it does not warrant marketing, it can be rejected. If it's inadequate, a conditional premarket approval could be granted. If it's adequate, you go on to ask the next question of potential use, which if it is predictive, it's Level II. The next question is population screening. If it is, it's Level II. The next question is rare. If it is rare, it's Level I. If it is not rare, it is Level II.

If more stringent review levels are needed at Level II, they suggested that we might consider using a conditional premarket approval based on various circumstances where the test is offered, whether treatment is available and it's used for reproductive purposes, whether treatment is available but the safety and efficacy has not been established, or whether treatment is available and the safety and efficacy have been established.

Again, as Wylie said, there were a number of comments that were concerned that we took out the criterion that kind of really differentiates genetic tests from other tests: the intended use; the availability of medical intervention; the implications for ethical and medical, legal and social implications. There was a request to reconsider those in our review today.

I'll stop there.

DR. McCABE: Thank you very much, Dr. Haga. The Committee really appreciates all the work that you went to going through these comments. We

certainly appreciate all the feedback that we got on the recommendations from the public, and you've done a very nice job of putting them together for us.

We have a bit of time to open the discussion. Now, actually, looking at the clock, I'm not sure that we do have a whole lot of time. I think we probably should not short-change lunch today. We will have time this afternoon to review these.

I think there are a few things that I'd just like to point out that we really need to review this afternoon and come to some closure on, and I'll just summarize some of the things that Susanne has mentioned.

We have to look at the three criteria that we established and determine whether the public has identified other criteria that should be considered. Are the definitions of genetic test populations, rare diseases appropriate? The Work Group on Rare Diseases has been tasked with defining criteria to raise rare disease tests from Level I to Level II, but is there guidance that the Committee could provide on this issue that would be useful to the work group?

The informed consent and genetic counseling requirements must be addressed, and they've been identified again by the public. We need to begin a focused effort to define when the documented consent should be recommended and who should be responsible for obtaining that, and the informed consent IRB work group should look at that. Should the counseling issues be delegated to a work group or can they be addressed by the full Committee at this meeting?

Is the overall schema appropriate? Does it result in appropriate

decisions? This gets back to Wylie's concluding comments. Are there other models proposed by the public that we should consider?

So those are kind of laying out the work for us for the hour and a half that we have set aside this afternoon.

I think we will break for lunch now rather than getting a few minutes into the discussion and then breaking. We will return at 1:30. Members of the Committee, please proceed to Conference Room 9. Again, for others, there is a cafeteria on the first floor of the building in Wing A of Building 31.

We will reconvene at 1:30.

(Whereupon, at 12:35 p.m., the meeting was recessed for lunch, to reconvene at 1:30 p.m.)

AFTERNOON SESSION (1:35 p.m.)

DR. McCABE: Good afternoon, everyone. We're going to have a series of public comments now, and we actually have only allotted 15 minutes for this, and we have four speakers now. So I'd ask you to try to keep it to three or four minutes apiece. Yes, try to keep it to three or four minutes if at all possible.

Our first speaker or commenter is Barry Berger. Dr. Berger is Vice President, Laboratory Medicine, Exact Sciences Corporation.

Dr. Berger?

DR. BERGER: Thank you, thank you. Hello, everybody. I'd like also to start off thanking the Committee for their considerate and long and deliberate deliberations around these issues. I'm going to specifically address my comments towards informed consent and genetic counseling with respect to tests of somatic mutations that has been mentioned several times this morning.

Some of the other places that I come from I just wanted to put up because, basically, as a practicing clinical pathologist for years, I've had a lot of experience in implementing these types of programs in large HMO settings. The area of concern where we deal with is basically somatic mutations that show up in colonic tumors. What we do, and you all have seen these before, is basically we isolate DNA from cells that are being shed into the stool stream and look at those cells for acquired mutations that are known to be associated with colorectal cancer. This is going to form the basis of a screening test that will be applicable to 70 million Americans, about half of whom are Medicare Part B beneficiaries.

The work here is done by Curt Vogelstein, and basically we look at APC K-RAS P53 as acquired mutations, and the BAT-26 mutation of microsatellite instability, none of which, when you look at them a priori, tell you anything of predictive value of the germ line directly, in germ line issues for the patients.

So when we went through and we tried to model our test based on the current categorization scheme, of course the first thing to do is look at the definition of a

genetic test from the Committee, which we spent a lot of time working on. Basically, we're a DNA test of acquired mutations. We're associated with specific conditions or diseases, and we definitely will direct clinical management. Because this is a screening test, the follow-on test for it would be a colonoscopy and treatment in the usual manner. So it's basically a very low-risk test for the patient as there is a definitive follow-up test and a definitive treatment.

In the proposal the last time I was here back in September, we included about four gates: volume, population screening, predictive versus diagnostic, and significant social consequences as part of the categorization scheme. In the one published for comment today, there were the three gates that we saw earlier. Every test needs analytical validity. That's absolutely required. But population screening and the frequency of the disease in the population were the remaining gates.

So taking the opportunity to model our test based on the published scheme, basically we will be valid or we will not be out there. We will be used for screening entire populations of patients, which will put us in a high scrutiny Level II. With respect to the hurdles that a test such as ours will need to cross based on the number of patients that we're treating, Level II is absolutely appropriate for a test like this.

Part of being Level II, though, according to the report as handed out, basically included this, though. If you're Level II, the report specifically states "subject to SACGT oversight recommendations for documentation of written informed consent."

This is a very high bar for a screening test, we felt, and we felt that the intent of the Committee was informed decisionmaking as opposed to written informed consent. But there is no way in the categorization schema to take a test that's high scrutiny and not compel that.

Chapter and verse from the report that was distributed basically indicates that, for Level II tests, documentation of informed consent must be obtained for tests requiring high scrutiny, and genetic education and counseling are required only for tests at high scrutiny. So our specific request in this regard was that the categorization schema based on looking at the Level II and informed consent and genetic counseling seemed a bit excessive for a test looking at these acquired mutations where there's a known treatment and a follow-on test for confirmation.

So basically, knowing that the FDA, as we've heard this morning, is looking very closely to the recommendations of the Committee, and as their own process rolls out, I had thought -- I've been calmed down quite a bit by my conversations with the FDA this morning, I might add -- that such informed consent documentation and genetic counseling could be part of the labeling, in which case it would be compelled all the way through. We want to ensure that if that is not the specific intent of the Committee, as I don't believe it is based on a number of conversations I've had with Committee members here, that we would like to request specifically that such a recommendation for required written documentation of informed consent be removed for population-based tests at high scrutiny for somatic mutations, and that FDA be given

clear direction on this issue from the Committee as they put together their own process of coming up with labeling for these tests.

DR. McCABE: Thank you very much.

Wylie, and then Pat, very briefly please.

DR. BURKE: I had already said something, and I'll say again that we, at one point in our process, used the level high and low scrutiny and had a very clear intent that high scrutiny meant tests that had special concerns, were predictive perhaps, had social consequences, et cetera, and then really tried to get away from that and didn't go back and make things consistent. So I don't believe that there is any intent at this point to say Level II scrutiny in the current classification means written informed consent. I don't think that would ever have been the intention, for example, for newborn screening, and I appreciate your bringing this point up for an opportunity to clarify.

DR. BERGER: Thank you.

DR. McCABE: Pat Charache?

DR. CHARACHE: I think just like the Fragile X example helped us to understand processes more this morning, I think this raises parallel opportunities. As someone who was directly involved as saying now this test could be offered for patient care, we required that it be offered only for a specific ethnic group because we found that the false-positive rates for the general population were unacceptable. So I'm questioning that if you want to offer it to 70,000 people of all ethnic persuasions, then I think that, in fact, counseling would be essential, because it shouldn't be used except for

a specific population.

DR. BERGER: Dr. Charache, what would you be counseling them for?

DR. CHARACHE: Well, you'd be telling them if they weren't of that ethnic group, that this test does not mean that they are at risk for the disorder.

MS. BARR: May I?

DR. McCABE: Yes, Pat. Pat Barr?

MS. BARR: I'm just responding to what we all know is an incredible shortage of genetic counselors. So at some point we're going to have to say what kind of algorithm or information we give, because I don't think it's realistic. We can say that it's preferred, but I don't think we can, at this point, require it.

DR. McCABE: Right, and I think one of the comments that was discussed was whether this could be done through written materials, that certainly there are other ways that people are doing informed consent, with videos and other things these days. But I think that's an important point.

Barbara, briefly.

DR. KOENIG: Just very briefly. This may be another good example of the complexities of this, because is it also the case that certain germ line mutations might be rarely identified using this technology? And if it's not, then if that's the case, then I think it does raise at least some other issues. If it's not, then I totally agree with the issue in general that written informed consent would be inappropriate. If it's

targeted to particular human populations, then that's a labeling issue which we've discussed in general.

DR. BERGER: Last point of clarification. The test involved does not directly identify any germ line mutations. So that's not a Clintonesque-type comment. The BAT-26 mutation, which is a marker for microsatellite instability, when positive in a tumor in a patient, will sometimes find a previously undiscovered patient family that has HNPPC or hereditary non-polyposis cancer at the rate of less than 1 in 10,000 of these screening tests. The other mutations themselves do not have a predictive component at all.

DR. McCABE: Thank you.

We're going to move on to our next public comment. Dr. Neil Anthony Holtzman, Genetics and Public Policy Studies from Johns Hopkins Medical Institutions.

Tony, again, please try to keep it to three or four minutes.

DR. HOLTZMAN: Thanks very much for this opportunity. It's a pleasure and quite gratifying, as chair of the Task Force on Genetic Testing, which I know you're all familiar with, to come here and hear the progress that has been made towards assuring the safe and effective use of genetic tests, which is what our task force was about.

I've submitted written comments. In fact, I have to take the responsibility for this algorithm that Susanne showed you, and I'm greatly indebted to

her for making this intelligible from the way I had submitted it.

I just want to comment very briefly on a couple of things. First, it's interesting to hear David Feigal's presentation this morning which talked about intended use, and your current version which takes out intended use from your classification. Obviously, there are problems of reconciliation between where the FDA stands at the moment and where you stand at the moment, and that also applies I guess to the traditional use of Class I, II, and III that FDA uses in your Level I and II, and I think some more clarification is due the public on why there is that discrepancy.

FDA has talked about intended use, and this appears here. When I say potential use, speaking to Dr. Feigal this morning, it was my original intention that a manufacturer or a laboratory providing genetic tests or proposing to market genetic tests should list all potential uses. Now, apparently, that's not legal. There were amendments that were passed in 1997, and that unfortunately raises the possibility that a provider of genetic tests could give the least controversial use of that test to try to maximize the chance that it will go to Level I, to use your terminology, and then once it's out, promote off-label use.

As Dr. Feigal elaborated to me on the stent thing, the one that was used for biliary atresia, that the manufacturers are making many more stents that could possibly be used for biliary atresia. So obviously, the manufacturers know the expectations. I think this is a serious problem about intended use. When I mentioned this originally I was thinking about, say, marketing a test for diagnostic purposes which

could then be used for carrier screening or for predictive uses.

In the last week something else has come to my attention, and that is -- and some of you I'm sure have heard about this -- essentially the claim filed by the union representing the railroad workers against Burlington Northern and Santa Fe for Athena Diagnostics running for them a test for a very rare hereditary neuropathy with a liability to peripheral palsy for carpal tunnel syndrome on a work-related basis. When you look at the clinical dissimilarity of these two situations, both from the point of view of family history and age of onset, it's rather remarkable that a test that has been marketed -- and if you look at the Athena lab that's doing this, they describe HNPP, and there's very little overlap with carpal tunnel. And yet, they're making this test available for another use, to the point where within a week, EEOC jumped into the act and challenged them for using this, and they've temporarily withdrawn it.

But I think you have to be aware of these kinds of problems, and I urge you to at least address much more than you have this question of insisting on at least one intended use, and in review considering the potential uses.

Now, the other thing, and this was commented on by Susanne in summarizing, you said analytical validity should be considered. Why not clinical validity, and why not make it an explicit criterion for which data at least have to be provided?

Then finally, the other thing that you have removed is the question of the availability of an intervention, at least for predictive tests. There are three

possibilities. There's no treatment available but the tests will be used for reproductive purposes. The second is that treatment is available but safety and efficacy have not been established. The third, which could lead you to market the tests, is that treatment is available and safety and efficacy have been established.

For the second category in particular, this is clinical utility. Again, in your original document you made a big point about clinical utility, and you dropped it from your criteria. I think this is a mistake. I understand that for both clinical utility and clinical validity, that there may be real problems and real delays in getting tests to market before sufficient data are collected. FDA, as I understand it, has a mechanism of dealing with this for pharmaceuticals, and essentially it's what I call conditional premarket approval.

You ask a test developer who wants to market a test to indicate that there are protocols in place if the data have not yet been collected for doing clinical validity, collecting data, and this would often have to be a large collaborative study to collect data on clinical sensitivity, specificity, and predictive value, and that the developer should be aware at least of the state of collecting information on clinical utility. If there isn't an intervention available but its safety and efficacy have not been proven, then a test developer who is going to tell a person who has a positive test result, or expects a doctor to tell that person "Here's what you can do as a result of that positive test result," there at least should be some tie-in with collecting that data.

To give you an example, one of the problems with BRCA1 testing,

and you yourselves are aware of a number of problems with that, was that there was no attempt, either by the manufacturer or by NIH and other government agencies, to encourage a collaborative trial to look at the benefits, let's say, of mastectomy and mammography in women who had BRCA1 and BRCA2 mutations. I think this is a splendid opportunity, as you're making tests available, to insist that a test developer at least be aware of the necessity for establishing clinical utility, and yet give that developer, once these protocols are in place, and it speaks to other government agencies that it should encourage the development of those protocols, the formulation of those protocols, to give them the opportunity to market the test so that data can be collected.

By conditional premarket approval, the developer would be able to market the test, there would still be an informed consent, and I think it's appropriate here, indicating that data are still being collected, but where the test can go forward, the manufacturer could even mark up the price of the test to include a profit, and results could go back to the subject with a possibility in terms of clinical utility that the subject person, having a positive or negative test result, could be enrolled in a clinical trial that's going on as the result of a protocol for clinical utility.

So just to reiterate, I urge you to give much more consideration to the problem of intended use, to the problem of clinical utility, and to considering this notion of conditional premarket approval.

DR. McCABE: Thank you very much.

Yes, Muin, and Wylie. Briefly, please.

DR. KHOURY: Thank you, Tony. I think this captures a lot of what this Committee has been discussing.

The intended use, I think we had it at one point, and we struggled between diagnostic and predictive. Wylie, correct me if I'm wrong here. How would you classify presymptomatic tests for Huntington's disease? That's predictive or diagnostic?

DR. HOLTZMAN: I would call that a predictive test.

DR. KHOURY: Yes, we had that discussion earlier. You were not here to witness that. Would you call predictive anything that's done on otherwise healthy individuals?

DR. HOLTZMAN: Yes.

DR. KHOURY: For the purpose of predicting the future risk of disease, even though it could be 100 percent?

DR. HOLTZMAN: Yes.

DR. KHOURY: Okay.

DR. McCABE: Wylie?

DR. HOLTZMAN: There is, I guess, one possible -- if you did that and there was a well-developed, established safe and effective treatment for Huntington's disease, that still fits into the algorithm I've developed here. But until that's the case -- and I would still say it should be looked at to make sure there is a safe and effective intervention. If that's known, then it could go to premarket approval.

DR. McCABE: Wylie?

DR. BURKE: I think your points are well taken, and also your last remarks I think underscore that it probably isn't an easy matter to determine whether a test is predictive or non-predictive some of the time, because there will be arguments about how well established a treatment is that's available.

We clearly still have intended use in our scheme as part of our template. That is, the information has to be declared. We understand the restriction that we have to accept how the test developer is offering the test. I think we're stuck with that, even though any given test, others could imagine wider use of that test, and we know that that will happen.

I think your comments really speak to the fundamental point of what is reasonable to expect from premarket review. That is, to what extent can we determine things on the basis of premarket review that influence whether tests come to market that have to do with how a test is used, versus letting that be determined through development of clinical practice standards and decisions about what payers will pay for.

The point that you've made that I think is most challenging here is the extent to which the premarket review process should set up some sort of required data collection after the fact.

DR. McCABE: Thank you very much, Tony.

Our next commenter is Dr. Michael Watson, who is Executive Director for the American College of Medical Genetics.

Again, please keep it to three or four minutes.

DR. WATSON: It'll be the first time, but I'll give it a shot.

Thanks for the chance to come to speak to you all. I really appreciate the way you're approaching this. I was actually probably more appreciative of the way the FDA is talking about approaching this.

I think there are a few things, though, that need to be kept in mind. Time is marching on, and the clock is really, really starting to spin fast now. I want to make sure that, even though we're trying to capture the whole package here, that we don't lose sight of those things that have really driven the development of the task force that Tony and I were involved in, and this advisory Committee, which are a relatively small subset of tests right now which are really going to be those on which the clock is spinning very quickly and we'll start seeing come out, much like the Burlington Northern situation that Tony briefly commented on.

As best I can tell, that's a test being offered on the basis of a single family pedigree that was described in the literature in 1999, and it's the kind of thing that has stepped from family-based testing out into an application that is probably far beyond what the data would justify for that test.

One of my major concerns in the way I read the materials really boils down to not so much the models of scrutiny but the definitions that underlie them, because I think that's where many of the problems are developing. We use an incredibly broad definition of a genetic test, which is the definition that we developed on the task

force essentially, and I think it's correct. However, I don't think you can regulate from such a broad, general definition and think you really have to begin to break things down, because certain things are going to have to be looked at very differently.

Clinical cytogenetics is a genetic test under the definition, but it's just not something amenable to FDA oversight. Any of us that know the problems in that field know that it's not amenable to FDA oversight, because what I really think you're developing is -- you've pegged FDA because they have the power, but what I ultimately think happens is that FDA oversees a multi-agency activity that allows their power to be enforced through any of these things they delegate out to. So I think you need to really be tight with your definitions.

The definition of a test is probably the easiest. As a former laboratorian who used tons and tons of home brew, I did that because the manufacturing sector did not address the disorders of interest to my laboratory and to the patients who presented to my laboratory. Just because the manufacturers didn't do that, which they probably should have, or the cost incentives weren't in place, I think we have to be very careful not to overly regulate the laboratory side because they've essentially been dumped this problem, because we can very easily end up with a situation in which only the large major laboratories are able to fulfill the requirements of the recommendations, putting the academic laboratories that are heavily involved in translation and are actually operating very much in the public interest, they can be placed at risk.

So I think the definition of the test is a serious problem. Is it the

mutation, which is one of the possibilities? Is it the disease? If I define my test based on the mutation I'm looking for, you'll be hard pressed to find any test that gets beyond rare; whereas cystic fibrosis, 900 mutations now, or almost 1,000. I really am concerned that we don't constrain what is the look for that very rare or private mutation, because that is inherent in genetics.

We will never be able to convince FDA that I'm going to go looking in a patient for something that's unknown and previously undescribed, because the nature of genetics is that mutations can be restricted to one person or one family in the world, and probably 80 percent of the mutations in the cystic fibrosis gene are of that type and have been identified by scanning through genes and then taking standards to look at sequence variation and make a determination that that truly is the disease-causing entity, and it requires family-based testing to really do that.

So I don't want to have a situation in which it's very easy to get approved for all those easy mutations, and then all the people with the hard things are hung out to dry because no lab has the incentive to go after that sort of test because the system just doesn't allow it to happen easily.

I also think that one of the things that this group could very much focus on is where do we need standards. It worries me a little to think that FDA will be establishing the professional standards. We're trapped in a time when most of the genetics organizations are quite small, quite new, and are very limited in resources. But I do think that, to a large extent, the professionals need to be the people that begin to

establish the standards, and that those are ultimately enforced by regulatory agencies. So to the extent that you can define certain kinds of standards that aren't in place for these things to happen, for these oversight mechanisms to work well, then I think you've done a very good job.

One other thing. As I worked through the models, I found that those things that drove to the development of these groups got left out. Predictive testing, for instance, was very easy to leave out if I define my test by the mutation. It was very concerning to me that really the major problems could very easily fall out of Level II scrutiny, which I think we all agree is appropriate for many kinds of tests, but that the model precludes that from happening.

You really need to be very careful with those underlying definitions, or the laboratories will game the system, just like the manufacturers game the system so that we now have the problem in the laboratories.

DR. McCABE: Thank you.

Yes, Dr. Feigal?

DR. FEIGAL: I just want to make a quick comment. I appreciate your comments.

About standards and how they work, standards are things that primarily we recognize. We get involved in writing a few of them, but of the 700 standards that we recognize, we probably haven't been the primary author of more than a dozen of those. If we have an opportunity to participate in a standard-making body

that's writing it and it's a busy area for us, we will do that as well.

Then the other thing about standards is that a standard usually represents an acceptable way of doing something. So if you say you're doing it that way, that's okay. But it's not a requirement in the sense that if you want to do it some other way, or if you want to modify the standard in some way, you just have to explain the modification.

So it's a way of trying to take areas where there's consensus on certain standard operating procedures and not requiring documentation, not pulling through some of those things. So I hope it's a flexible process, and we very much value the standards that come from professional organizations and from standard-setting bodies because that's where we get most of them.

DR. WATSON: Don't misunderstand me. I have no burning desire to standardize everything there is, but I think there are some key standards which can be established which allow you to compare something that you haven't seen before against some clearly accepted standard. I think to the extent we can identify those and begin to define them and facilitate their development through national consensus processes, I think we'll get much closer to your ability to step in and do something better than register and know what we're doing. You'll actually know what we're doing and why.

DR. McCABE: Thank you.

Our next commentator is Dr. Michele Schoonmaker, who is director of medical reimbursement and government affairs for Vysis.

Again, if you could keep it to three or four minutes, it would help us.

DR. SCHOONMAKER: Thank you for giving me this opportunity. I just thought I'd come up here and clarify a little bit the model that Susanne put up that we had presented. It wasn't our intent to rewrite the whole data team model but to try to put it into a language that we were familiar with.

Basically, when you look at a model like this, we have two tasks. The first task is to classify a test into a scrutiny level -- high scrutiny, low scrutiny, or exempt. The second task is to define the data elements within that classification level that's going to lead a test to be approved or rejected. So I'm going to kind of start at the end here. Once something is classified as a higher-risk test or a lower-risk test, what actually makes up the contents of the review, the PMA or the 510(k) or whatever process it's going to go through -- and the FDA can correct me here -- there's some flexibility in defining what those elements need to be.

So if you have a test that's been around for the last 20 years and it's a high-risk test, and the level for approval is here, if there's a wealth of literature showing that that test works, then you really only need to collect a little bit of data to go over the approval and meet the threshold of approval, whereas versus something that's new, you may have to collect a lot of primary data.

So basically, going through this, we feel that nobody is really going to approach the agency unless something has shown analytic validity. If you can't detect your target, then why bring it to the table? But I don't know, maybe they do.

We did have a problem with trying to visualize what was meant by population screening from the definition that was given, and we thought that perhaps the real concern was are you going to test healthy people versus people with signs and symptoms where a test is providing supporting information versus stand-alone information about a disease? If something was going to be used in a healthy, asymptomatic population, then that's going to require a higher scrutiny.

Again, if something has been out there for a while and there's a wealth of literature, you may not have to collect as much evidence to meet that standard of approval as you would if it's not been published before.

If there are signs and symptoms present in a patient or a proband, and that would include personal history, you ask the question whether it's for a rare condition. If it is rare by whatever standards that the Committee comes up with, then that test would be exempt from formal review. I mean, there are just some conditions that you're not going to be able to do a clinical trial for, and we need to recognize that and not over-burden, as Dr. Watson said, the small labs from being able to provide testing for those rare conditions.

If it is a common condition or not rare, the next question would be is there significant medical risks that are associated with the test? For this model, mostly somatic, acquired, and low-risk inherited tests would come through a lower scrutiny model and be reviewed as a Class II 510(k). If there was a significant risk associated, you would ask if the test was for an inherited condition, because that risk would apply

not only to the individual being tested but may also have other risk information for the family members, and that may push it up to a higher level of scrutiny.

This type of model we feel would deal with the pharmacogenomic question in that it's testing for somatic acquired traits that could be a lower scrutiny versus trying to push it into a higher scrutiny model because it's going to be applied to a larger number of people. The primary point is what do we know and what do we not know about the test, and how do we plan for the collection of what we don't know while also allowing things to undergo further innovation in small labs or wherever they may be.

This is going to have to be a phased-in process, and I guess the standards as far as what actually gets submitted for review in a 510(k), in a PMA, that may change over time as you have an initial bolus of tests that get approved. By presenting the literature that's up there, maybe it's easier for them to go through it, but as the process gets rolling, you change those criteria a little bit to adapt to newer technologies and novel technologies.

We can look at non-genetic tests for models and templates that have the same type of intended use. How are things currently monitored for other non-genetic tests that may be intended to be used in a healthy population to predict risk of heart disease or something along those lines. I guess long term, as we go through and work on the second part of it, not so much classification into high or low scrutiny but exactly what data are required to be collected for different tests, we may want to include

HCFA and other payers and their criteria of medical necessity to see if, while we're trying to meet the standard of safety and effectiveness, is there something we can also do to try to prove medical necessity at the same time and kind of mesh those two into one data collection effort.

DR. McCABE: Thank you very much.

Any questions for Michele?

Yes, Barbara.

DR. KOENIG: Just a small point. In the fourth diamond down, is there significant medical risk associated with the test, I know you've testified in the past that you are urging us to not look at the ELSI kinds of risks associated with tests in the classification scheme. So can you just further define what you mean by medical risk there, so I can understand what it is that you're really concerned about or how that would come into play?

DR. SCHOONMAKER: Medical risk, that whole diamond could have a whole triage underneath it. What we mean by that is that you would consider a lot of the other elements that have been put up here. Is there an available treatment? What stage are you looking at? Late-stage disease? Early-stage disease? Is the test linked to a significant therapeutic such that a false-positive or a false-negative on the test result is going to impact what therapeutic is applied to that patient, so that you kind of bring along risk from the therapeutic side of it.

Again, I still have a great deal of difficulty visualizing how to

incorporate social risk. The agency right now doesn't review things like that, and how to incorporate that kind of data collection into a clinical trial to meet approval -- I mean, I guess I have a lot of difficulty trying to figure out how you would quantify that in such a way that you say, okay, this has this social risk, it's been measured, we have to keep this test off the market, versus here's what we've done to overcome it and this test should go on the market.

So from a burden of evidence and data collection standpoint, I find it very difficult to put into the type of review that we have now, because the test is a tool, as we've commented before, and it's what people do with the tool that we feel brings the social risk, not the test itself and how it performs.

DR. KOENIG: Yes, although I would argue that, in reality, the medical risks that you mentioned at first -- for example, being able to diagnose something that you then can't treat -- could just as easily be called a social risk, because you're identifying risk for which there is no consequence. So maybe we're just having an issue of definition.

DR. SCHOONMAKER: Probably.

DR. McCABE: Thank you very much.

DR. SCHOONMAKER: Thanks.

DR. McCABE: One last brief comment from Dr. Chris Palatucci from Athena.

DR. PALATUCCI: Thanks. I'm Chris Palatucci, and I happen to be

with Athena Diagnostics. So since it came up in two of the previous comments, I thought I would just respond to clarify the record.

First, we have not pulled any test from the market. What has happened is we have stopped accepting samples from Burlington Northern, and Burlington Northern has agreed to voluntary suspension of using that particular test the way they had been using it while they're evaluating the situation.

I guess the comment is that we feel that it is important to respond to developments in the literature, in the same way that, for example, in the spinocerebellar ataxias, or in any of the triplet repeat disorders, when you have, for example, a redefinition of the categories that define normal, affected, and premutation conditions, I can think of an example with a new restriction digest that was identified that helped redefine those categories, we feel it's important to try to bring those to the market as quickly as possible.

In a similar sense, when there are data in the literature that suggest that tests can be used to help differentiate between conditions with similar symptoms but that are masquerading as one condition or another, we feel it's also important to bring those tests to the market as quickly as possible.

Thanks.

DR. McCABE: Reed?

DR. TUCKSON: Let me try to understand. Boy, your expertise is so important here.

You're saying you're not taking samples from Burlington Northern anymore because -- is it because they're trying to use a test that you're producing in a way that's contrary to the literature? Or are you saying -- what are you saying?

DR. PALATUCCI: Well, what I'm saying is we're not sure, and I think in the same sense that Burlington Northern is trying to figure out what's going on, we are too.

DR. TUCKSON: Now, did you give them -- because one of the things that we're focusing on, which we're really focused on, is providing information about how a test should be used to people who are using it. Did you provide them information about the appropriate use and indications for this test?

DR. PALATUCCI: No, and I have to say that I really can't comment any further. There is ongoing litigation and we're just not allowed to comment any further. But to my knowledge, we did not go out and specifically say to Burlington Northern, "This is an appropriate use of this test."

DR. TUCKSON: Can we assume that you're saying to them, by not taking their information, that they are not using it in a way that you would feel is appropriate?

DR. PALATUCCI: I don't know. That's what we're trying to figure out. But we have not pulled the test from the market.

DR. TUCKSON: Based on the lessons that you have learned --

DR. PALATUCCI: Yes, Your Honor.

(Laughter.)

PARTICIPANT: Never speed again.

(Laughter.)

DR. TUCKSON: Does this teach us a lesson about what this Committee might want to make sure in terms of the designation, the specificity, the clarity with which a test's purposes ought to be declared?

DR. PALATUCCI: I will leave that to the Committee to determine, but we are providing tools for physicians to use.

DR. McCABE: I think what it says is that labeling becomes very important, and it also tells us that it's very important to have that labeling available to the ordering physicians, and probably to the public as well, so that people understand what purpose has been investigated and shown for that test. I don't know if that clarifies the point.

MR. HILLBACK: I would just second where you were going with that, Ed. I think what it says is that we have to be very careful in telling people what we know and what we don't know. Sorry for my old phrase. And we also, I think, to come back to a drum that we've been beating for a long time, we need to have users that understand this whole area better so they don't do stupid things. We can't totally legislate against stupid things, but we can come close if we have much better educated users. I think this Committee does have a subcommittee working on that, and I think it's just ever more important. These events prove it to me.

DR. McCABE: I also think that that case is another example of why it's very important that we be proactive and not reactive, and the fact that we have been considering these issues for some period of time I think puts us in a much stronger position than if an event occurs and then there's a reactive response to that.

Victor, and then we're going to have to move on.

DR. PENCHASZADEH: My comment is that in the case that we're discussing, probably the most grave situation is that the test was probably not indicated autonomously by any physician. Whatever physician wrote the indication for the test was writing it under orders of the corporation and not thinking of the real health need for that test.

DR. McCABE: Thank you.

We're going to move on now, and I'd like to thank all those who provided public comment. Again, there's more time for public comment tomorrow. We have some people signed up, but if there are others, please sign up at the desk outside.

We're now going to have an update from CLIAC. We'll hear from Dr. Pat Charache, liaison between SACGT and the Clinical Laboratory Improvement Advisory Committee. Dr. Charache will give us a brief update on last week's CLIAC meeting and the group's progress on proposing changes to CLIA to address laboratory quality control and assurance issues in genetic testing. Thank you.

DR. CHARACHE: Well, I've provided a lot more information than I'm going to cover, and I'll indicate where I think you may be interested in looking at

some of it as I describe it.

What I'm going to cover are two things. The report to CLIAC, which was made last week, about the activities of this group, and I'm just going to put a couple of slides in on their response to a couple of the issues that came forward. So I'll comment on particularly their vision of classification. I won't go into detail because much of their concerns have been expressed by others here already.

There was a great deal of interest in the working groups, and there was interest -- and I'll just have one slide on that -- in the response of Secretary Shalala, and we went over her support of SACGT and what she recommended. Then the bulk of what I'll comment on is the discussion, which was a full day, on genetic testing, which was related to the output of the Genetics Working Group, which met on December 7th and 8th. I'll come back to what they covered.

Just one comment on this. This Committee again supported this concept of when the various bodies kick in, when the IRB has responsibility, CLIA and FDA, and the CLIAC pointed out that 2B, which talks about research, has to be under IRB because it talks about research. That's a very minor point but a correction on what we had before.

The discussion of the triage system, the scrutiny level system, was addressed in the context of the perception of the charge to the Secretary's Committee, and we had talked about the interest in establishing this Committee in the first place to address public concerns referable largely to medical and social impacts of genetic tests,

to ensure the quality of the tests for which the FDA was charged with the test oversight, including adding home brews, and the strengthening of CLIA. Then finally, to ensure this quality in a manner that's not burdensome to investigators or inhibitory to new test development.

Now, with that in mind, when they looked at the condensed version of what we had said, first you establish validity, you get into scrutiny Level II if it's not a rare disorder or if it's involved with population screening. I'm just going to point out a couple of the areas in which CLIAC had issues of concern.

The first was pointed out that the prevalence and incidence is not known for many diseases; that the frequency-based triage removes consideration of medical and social concerns; and then the fact that up to 90 percent of the genetic tests fall into Level I. In fact, if you look at the report that we received from Muin today, the work that was done by his group and Joe Boone, it turns out that of tests that are not screening tests, less than 4 percent -- it was 28 of 751 -- would fall under scrutiny Level II. It was felt that perhaps this was too permissive as a function of what scrutiny Level I was.

Now, most of the other added considerations were of a practical nature. Who makes a determination of level of scrutiny? This is not necessarily the FDA's strength area. What is a new test which will be evaluated differently than established tests? What is high-level scrutiny? What is low-level scrutiny? And how do they fit into the FDA's legal responsibilities?

Then, what is CLIA's and HCFA's responsibility for monitoring the issue of informed consent? That's all I'm going to say about this, but it was of interest and concern.

I've put in one slide pertaining to the Data Working Group. There was a lot of concern -- this is a laboratory-based group -- about what the laboratory responsibility is to provide information, as opposed to the responsibility of the clinicians, and who reports the kindreds and so on for which the data is collected. Then the issue of when can you merge data when the methods are not identical. We talk about this in terms of diseases, but when you get into the laboratory definitions, when is it the same and can be merged in terms of predictive values, validity, incidence and prevalence, and so on, if the methods are different?

I put in one example of a lot of information we provided on Dr. Shalala's response, and this is of great interest to them and all of us, and that's the issue of HCFA identifying labs that are providing patient results and are currently under IRBs and the investigators don't know that they should also be under CLIA. This particular issue really has to be handled I think in a sensitive way. There was a lot of interest in that.

There were examples given by Joe Boone in introducing the work of the Genetic Working Group, the CLIAC Genetic Working Group, on what the laboratory division is doing to advance genetic testing, and I thought you'd like to see the range of initiatives. These are all areas in which there are either working groups

established or in which there have been contracts let to work on specific areas of genetic testing. The one we're going to highlight today is the revision of CLIA.

But there's also an initiative to look into the provision of QC material and proficiency testing material, particularly for rare diseases; to create a disease-specific database; develop guidelines on interpretable reports, what should be in a report that goes out, what's the responsibility of the laboratory to provide information; and then there's a major thrust on development of educational materials. So they're working not only on the specifics of the material that I'm going to be talking about, but a range of other products as well.

The rest of the time I'm going to highlight a few of the areas in which the genetic working group of CLIAC has made specific recommendations. There were 41 slides. I've put a little over 20 in the handout of areas that I thought this group would be particularly interested in, and I'm going to show you just a little bit about how they fit together.

The Genetic Working Group is a body of 13 people, of which 11 were either in advanced laboratory diagnostics, mostly molecular diagnostics, and genetics. We had a representative of the public, an ethical lawyer who has been particularly contributory in the past as well.

I'm going to leave this out. I'll skip this. Sorry.

This is the timing at which all of this has happened. The first thing I'll show you is our look at the definition, and there were some changes made in the

definition. The major change was to separate cytogenetics and molecular genetics, which was recommended by this body. There were a few words that had to be changed for that purpose. But this is how the committee looked at it, and they felt that the acquired inheritable should be under each category because technically, in terms of the technology, they're the same whether it's acquired or inherited. It was believed that we should retain both the heritable and the acquired.

Now, clinical validity has very high priority. You may have noted when I showed that slide of the classification, I just put validity at the top because the group feels strongly that clinical validity is essential to interpretation of the test, and the extent of the clinical validity and how you define how much information is required would be negotiable. But the concept of clinical validity they felt was not. They liked the definition put forward by this Committee.

Now, according to the regulations of CLIA, it's the laboratory director who has responsibility for everything that goes on in the lab. So the laboratory director has to be responsible for ensuring that any test offered by their facility is clinically valid for the purpose for which it's offered. They can delegate that responsibility, but ultimately he's responsible and he loses his license to practice, his CLIA license, if he doesn't do this.

This is a comment on the issue of who can order a genetic test. Can one self-order? All of these recommendations I'm showing you were approved by the parent CLIAC committee. The working group recommends to the parent committee. It

was felt that we should defer to state laws, that in those states in which self-ordering is acceptable, provided the laboratory is qualified to accept ordering and meets informed consent requirements, that the self-ordering should be permitted.

In terms of informed consent, a great deal of discussion. This presents a very major problem to the laboratory in terms of documenting that the consent has been obtained. It was agreed that the laboratory should not be responsible for the content of the consent. But if consent is required for a given test, there should be perhaps a check box or a signature on the requisition so the laboratory would know that consent had been obtained.

This is extremely problematic because many tests don't get sent from a physician to a laboratory, but from the laboratory who receives it, it gets sent on to a different laboratory. It can be very cumbersome and extremely expensive to try to document something that's required.

These are just a few of the examples. I'll just read you some of the titles. We got into re-use of samples, when can you save them, what do you do with patients who don't want their sample saved, what has to be on a test requisition before you can do the test, what are the qualifications of the various personnel required for genetic testing of different types.

The issue of genetic counseling. It was felt the laboratory should facilitate access to counseling but shouldn't do the counseling themselves.

Issues pertaining to quality control, test validation, efficiency testing,

results reporting, what do you have to include in a report. You'll see that it includes a statement of limitations of the test and a signature, and a way of reaching the person who has sent the report.

Retention of records, how long do you have to retain records, how long do you have to retain the specimens.

Consultation and guidance, when do you need these.

These slides are all in the handout if you're interested in any particular ones. I didn't know I had included this in the handout, but I did. Let me tell you that the slides you've been looking at were furnished by Dr. Boone and Larry Silverman, who is chairman of our committee. I thought you might enjoy his last little vignette, which may be the wisest things I have told you.

Thank you.

DR. McCABE: Thank you, Pat.

Any questions for Dr. Charache?

Yes, Barbara.

DR. KOENIG: Could you say anything more about the decision about self-ordering or why that was considered to be appropriate, or was it just purely a sense that this was a state right, and so it was just purely political and had nothing to do with anything else?

DR. CHARACHE: There are a high percentage of laboratory directors who feel that self-ordering is inappropriate. It leads to the worried well, it

causes all kinds of problems. But it was felt that it should be deferred to other authority rather than that of the laboratory director to control.

DR. KOENIG: For all categories of tests?

DR. CHARACHE: Yes.

DR. McCABE: Thank you.

We're going to move ahead, then, and go back to our discussion of the proposed genetic test classification methodology. We will take about an hour on this discussion rather than the hour and a half that we had allotted. So I would hope that we could focus on some of the issues that we went over this morning. But there are a number of these issues that we do need to address.

Again, the criteria that we established, are there other criteria that the public has identified? Are the definitions for the various topics -- genetic tests, population, rare diseases -- are they appropriate? Do I hear any discussion?

DR. FEIGAL: Just as a starting comment, some of the way that some of the comments were organized around the theme that they needed to sort of better map out the relationship between the scrutiny levels and the FDA process and the FDA regulatory things. I actually don't think that's the case. I think that you don't need to actually get that level of detail. I think the scrutiny, because of the inherent things that make a genetic test different, are the things that this group should consider and not worry about exactly how does it map to CLIA, to the CLIA process, how does it map to the FDA process, because I think at a simple level, if we can get the tests, which are

along a continuum but you have to make a cut point on that continuum somewhere, if we can get that cut point defined of the test to pay more attention versus less, then I think the kinds of things we presented this morning will be the outcome of having such a classification rather than the classification driving how we do it.

So, for example, the discussion of intended use, which is near and dear to our hearts because it's just the way we've done labeling across product areas, is definitely something we will do irrespective of whether you find it useful or not. Don't worry about having it because we use it, is my point. If it's useful to making the cut on the continuum, take it. But don't take it because you're trying to map to the FDA process.

DR. McCABE: Just a follow-up on that, the classification scheme that Dr. Schoonmaker presented, which is basically a variation on ours using more of the standard procedures that you use in the FDA, you would see taking ours and developing a map something like this. Is that what you're saying?

DR. FEIGAL: Well, no, I don't think you need to. I don't think you need to say, for example, what would be FDA Class III versus 510(k) Class II versus 510(k) Class I. I think the important thing for us is to have a way of identifying what it is about a genetic test that makes it of high level of concern versus a low level. I think actually there's more detail in that presentation than was needed. But I think what's been really useful to us about the process is the educational part of learning what it is that's unique about this large body of tests that identifies risk factors that we don't see for

many other kinds of tests.

DR. McCABE: Thanks.

Wylie?

DR. BURKE: I have two comments that are really in the form of questions to FDA. The first follows on your comments, and that is if, in fact, what we're accomplishing is having a premarket review that looks at a defined set of pieces of information that have been provided according to a template, and FDA is then going to look and make sure that that information is accurate and satisfactory, do we need any difference in levels of review? In other words, are we really just saying we need premarket review, and once a test comes into premarket review, providing the information FDA has required, is there any need for us to separate tests into different categories?

As a sort of corollary to that question, because I think it's part of the same question, I think there's a general consensus from all parties that a test has to demonstrate satisfactory analytic validity. In terms of other properties of the test, is the FDA process likely to be looking at the package and making sure that it hangs together, or is it likely to focus on certain kinds of criteria that need to be met in different boxes in the template, such as clinical validity?

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

DR. FEIGAL: Well, the template is suggested as a way of streamlining and simplifying the application process and realizing that it's a single-

source in-house clinical test we're dealing with, not a manufacturer who is making kits for other people to use and shipping them all over the place. I think that there will be different levels of concern based on different settings. The one that was raised in one of the comments, for example, where someone is working up a kindred and it may be the only family you ever see like that, that's probably one we would have very little interest in having any role in.

On the other hand, you don't have to go very far from that to say, well, we've added another variation to the cystic fibrosis family, or we've found a kindred that seems to have some very interesting things for us to learn about carpal tunnel. What can we do with that?

So it's really a spectrum. It really isn't clean-cut. But I think the reason we focused on templates and on standards is that we want to accomplish the goal for the consumers of these tests to know what's known about the tests, and then we play a role largely in helping set the rules for that and being an independent validator of that information.

DR. McCABE: David, I'd like to clarify just one point. I've made some presentations to various groups, and you made the comment that for a rare mutation that would be found in one pedigree, you, the FDA, would have little interest in that. There has been some concern in the genetics community and in the pathology community that the lack of interest could become a roadblock, that if there needs to be approval by FDA for a very rare test or a very rare mutation or a very rare disorder, that

that might be triaged low on the priority list and therefore could become a roadblock to that.

So I just would like you to clarify in terms of the little interest whether that would mean a quick review, a different type of review, or would it be a lack of review, and what the implication would be for lack of review.

DR. FEIGAL: Well, I think there are still many things that clinical laboratories do that are appropriately regulated through the CLIA process and do not require FDA intervention. So that's one type of cut.

There is another lower level of regulation where many of the things that are required to be submitted are submitted in a summary form or dealt with in a different kind of format. In general, the things that are classified lower for us that are lower on our scale are actually easier to bring to market, not harder.

DR. McCABE: Okay.

Barbara?

DR. KOENIG: Thanks. I just wanted to sort of backtrack a little bit and maybe revisit the issue of why intended use came out of our schema originally just to make it clear, because it had been there originally and then it was taken out. Wylie and I spoke about this yesterday, and I don't really remember why.

Wylie, do you want to address it, or maybe Pat? Just so we're all clear, so we're all at the same starting point in this discussion.

DR. BURKE: I'll comment on the history as I understand it, and then

anybody else can comment.

We were very interested in intended use as a criterion for level of scrutiny, and we particularly were interested in whether tests would be used for predictive versus diagnostic purposes.

What we discovered, and I think this discussion mostly occurred at our last meeting, was, first of all, that there was likely to be a lot of difference of opinion about what constituted a predictive versus a diagnostic test. One example that was given that came up for discussion was whether or not a pharmacogenetic test -- that is, a test done to predict the response to a particular drug -- was a predictive versus a diagnostic test, because some laboratories suggested that would be a diagnostic test, others thought that that seemed to be pretty clearly a predictive test.

Another example, a common definition that's offered for predictive test as a clean definition is when a test is done in an asymptomatic person. Yet I think we just heard in earlier discussion that if you have a test with very high predictive value for which there is an intervention that's well established, then that's not the same kind of test done in a healthy person as a test that predicts a probability for which there may be a less certain or unavailable intervention. There's more nuance there than that definition seems to imply.

So what my understanding of what happened was that we had that discussion and decided that a test classification scheme that had the purpose of putting tests into different scrutiny levels had to be simple enough and unambiguous enough

that it could be easily administered, and if you had that much disagreement about what the terms meant, you couldn't use it in the classification scheme; not that intended use wouldn't be a major factor in looking the test over, but rather that that couldn't play a role easily in a classification scheme.

A corollary issue and concern was that very few tests that would be used or have the potential to be used as predictive tests would not first come through as diagnostic tests. So for the purpose of premarket review, it wasn't solving the problem to focus on predictive tests. That's my understanding of what happened.

DR. McCABE: That's my recollection also, that we had tried to streamline the triage process and felt that some of the issues like intended use that had been on our initial schema were too complex for the initial triage but would become part of the evaluation.

I have on my list Elliott, Muin, Pat Charache, and Joann.

MR. HILLBACK: I guess I wanted to go back to Wylie's earlier question, David. One of the issues that led us to talk about different levels of scrutiny was the fear that for most tests that didn't need it, we were going to get an awful lot of evaluation that would slow things down. When I listened to you and Steve today and saw this template and heard your very clear statements about making sure that the template was complete but recognizing that boxes like clinical validity might have very little data in them, if you really mean that, that that's acceptable and that it's not going to be an impediment to get a test into the market, then I would re-ask the question Wylie

asked, which is why do we need to try to create some artificial groupings?

If, on the other hand, we're going to have some cutoff that says clinical validity of X or Y is going to be required, and if it doesn't fall above that we're going to have a clinical trial required and everything else, we're going to have a much more complex system to try to deal with.

So I'm trying to get a feel, I guess trying to ask you again how your process works.

DR. FEIGAL: Well, actually, as I understand the question better when you restate it and I think about it a little bit more, particularly because I think Steve and others have worked hard to frame most of this within the 510(k) flavor of regulation for the tests in the home brew setting, it may well be that you actually could use a single template framework for supplying data. I guess the question you're asking -- and I'm not trying to answer it by just rephrasing your question -- is are there blanks on the template that would be unacceptable for some tests?

MR. HILLBACK: Right. Could I clarify for one second?

DR. FEIGAL: Sure.

MR. HILLBACK: I think if intended use was blank, I don't know how you could send it in.

DR. FEIGAL: That's right.

MR. HILLBACK: If analytic validity was blank, I don't know how you could send it in. So I think we would believe that some boxes would have to be

filled in, but there are others -- and that's the issue of clinical validity versus clinical utility. If the only utility is the patient could self-monitor and watch the developments around a certain disease because there may be some risk, that's utility to some people. If that's where we are, then it's a different ball game from where we have been, or where some of us feared we might have been.

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

DR. GUTMAN: The issue of classification is one that has been discussed. It's sort of a light motif in the background of the Professional IVD Roundtable. We have, in fact, been trying to find ways to accommodate, to match our program, which actually has three classifications, but it's even more interesting than it might seem, because Class I actually comes in two flavors, Class I reserved that we review, and Class I exempt that we don't review. We have a history, even though we're not using it very aggressively now, of taking products from Class I or II and triaging them, so that some have intense clinical reviews and some are brought down to labeling reviews.

The suggestion was put on the table in the context of the Professional Roundtable that we ought to consider a uni-class, that they were all a single one building off the template, and we do have always this special right, depending on how generous or non-generous David and my management would be, that if we see a new device that's frightening or that raises what we would consider new issues of safety and effectiveness, we never give up that thought of taking a particular device and trying to hound

management into allowing us to review a particular device at a higher level.

So the fact that we might treat many of these, most of these, perhaps all of these based off a standardized template in a user-friendly way doesn't preclude us from saying, oh my God, what have you done? This is a PMA.

DR. McCABE: Muin?

DR. KHOURY: I just want to go back and revisit some of this discussion. It looks like from our discussion over the last six months, on and off, plus a whole host of public comments, plus the roundtable CLIA work, our evaluation of the gene tests, I think it's safe to say that no new elements have been identified, that all the issues are on the table.

MR. HILLBACK: Beating a dead horse, is that it?

DR. KHOURY: Well, not a dead horse, but maybe dying.

(Laughter.)

DR. KHOURY: I think this is sort of a revisiting of the issue of whether or not we should have different levels of classification, especially if there is a common data template or an application template. I'd like to reiterate my position here, because if we're working at the premarket level, that's one thing, and we'll have a lot of empty boxes. But a lot will be done at the postmarket level, and I think it's important to make a distinction that would help us and other groups to prioritize from a public health angle where we need to emphasize a lot of the resources.

Let me just revisit the analysis of the gene test database. That number

is not high right now, although it will get higher. I mean, we can fine-tune that classification. We're dealing with 10 percent or less of the existing tests. But there are issues that need to be resolved there.

For example, pharmacogenomics doesn't fit, the issue of using two different cutoffs. I mean, some of the issues I put on my slide, and I think we can resolve some of these issues and then move forward, because I feel we've reached the point in the curve where we're approaching infinity or 100 percent situation, that no matter how much we massage this a bit further, we're not going to identify any new issues but re-hash the old issues. At some point, this Committee has to give the work to the agencies to implement that work and then hear a status report, what the FDA is doing, what the CDC is doing, what CLIA is doing, and then reserve the right to revisit these issues a few months or a year or two down the road.

DR. McCABE: Thank you.

Pat Barr?

MS. BARR: Oh, you saw me. Okay.

DR. McCABE: Can you put the mike closer to the phone, please?

MS. BARR: That just brings us back to an issue that a number of people brought up and another Committee member brought up, and that is will there be a time, and would it be possible, to condition in this review process postmarket data collection? Is that going to be an option as part of the FDA review, or is that absolutely off the table?

DR. McCABE: David?

DR. FEIGAL: The usual requirement in devices for postmarketing studies are for safety reasons, not to establish new indications or efficacy. The usual standard is that if there is a credible, established safe and effective use, then the product can come on the market for that use, even recognizing that there will be all sorts of off-label uses and even overly creative uses in the practice of medicine. The manufacturer often, for a variety of reasons, does the studies in the postmarketing period to add indications over time, and that's much of the postmarketing that Muin was referring to.

But other times, they will not. They will simply market it based on the indication that they have and let the practice of medicine expand the use of the product. So there isn't an accelerated approval on the device side the way there is on the drug side. There it's also fairly limited.

I think where the rubber hits the road is with these issues where you might have a laboratory which can very reliably detect an interesting gene, and is that a sufficient indication? Or how much more needs to be known about the genetics? How large an experience of the clinical correlation between that gene? Or do you make this a marketplace, let the clinician beware? They know they're measuring the gene. They may know that nothing else is known, and if they wish to measure that, should that be allowed?

These are the sorts of questions that get back to the issue of how many boxes can be left blank, because if the indication is to measure the gene, the company

can measure the gene, you've got analytic validity for the gene, and you've got one kindred, is that your minimum data set to come on the market, and then hope in the postmarket period you'll find much more specific useful information? It's a very hard question. It gets back to our framework of risk/benefit. What are the risks of that information? And there are many people, which has been alluded to in some of the comments, who value the information per se as information and don't need an intervention to make the information useful to them. Those are very hard questions for us.

MS. BARR: I guess my concern is that we've all agreed we're entering into a new stage and this is a new technology in the sense of the way it can explode, as some of us feel, at least, the lawsuit of this week or last week shows once again. It's not the first time. And we also agree that these tests become far more valuable to the consumers, at least, when they are better understood.

So I still struggle with that. So I just wanted to put on the table that I still struggle with that.

DR. McCABE: Elliott, brief follow-up.

MR. HILLBACK: Pat, I'd like to respond to both your point and David's comments. I think we all agree that there are several things that help mitigate that, but we certainly need to keep doing the work. One is that lab directors who are signing out the cases, which is a requirement, are reviewing the literature and are going to continue to cast their net as wide as they can to get as much literature as they can to

improve their knowledge about the results they're sending out.

I think the fundamental problem we've all struggled with for years, Pat, even back to the previous committee, is that the source of this information generally isn't the lab. So the work that the CDC is taking on and that Muin has started, that whole set of efforts I think we have to find some way to continue to support. But to put a requirement on the laboratories to try to chase the data, they're not the primary source of this data. It's really the whole medical system that's the source of the data. I think it's the onus on the lab director to continue to stay up to date that's going to at least keep them reviewing whatever the latest, current bolus of data is.

DR. McCABE: Pat Charache?

DR. CHARACHE: Two comments, one on scrutiny levels and the other intended use.

On the scrutiny levels, I certainly see an advantage in having a separation between those tests that are of greater concern and those that are lesser if we can come up with it. With the current criteria, I have express concern with the fact that over 90 percent of the tests are considered rare, and I'm not sure Mary wants to address all of those in her committee group when it meets tomorrow when you try to use that type of a separation.

I think there is a risk in having only the frequency of anticipated use as the dividing point when you get into setting precedents for other tests which will follow. It won't just be genetic tests but it would divide a lot of tests potentially that the

FDA sees into populations and remove a lot of oversight potential that may be less structured than the genetic tests.

In terms of the intended use, Wylie is correct. When it was tried by the Genetic Forum, it didn't work, because all of the tests that were explored were both. So we saw it just being used inappropriately to get tests through the door as diagnostic, when in fact it could be diagnostic on one member of a family, predictive on others, and so on.

At the same time, the intended use was not discarded as a component of what you looked at in terms of your evaluation. There it became very important, and here I have a question of the FDA. If a physician uses a drug off-label and uses that drug in a way that was not approved by the FDA, and there's patient harm, that physician is legally liable for having used it against the FDA recommendations, or not?

DR. FEIGAL: No, it doesn't have anything to do with the FDA. It's practice of medicine. You see, with the pharmaceutical and with devices, the real focus is on FDA regulating the manufacturer. The area where you might be able to make a case that there was an issue, but it wouldn't be a liability issue, would be whether there was unsafe experimentation, and whether by even using an approved product in an experimental way, you had violated the federal law of using a product experimentally. But off-label medicine is explicitly legal. There is no FDA penalty for off-label use.

For a clinician to promote it to the extent that they become a manufacturer, a purveyor of an unapproved product, then that gets into that gray zone.

Misadventures in the practice of medicine are regulated by the tort system and the by medical licensing and the states and not by the federal.

DR. McCABE: Kate, would you like to share the comments you made over lunch regarding the FDA?

MS. BEARDSLEY: Yes. I was going to say that I'm not an expert in medical malpractice, but I've occasionally read a bunch of lawsuits in medical malpractice specifically for FDA implications, and what you see historically in all the old cases is that FDA never even comes up. The question is, was what the physician was doing standard of care in their local community?

In the more recent cases, people begin to ask the question, well, at least was it disclosed to the patient that the treatment that was being given was not an FDA-approved treatment? I'm not sure that I've seen any case in which that has swayed the result, but it is at least coming up in the evidence at this point.

DR. McCABE: The list I have now is Joann, Kate, Michele, Victor, Judy, and Reed. So if I've missed anyone, please let me know.

So, Joann?

DR. BOUGHMAN: I would like to encourage us to incorporate the materials that have been presented today in the next steps of the process rather than simply staying wed to what was on paper before. In very important ways, it seems to me that the template presented this morning by the FDA actually has the consequences of tying the intended use to the problems that we have had when we were trying to fit

this into a yes/no scheme. What the template has done is asked for intended use right up front, and then in the third and fourth page, when information is requested on clinical validity, the various kinds of quality assurance, clinical interpretation, it says assay limitations. I might go beyond just the assay itself and talk about test limitations that might include limitations of the interpretation of the results, and then clinical utility.

If, in fact, the intended use has one of those more difficult, more complicated or red flag issues that we have all come to, I think, some consensus about, then there would be a different level of expectation in the other boxes there in the amount of information or whether referral of a patient or inclusion of documentation of informed consent or any of these other issues would be tied. But I think they have given us a way to, in fact, incorporate the more difficult questions rather than forcing ourselves into a strictly yes/no dichotomy.

Which leaves me with the last box of the rare and whether, given us drawing a bright line and saying does it fall on the left or the right of that line. I'm not sure that we need to necessarily fall into that trap at this point either given this kind of format. If this is a rare disorder, no matter what the incidence is or whether it's this year's incidence or a cumulative incidence, then the expectation would be that the documentation would support the use as intended and declared by the submitter of the application.

So it seems to me that we actually have taken a step beyond our dichotomous classification scheme.

DR. McCABE: Wylie?

DR. BURKE: I think you're saying, Joann, that we've got a scheme now that says analytic validity yes/no -- or maybe it doesn't even say that. It says test comes for premarket review. Analytic validity is probably the first thing FDA looks at, and subsequent to that there's a template-driven analysis. But it seems to me we are removing levels of scrutiny.

DR. McCABE: Do you want to respond, David?

DR. FEIGAL: I think that the more we talk about it, I think that we do find that the template may be a way of bridging some of these areas.

The other question that we're not really addressing, and it isn't very well addressed in some of the public sources of what's known about these tests, is which of the tests would we still consider developmental and still in an experimental stage? That also is another variation on the question of how many of the boxes can be blank and the product still be available? Is it available as an experimental product with the controls, or is it one that is considered for approval?

DR. McCABE: Pat Charache. Briefly, please.

DR. CHARACHE: I think we want to get away from the concept that something is for research only and the results go back to clinicians. So I think the concept was that if the report goes back to a patient, there must be enough clinical information available that it can be interpreted. Now, the limitations may be very great, and you may say this is the only thing I know about it, but I know something.

Then the question is who makes that decision, and what the level of the fence should be that you have to jump over if it's a rare test and there are very few patients, versus a common test and it's easy to do. I think we can come back to that issue, because there will be differences in the quantity of information in these boxes depending on the test and the intent.

DR. FEIGAL: Well, I think you set a very high bar if you say that a product, the results can only go to the patient if it's not experimental, because there are some settings where you wouldn't be able to get the clinical information that you need for the approval without providing it to the patients who had participated in the studies to get it to approval.

DR. CHARACHE: Yes, that was the reason for these Level IIA and IIB, when you can give information to a patient. IIA was very limited data available. IIB was when the FDA kicks in and there's more information. But they're both CLIA, they both come under CLIA.

DR. FEIGAL: Well, this might be another topic. I don't know if we're getting off the topic, but the experimental use of medical products very heavily involves testing in patients. Patients know they're being tested, know what the results of the tests are, whether it's a drug, a device, or an in vitro diagnostic. So am I misunderstanding that the framework says that for clinical results to be provided at all, the test has to be approved?

DR. CHARACHE: No. The lab has to be operating in a manner

that's consistent with CLIA approval.

DR. FEIGAL: Okay. I guess the question is, is there any role for -- one of FDA's mandates is safe use of experimental products and requiring informed consent and protocols and all that type of stuff. So how does that fit in with these products? Because some of them have so many empty boxes that when you look at them, you say you're still collecting data on your product, you're not ready yet to present a submission. So you should still continue to collect the data, but it's still an experimental product, not an approved product.

DR. CHARACHE: That's true, and that's why the IRB is involved and there is informed consent, when appropriate. But we can talk about this also.

DR. McCABE: Kate?

MS. BEARDSLEY: I had two thoughts. I thought on the first one, on the classification system, I'm kind of going with the flow here, but it seems to me that if we're not going to really tie our levels to a particular regulatory process, it may be that we don't need them. It also seems to me, though, that we've had a lot to say here over a fairly long period of time, and it would be nice to capture what we've had to say in some sort of an organized way so that we could give it to FDA so they would at least have a list of things to be thinking about.

It may be that even within categories -- for example, you might say, well, we want a higher level of clinical validity for this test because of this factor, and we'd accept a lesser level because of this. But I don't think we can deal with that. I

think we have to trust FDA to deal with that. So I would propose that we try to capture what we've said in some sort of list.

One other thing. I also want to pick up on what Pat Barr said about post-approval information collection, because that seems to me to be really important. I think we're going to be putting a lot of pressure on FDA to want a lot of data if we don't have some way to capture data after tests are already on the market. I don't know how to get there, but I wonder if there's some way to think again about the extent to which the tools that are at FDA's command to help us do that.

DR. McCABE: Michele?

DR. LLOYD-PURYEAR: I also want to go with one level of scrutiny, mainly because it focuses on the label and the idea of truth in labeling. I really like that in filling out that template. But one question for FDA is at what point do you step in for market approval, because some of that filling out of the template is premarket.

However, what I also like about it is that it allows a focus or it pushes a focus on the importance of educating the users, users broadly, both consumers and health care professionals, because I think that's where some of the decisionmaking needs to take place, and I think we need to start reflecting that. We cannot regulate behavior or solve the problems by regulating behavior through FDA. I think we need to recognize that resources need to go towards consumers so they know how to make good decisions about those tests, whether or not to accept them, so you don't have what

happened at Burlington happen widely, but also you don't have health care professionals using the tests unwisely.

But at what point would the FDA then step in? Doing what you're doing, at what point do you step in and say this is ready to go on the market for that intended use? That's what you need, is how to fill out that template, then. Right?

DR. McCABE: Do you want to respond, David?

DR. FEIGAL: Well, if you work back to how much data do we need, many times you end up coming back to the problem where everybody says, well, you obviously have to have analytic validity. To have analytic validity, you've got to have samples, and you've got to have enough of them that you can establish the reproducibility of the test and some of these types of things. So some of the rhetorical questions, including the ones I've asked, like how many kindreds are enough, really get answered by having to answer some of the questions on the template.

Let's say we had a really good predictor of carpal tunnel. Is there any labeling that would prevent an employer from using it in a way that was socially unacceptable, as opposed to medical bad information? No, probably nothing in the labeling. I think those are probably different sets of societal controls than FDA's.

DR. LLOYD-PURYEAR: But as far as changing your intended use, which gets to what you're talking about, as you gain more knowledge, you can change the use, and that would demand an active collection of data, both clinical data -- well, clinical data.

DR. FEIGAL: There are often competitive pressures for people to have accurate and up-to-date and expanded labels. I mean, Elliott doesn't want to hide his newest findings under a bushel or anything else, and so these things get brought to us all the time. Then the question is what are the rules for evidence for additional claims and all those kinds of things. We have a long history of negotiating those kinds of things.

MR. HILLBACK: But I think the other point is that -- remember, we do have a lab director who is an M.D. or a Ph.D. signing out these cases, and they come as close to practicing medicine in a commercial setting as anyone I know in the world, and they are professionals who demand as much data as they can get in order to make appropriate reports. That is an incredibly important factor that we sometimes forget about. They taught me this factor. They keep reminding me all the time. But I think we should remember that that is there.

DR. FEIGAL: I think that's true now, but there are products that are currently done by the tens of thousands robotically, overnight in laboratories that go out in the morning, and we're looking at arrays that measure 10,000 things at a time. So I think that we have to think of not just today's challenges when we're picking these things off one by one, but what happens when people take advantage of the common technologies and give us information from a fire hydrant rather than a faucet.

DR. McCABE: Victor?

DR. PENCHASZADEH: Some of the things I was processing while

we were having all this discussion were voiced in large part by Joann, in the sense that it seems -- you know, what makes me a little bit uncomfortable with the scheme that we arrived at last time is that this kind of schema that we arrived at last time that this reneged on all the concerns that we had been voicing, particularly about intended use, particularly about the need for clinical validity and clinical utility information, and about all the medical and social risks.

But then thinking about why we've done that, I guess most of what we are trying to do is to strike a balance between the capacity and the need for regulation on the one hand, and the availability and accessibility of tests on the other. Probably as the survey that Muin's group did proves, we kind of shifted our bar or lowered the bar too low, resulting in less than 10 percent of the tests actually going to a scrutiny that we felt was a scrutiny for complex tests of some sort.

Now, I'm really baffled by the issue of intended use, because it seems that, from what I'm hearing, it's useless, it's a futile exercise, because the intended use will always be the one that requires the least scrutiny. Now, once that happens and you have something on the market, then you get the off-label use, and from what I hear from David is that it's almost impossible to prevent off-label use. The off-label use will go essentially under a different category of guidelines, and this will be essentially standard of practice or professional organizations' guidance and so on.

So I'm not clear, and this is one of the questions I have, about how often it is for tests, at least, you get requests for additional intended uses, because from

what you're saying, they're not needed or the medical care establishment or whatever doesn't require an additional intended use once they have a product on the market. So all the expectations put in postmarket data gathering, what will they accomplish? They will eventually come up to reverse a product that has been approved only if severe circumstances of efficacy or risk are proven by the data. But if that is not the case, and correct me if I'm wrong, but the product will stay on the market.

A related fact or matter is the question of the template that David has put forth, and I'm still unclear as to what role or who and how the criteria for clinical validity and clinical utility will be used for market approval. The template says clinical validity, but will many of the things that we have been discussing here for months be here, and what weight will they have in an FDA decision to approve a particular test? The same is true for clinical utility. I agree that most times you will not have it at the time of approval.

Then the second question is the issue of is there anything between market approval and rejection. I would like you to explain what Tony was referring to as a condition of premarket approval. Is it something that is a category that does exist, and what would it entail?

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

DR. FEIGAL: Yes, just quickly. The conditional approval is also called accelerated approval. It only exists for drugs and biologics, not for devices. It required confirmatory tests to demonstrate clinical benefit for a product that had usually

established benefit from a surrogate marker. So an AIDS drug could show that viral load had fallen, and then studies would be continued to show that that prevented disease progression.

Your question about clinical validity and where does that fit in, it relates to the basis for approval of in vitro diagnostics, that they have to measure something that's known to have some clinical value. That's the benefit. So the question is sort of how far can you extrapolate from that? PSA might be a good example. It's a test that was approved because it could detect tumors earlier. The real clinical utility would be whether or not that affected long-term survival. That was never demonstrated, but it was considered biologically plausible that there would be some utility to finding tumors at all and finding tumors early. Had they come in and said it's just PSA, we want to market it as just PSA, as information that someone might find interesting, that would not have met our criteria for approval.

Some genetic tests won't have any problem with their clinical validity. Somebody comes in with a new way to find a sickle cell mutation, we already understand that. The new manufacturer won't have to reestablish that. There are some other areas where there's a gene, but it's a gene in search of a disease, or there's a complex relationship between multiple genes and the disease. These will be the hard dilemmas in the clinical validity part of it, but it's very much part of the FDA process for the approval of an in vitro diagnostic. I'm not sure I got all your questions.

DR. PENCHASZADEH: Yes. Now just to conclude, the last

question is for everyone, whether we really need different levels of scrutiny. That perhaps would be a specific question for you, David, in the sense that whether or not you feel that if we just outline concerns to be addressed by FDA in their approval process, whether you consider that that would delay the approval process to unacceptable levels.

DR. FEIGAL: Well, there's again a spectrum of issues. I think that there are certain things that are difficult to establish in clinical medicine. One of the things is to predict late events or to predict things where there's a complex relationship and it's only partially predictive. It's all those areas where something isn't obvious, and those have been the tough points.

Let's take Alzheimer's as an example. You want to predict Alzheimer's. You get your test result, and you have to wait, particularly if you don't have some mechanism of working with patients who already have the disease. So it's a question for those kinds of products. Do you put them on the market with labeling, saying well, we don't know much about this, but it reliably measures this gene, or do you have to establish that there's some clinical value to the test? The FDA standard historically has been that there needs to be clinical value.

I think there are many, many conditions that we think will be targets where the value will be self-evident because of the known relationship between the gene and the disease, and those examples come up. But there will be others, such as predicting cancer risk, other kinds of things where it will take time to do those studies to

find those kinds of relationships. It would still be our position that it's not appropriate to market that you know those things will predict cancer until you've done those studies.

DR. McCABE: I have a list of seven people that we have to hear from, and we have about 10 minutes left. So I would ask you to be relatively brief.

Judy?

DR. LEWIS: As I've been sitting here listening to us discuss our schema, we're discussing it in terms of those conditions and those tests that we know about today, and we're trying to develop one that's going to be usable for things that we don't even know exist yet in terms of the future. I think that that might be a piece of our struggle, that we're trying to do something that's going to cover all possibilities when we don't have a clue what the possibilities mean.

I think when Pat Barr started talking about the need for postmarket data, we may need to have this template that's going to be very flexible as new data come on board, and that what we're trying to do is to develop something that's going to cover all possibilities because we're doing it based on what we know and we're trying to predict things that we don't have a clue what they're going -- we have maybe a little clue what they're going to look at.

So I think that might be part of our struggle and might be one of the reasons that we need to have something that we revisit on a regular basis.

DR. McCABE: Reed?

DR. TUCKSON: I am, like everybody, struggling, because I

embraced and celebrated the simplicity and elegance of what we had. I must say that I am really thinking hard now about how can we avoid the intended use, the clinical validity, and the experimental versus ready for prime time question when I think about the question who is going to pay for any of this. Given that we are talking about a very fast-forward, as we said that the clock is spinning rapidly for us, at the end of the day, somebody is going to have to make some decisions about paying, and it's not going to be on the small scale of somebody going in their pocket individually. At some level, it's going to quickly get to the employers and that whole benefits determination decisionmaking.

So at the end of the day, if you do not have information about what this test is intended to do, about its clinical validity, and it's not clearly stated, it's just not going to be relevant. We're going to wind up having to go back in again and rediscover fundamental things. So there's a whole pathway that we're not discussing here. The Access committee meets tonight or tomorrow morning and will report, so I don't want to preempt what they will described.

If we're worried about the off-label use question, again, at the end of the day, professional societies are going to be the ones to make the standard of care decisions, but they're going to make it based on evidence-based medicine, which is based on postmarket data, and then go back and redefine and update the intended use. So we keep coming back to the same place.

I guess where I'm stuck is I just don't think we can avoid this question,

but I don't want to wreck the elegance of what we have. I'm trying to figure out the answer to it, but I think we have to figure it out.

DR. McCABE: Muin?

DR. KHOURY: Can I present this briefly?

DR. McCABE: Briefly.

DR. KHOURY: (Inaudible.)

DR. McCABE: Why don't you wait until you get to a mike so we can capture your thoughts? You don't have to be so brief that you talk and walk at the same time.

DR. KHOURY: It seems to me --

DR. McCABE: Use the lavalier mike, please.

DR. KHOURY: Forgive my handwriting here. I always put it upside-down.

It seems to me we're trying to marry two concepts here. One is an initial classification scheme with the idea of a data template. We've seen earlier this morning how powerful that can be in showing what we know and what we don't know, from the premarket phase all the way to the postmarket phase. It seems to me, from a public health angle again, if a test comes on the market today where all newborns are going to be tested for it, not only do I want to know about its analytic validity and its clinical validity, but also its clinical utility.

It seems to me this could be a quick schema to differentiate between

the Level II's and the Level I's in which you can apply a certain standard of review at the FDA level, and then follow with that the postmarket level where you require all the boxes to be filled. For example, the analytic validity is a requirement for all tests. If it's not analytically valid, it's a useless test to begin with. In terms of the clinical validity, you want it definitely for population testing, and I'm thinking about pharmacogenetics right now at the same level as Level II, because it will affect medical practice, it will affect the way drugs are given.

Where you get into this gray zone of how much data do you need, especially for the rare diseases, where you know upfront that there is not much data available, so you might apply perhaps a more lax way of reviewing things, where you say this is based on only five families, we know it's rare. The clinical utility may or may not be relevant, but if it's associated with an educational or a counseling component -- so if there is a way, and I'm starting this as a way to capture what we've done before, not throw away the classification scheme, but tie it or some variant of it with the template that we've been working on and the levels of data that we want in terms of the initial review.

So I don't know if people agree with me on at least the first two columns here, where you need all these three elements to evaluate a test that's going to be used for whole-scale population screening or the administration of drugs. Where I tend to break down a little bit is in this rare versus common category. I waffled a little. I mean, clinical utility will definitely not be available. Clinical validity may or may not

be available. So I'm offering this as a starting point for discussion, perhaps for more thinking about this.

DR. McCABE: Wylie?

DR. BURKE: I actually think that Muin is offering us a concrete example of perhaps where we need to go. The comment was made earlier that we've had a lot of rich discussion, and if we go to some simple scheme that doesn't have different levels of scrutiny, we don't want to lose it. I think it's already clear that we're not going to lose it because we're already beginning to incorporate it into the template.

I think one of the reasons why we feel like we've really made some progress is that we begin to see how a template might be used and would incorporate elements that we've already seen are critical. In particular, I think FDA's version of the template showed us how intended use comes in right at the beginning and becomes part of what you look at in a test.

What I think we may want to think about in moving forward is how much of our discussion is captured in the template, and to what extent we might want to see further work on the template, maybe something interactive between the Committee discussion and FDA's thoughts about how to go about it, that incorporates some of the ideas that Muin has outlined here. So as one looks at the template, it's not just what blanks are filled and is it enough blanks, but depending upon what's in one box, you look a little more critically at what's in another box. I suspect that a lot of the discussion we've had already would inform that process.

I think, as we think in those terms, that we might want to have some very concrete discussion about what additional guidance we might then provide to FDA, or advice we might provide to FDA above and beyond the structure and the content of the template. That is, we might want to think about providing some general guidance points to consider that have to do with types of tests or types of testing circumstances that should raise cautionary notes.

What that really means is that we might want to operationalize those test characteristics that would make us want to think about documentation of informed consent. What kind of tests are those? Can we operationalize that? We might want to try to operationalize, to the extent that we can, circumstances that raise high concern about social risks, and some ideas might be testing in children, a test that has an intended use that would result in testing in children, a test that has an intended use that would result in testing a racially or ethnically defined population, a test that tests for multiple different conditions, a test with what would appear from the data provided in the template to have very low predictive value.

I just want to note, because I know we're all feeling pressed for time, that some of that discussion can come up very naturally tomorrow when we discuss public comment on the template.

DR. McCABE: Yes, I think we're transitioning very quickly into tomorrow's discussion and beginning to wrap up this discussion.

Elliott, Joann, and then Ann.

MR. HILLBACK: I'd just like to follow on the comments several people have made. I think what we have to remember is that what we've been looking at here is a template to try to help us at the time we begin to use a test out in the environment. I think we all have to remember that this is an iterative -- to use my other favorite word -- process from that moment for the next X years, maybe forever, which is a long time, or just short of that, where the database, the data set is going to keep changing.

I think this deals, Reed, with your concerns about who is going to pay. There are some payers that will pay immediately with almost no data, and there are other payers that will not pay for years. We may not like that, but that's the way they are. It's the same with intended uses, to go back to Victor's question. If a laboratory or anyone else wants to market various intended uses, then they have to show that those intended uses make sense.

So the knowledge set will grow because the test will be used more, and more information will be generated. I don't think we want to say it's easy to get that data together, because we've been saying for years, both in the task force and in this Committee, that it isn't, and that's why Muin's work is so important, and others, and the rest of what HHS has been doing. But I don't think we should say we've got to have all that done before we get a test to the market. We have to say let's get it to the market with a hurdle that we're comfortable with, and then a process that includes the entire medical community, not just a laboratory, to update that in some regular way to make it

useful.

I think if we can get past that, then we can deal with the pre and the post and the ongoing, whatever.

DR. TUCKSON: I agree with that, Elliott. I think what I just was concerned about is that if you create a system that is the essential regulatory determination system that is, therefore, the hurdle that everybody must jump over, if you don't build in the data elements, like saying what the heck is this test for, I'm worried that it becomes an enormously complex, expensive, and bureaucratic nightmare to go back and recreate that data path, when if you had just built it in on the front end, it would be so much more streamlined. I think Muin and them are dead if they don't get that stuff on the front end.

MR. HILLBACK: But you can't offer a test if you don't know what you're using it for.

DR. TUCKSON: So just declare it.

MR. HILLBACK: That's right, and that's why it's so important that it's in the template that Wylie's committee that worked on the template originally defined, and the FDA took it a couple of steps further, which I think was great, and I think we just have to make sure that that's there and that that is a crucial element that we have to have in the process, because that's the first thing that a reimburser, whoever it is, the government or private reimbursers, says what the hell are you doing with this test? If you can't answer that question, you don't deserve to get paid.

DR. TUCKSON: I completely agree with you. I know you've got to move on, but I don't want it to be that we're talking about, and I don't think anybody is, burdening the labs as the only place. I'm saying you've just got to get that stuff in on the front end, and if you don't do that, then you're going to spend a fortune.

DR. LEWIS: I think some of this is going to come out when we report out on the Working Group on Access tomorrow in terms of some of the reimbursement issues.

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

DR. BOUGHMAN: I know several people in the room have been involved in one way or another with the FDA process. One of the things that I am sure of, and I'm not sure of a lot of things, but one of the things I am sure of is that this group nor any specific group in the FDA is going to be able to predict or cover all the contingencies at the beginning of this process. We will never be able to explain, account for, or stop a few of the people or labs or corporations or manufacturers who will try some very strange things.

However, I think we do need to depend on some combination of common sense and consensus built upon both the science and the art of the practice of health care, and what the FDA folks brought to us this morning brings with it years and a broad experience in similar kinds of applications or processes for other testing processes. To that end, Wylie, I think your approach is right on target. I would encourage us to focus on those issues that tend to be specialized or special to the genetic

testing process, because FDA has been through some of these others.

The question of is a thousand samples to have already been tested enough or not enough? Well, it depends on the range of values that those samples showed, and every one of the presentations is slightly different. We have to be able to depend on the process.

To that end, I would also suggest that the beauty of the template here, for those of us who know we will continue to be involved in this FDA process, the idea that the intended use space would actually accommodate bundled or microarray-based tests for two or two thousand tests, and if that's the intended use, then I expect to find on the other pages the explanations that go with the bundled or all of the microarray and how that information is going to be presented. That's the beauty of the flexibility of this approach.

DR. McCABE: Ann?

MS. BOLDT: I'm also having just a difficulty understanding who is going to make a decision if these tests are high scrutiny, or are we even taking about that anymore in terms of informed consent, and also genetic education and counseling. You did touch upon that. Is this template actually going to provide us -- if we have empty boxes, then that's going to be a high scrutiny?

DR. BURKE: I think I go with iterative. I like that word, too. But it seems to me that is really where we should focus our attention. What we figured out, I think so far into this process, is we can't create a simple classification system that's easy

to administer that points directly, bingo, to the high scrutiny test. But I think what we have done, with now at this point a great deal of consistency, begun to articulate what mix of qualities of a test make it a worrisome or high scrutiny test, and I think we should make that explicit in the form of points to consider for FDA.

DR. McCABE: Pat Charache?

DR. CHARACHE: My comment can go tomorrow.

DR. McCABE: Okay. Thank you very much.

I think this is a natural transition into tomorrow's discussion. But before we leave, we had some time for general discussion, but I'm going to structure that a little bit.

Michele, this would be a good time to perhaps report on your meeting with state legislators in light of some of the discussions that we've been having today.

DR. LLOYD-PURYEAR: Both Sarah and Ed had wanted me to report on a series of meetings we've been having with state legislators. We've had four meetings, two of which both CDC and HRSA were at, but no other federal agencies. But some state public health executive officials.

But the main focus, the main audience in all the meetings were state legislators from all over the country. The last two meetings we had were in January. One was in San Diego and one was in Tampa, Florida. Ed was at the one in San Diego. These last two were held in the form of focus groups to actually look at issues around the Secretary's Advisory Committee's report that had just come out, and also some

specific areas of newborn screening that were of interest to us.

There were two things that I thought were probably of interest to this Committee. We will have a summary available, but it's not quite out of draft form yet. This was coming from quite conservative legislators. This was around the role of the federal government, and this was sort of surprising to me. They were all, whether they were coming from conservative states, Republican or Democrat, very concerned about the issue of privacy and confidentiality.

But at the end of the day, they said that we were fooling ourselves, we meaning the states, if we could really ever protect anyone's privacy and confidentiality. What was really needed here was a strong role from the federal government to come up with legislation that addressed protection against discrimination. That was surprising but also reaffirming that the federal agencies had taken that position, and also the Secretary's Advisory Committee had taken that position also.

DR. McCABE: Any questions for Michele?

(No response.)

DR. McCABE: It was really, for me, the one I participated in in San Diego was extremely enlightening in terms of the ability of the people in the state legislatures and the governors' staffs to really home in very quickly on critical issues that we've been talking about, sometimes talking around, for quite some time.

Elliott?

MR. HILLBACK: We had some discussions a couple of years ago in

Massachusetts over some legislation they were trying to get through on privacy, and we ended up in the same place. Although they did put something together, it was relatively ineffectual, and they really decided that what they needed to do and have not yet done was to do something on anti-discrimination, that in this day and age, again to use your phrase, you're kidding yourself if you thought that you could protect on the privacy side. But, therefore, the way to go about it was to go after the anti-discrimination side or the discrimination side in a very strong way.

I think we should continue to be supportive. I know BIO has been supportive of anti-discrimination. I know various other organizations have been, and maybe we should continue to be very strongly. I'm sure we should be.

DR. McCABE: If there is no other discussion, we're now going -- oh, Reed, I'm sorry. I wasn't sure whether you were aware that you were going to be called on, so I was going to give you a break until tomorrow. But if you could perhaps talk about some particular concerns that you had raised.

DR. TUCKSON: I'll be very brief, actually. There's probably not much we can do about it. I'm a little bit nervous about even bringing this up, but I'm always concerned or interested in the historical record of a Committee like this and people looking at what kinds of questions did we ask and what kinds of questions did we talk about, what didn't we talk about.

Given that we're here to talk about how to protect or advise or guide or have the interests of the public at heart, we really haven't talked very much about

what to do with screening tests, prenatal diagnoses, issues. I mean, every day in the media now we see this discussion going on about someone with some unusual illness, and the ability not to detect that disease, and what do you do with that information. I have spent so much of my career working with people with sickle cell disease, and I would always ask them the question: "If you knew that you were going to have this disease, would you still choose to be here?"

I used to run the Mental Retardation and Disabilities Administration here in D.C., and I used to have to struggle with some of these issues every day. We had to struggle with those kinds of issues. So the notion becomes is there any responsibility that we have to deal with any of the implications of genetic tests in regard to these matters?

The reason why I am being so cautious about saying anything here is because I'm well aware that we have, first of all, a ton of stuff on our plate and no spare time. Number two, I'm concerned about the political implications of any of this, particularly with the new Administration and the country being where it is.

But I think not to have raised it, or for us to at least have raised it on the table and then decide to postpone it -- anything, as long as the record will state that we have at least brought these issues up and have thought about any responsibility in those regards. I just wanted to get that out there, but I'm not saying we need to make that a new subcommittee today or anything like that.

DR. McCABE: Wylie?

DR. BURKE: I just want to pose a brief and I think partial response. First of all, I appreciate your raising this issue, and I think it's important for us to have this on our plate in some form or other.

The partial comment is that I think as we go forward with the discussion that tries to define what components of a genetic test would be reasons for caution or special concern about the potential for social risks, I think a very important piece of that is who is getting tested, what is the test being used for, basically the test context. So that a test used for prenatal diagnosis has different implications than the same test used in diagnosis in a child or diagnosis in an adult. I just want to lay out that I think we could capture some of that concern in that discussion.

DR. McCABE: Any other discussion of Reed's point?

(No response.)

DR. McCABE: Again, I think it's important that this be raised, and we can be sensitive to these issues as we go forward. I think similar to what Wylie just said, carrier screening also carries certain definite issues, and we know how carrier testing and identification of carriers has been misinterpreted by both the professional and the non-professional communities in the past.

DR. TUCKSON: Well, at the end of the day, I appreciate these comments and just being able to put it on the table. If you think about what would the average person looking at our report, the sum total of what we do, you start thinking about the two or three things that are most on the average person's mind as they flip

through, that's going to be one of them. So they're going to be looking for that part. All right, tell me what to do. How should I deal with this? How do I evaluate that? What's the ethical guidelines for that? What's the way to work through that decision tree? Where's that chapter?

If it ain't there, I'm worried how we'll -- what happened?

DR. McCABE: Barbara?

DR. KOENIG: As we're putting things in the record to think about for the future, the other issue that's very, very important is the "non-medical" use of genetic tests, which I constantly bring up. Today, as we've been going through the template and the classification discussions, it's become increasingly clear to me that I think probably this can't be all done within one framework and that some of the non-medical issues need to be dealt with in a very different way. So I think we do need to start proactively thinking about how to move that agenda forward at some point. At some point, that needs to be on our list of tasks as well.

MR. HILLBACK: Which are non-medical, Barbara?

DR. LLOYD-PURYEAR: I'm looking at ancestry issues.

DR. KOENIG: Tests for ancestry, tests for gender.

MR. HILLBACK: Gender is medical.

DR. CHARACHE: Under CLIA, it also includes medical/legal paternity.

MR. HILLBACK: Forensics, medical. Okay.

DR. CHARACHE: Right.

MR. HILLBACK: Thank you.

DR. McCABE: Okay. At this time, then, we're going to recess. We'll take a 10-minute break after my comments so that people can before we reassemble the work groups. The full Committee will reconvene tomorrow at 10:15 in the morning. At that time we will be briefed by the chairs of the work groups, or in the afternoon tomorrow we'll be briefed by the chairs of the work groups, and that briefing, just to remind the chairs, should include a timetable of deliverables for each of the groups.

Some housekeeping things. The work groups are to go tonight until 6:30. Education will be meeting in the Conference Room 9, Informed Consent in Conference Room 7. For those on the Committee, we'll be meeting at 7:20. We'll talk about the shuttle schedule too, but we'll be meeting in the lobby at 7:20 tonight if you're going to dinner, or assembling over at the restaurant La Miche at 7:30.

Tomorrow's work groups will convene at 8:00 in the morning and will run from 8:00 until 10:00. Access will be in Conference Room 9, and Rare Disease Testing will be in Conference Room 7.

Regarding the shuttle, the shuttle will be outside of Building 31 at 6:00 tonight. But since the work groups go until 6:30, we will be sure that we're not leaving any of the work groups behind. So I anticipate that the shuttle will leave between 6:00 and 6:30, depending on when the work groups have completed their tasks.

Tomorrow there will be two shuttles, one at 7:30 in the morning for

those attending the work group meetings at 8:00, and one at 9:30 to get people over here who are not part of the work groups that are convening tomorrow morning.

Elliott, you cannot reassign yourself to the work groups depending on the shuttle schedule.

Yes, Wylie?

DR. BURKE: Actually, the data team wasn't scheduled to meet, but some of us have felt that it might be useful at least to have an organizational discussion about what we're doing. I realize that that presents a conflict for some people, but I think I would just say those on the Data Working Group that are able to meet will meet at least for a portion of the time this afternoon in this room.

MR. HILLBACK: Actually, Wylie, we made arrangements to make sure that the restaurant has paper napkins.

(Laughter.)

MR. HILLBACK: In the great tradition of Wylie and the dinners, we're going to do that on paper napkins at dinner.

DR. McCABE: Okay. So the Data group, then those who are available this afternoon will meet in this room this afternoon. If some of you have conflicts, and I know you do, you can try and sort out those conflicts.

So, then, Education, Informed Consent, and Data are meeting in Rooms 9 for Education, 7 for Informed Consent, and Data will stay in this room.

(Whereupon, at 3:58 p.m., the meeting was recessed, to reconvene on

Friday, February 16, 2001, at 10:15 a.m.)