DEPARTMENT OF HEALTH AND HUMAN SERVICES

SECRETARY'S ADVISORY COMMITTEE
ON GENETICS, HEALTH, AND SOCIETY

Second Meeting

Wednesday,
October 22, 2003

Monet Rooms 1 and 2
Loews L'Enfant Plaza Hotel
480 L'Enfant Plaza East, S.W.
Washington, D.C.

IN ATTENDANCE:

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C O N T E N T S

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P R O C E E D I N G S (9:02 a.m.)

DR. McCABE: Well, good morning, everyone. Welcome to the second meeting of the Secretary's Advisory Committee on Genetics, Health, and Society. The public was made aware of this meeting through the notices in the Federal Register, as well as announcements on the SACGHS website and listserv.

A couple of announcements. For those of you with microphones, you have to press the button in order to speak or you will not be picked up. I'll try and remind you, but the red light will go on when you can speak, so please do that. We've also had requests from the press and from our transcription service to please state your name as you're beginning to make a statement so that it's clear who you are for the record.

At our inaugural meeting in June, we had a number of presentations on the scope of issues encompassed by the SACGHS charter. We heard about the work of our predecessor committee, the Secretary's Advisory Committee on Genetic Testing, or SACGT, and were informed of the issues that our ex officio agencies think should be our top priorities. We identified several issues to explore in further detail. Two sessions today and tomorrow are in response to a request at the first meeting to be briefed on two of these issues. First is the status of federal efforts to enhance the oversight of genetic tests; and the second is genetics education and training and genetics workforce issues. With that information, we feel that we can make an informed decision about whether any further attention on our part is warranted on these issues.

Before reviewing the agenda for this meeting, I would like to turn our attention for a moment to the draft minutes of the June meeting. This is at Tab 2 of your briefing books. Before approving the minutes, I'd like to have a sense of the committee that the draft minutes are a fair and accurate representation of our June meeting. Do members have any comments or suggested changes to that document? I'm sure you've all memorized these minutes.

(No response.)

DR. McCABE: Any concerns, issues about those?

(No response.)

DR. McCABE: If there are no substantive concerns, then we will approve the minutes. Is anyone concerned about that?

(No response.)

DR. McCABE: Okay. So then let's move ahead.

The other thing about the minutes, I'd like to ask the committee to be thinking about whether or not we might want to rework them into a formal report to the Secretary. These reports are our means of communication with the Secretary and we provide the Secretary with an overview of the current status and future directions in genetic technology, the issues associated with them, and the determinations we made about which issues we think are of highest priority. So I'd like you to think about that and we'll revisit this idea later in the meeting and ask that you give some thought to it in the meantime, and you might want to look over those minutes with that as an idea.

You'll recall that in June we had an extensive briefing from Kim Monk from the Senate Health, Education, Labor and Pensions Committee, the Senate HELP Committee, about the Committee's passage of Senate 1053, the Genetic Information and Non-Discrimination Act of 2003, and the prospects for further development of this issue in the Senate and the House. After Ms. Monk's presentation, we agreed to send a letter to the Secretary commending the administration for supporting S. 1053 and urging the Secretary to continue pressing for passage of legislation in the full Senate and House.

I'd also like to comment that I think it's important to note that the first action of the

Secretary's Advisory Committee on Genetic Testing with both administrations -- so with Secretary Shalala and then with Secretary Thompson when the new administration came in -- was to write a letter supporting genetic non-discrimination, and the first action of this committee, the first correspondence of this committee with Secretary Thompson was in support of genetic non-discrimination, and I think that is a measure of the public's concern about this issue.

A copy of the Secretary's very positive response is in your table folders. Naturally, we were all delighted with the Senate's unanimous approval of the bill last week. That was very welcome news indeed because of our support that we've given it over the course of these two committees.

Now, of course, the focus shifts to the other chamber. Later today we will be briefed by Kristin Fitzgerald from the House Committee on Education and the Workforce, one of the three House committees with jurisdiction over this issue, about prospects for passage of genetic anti-discrimination legislation by the House of Representatives. Most of our agenda today will be devoted to a series of briefings by the federal regulatory agencies on the roles, activities and plans with regard to the oversight of genetic technologies, marketing and laboratories. This issue was a major focus of the work of SACGT, which made a number of recommendations about how oversight might be enhanced. Our briefings today will review how the agencies carry out this information and provide an update on their future directions and plans.

We will start tomorrow with a look at how other nations are addressing issues raised by advances in genetics research and genetic technologies. We will hear presentations from Philip Webb of the UK Human Genetics Commission and David Weisbrot of the Australian Law Reform Commission about recent reports of their commissions and relevant policy developments in their countries. Following their presentations, we will engage with them in a roundtable discussion of the issues.

The remainder of tomorrow will be spent hearing about federal and private sector efforts to enhance the education and training of professionals in genetics. You'll recall that at our June meeting, one of the issues we discussed was the importance of ensuring that our health professions workforce is well prepared to apply genetic knowledge, services and technology, and we decided that we should learn more about what federal agencies in the private sector, where most of the responsibility lies, are doing to address this issue. A series of presentations are scheduled on these important activities.

Let me also point out that we have public comment sessions each day. I am pleased thus far that 10 individuals have registered to make public comments during these periods. We're extremely happy that the public is interested in and wishes to contribute to the committee proceedings. If there are others here who wish to make comments, please let us know by signing up at the registration desk. We also have received written comments from a number of individuals. At latest count, 20 individuals or groups have sent us comments. These are in your briefing books at Tab 1.

So with that as an introduction to this meeting, let's proceed. Bio sketches for all of our presenters are at Tab 1, and in the interest of time we will forego formal introductions for most of our presenters. Background materials for oversight sessions are at Tab 4 of the briefing book, and presenter slides are in your table folders.

We will begin with presentations on the role of the Clinical Laboratory Improvement Amendments, or CLIA regulations. CLIA is administered by the Centers for Medicare and Medicaid Services, CMS, with scientific and technical advice from the Centers for Disease Prevention and Control. We'll begin with Ms. Yost, who, as director of the Division of Laboratories and Acute Care, directs the CLIA program at CMS.

Judith, do you want to join us here at the table? Okay, so you're going to talk from the podium?

MS. YOST: Yes, so I can do my PowerPoint. I have to be in control.

(Laughter.)

DR. McCABE: Thank you.

MS. YOST: Okay. Thank you and good morning, everyone. It's a pleasure to be here among this distinguished group. There are some familiar faces and some new faces, so I thank you. I also want to apologize to those of you who already know everything there is to know about CLIA versus those of you who are novices. This is kind of a basic presentation so that at least you can get the general idea of the standards and the approach for CLIA that CMS has taken at this time.

I guess the first and most important message is that genetic testing is already covered under the CLIA regulations as they currently exist. Just as a bit of background, the reason that CLIA came about was because there were a number of cases that were reported of people who had died because of incorrectly read Pap smears due to laboratories that were performing well above a threshold of workload and the inability to recognize positive smears. Also, in the late '80s, early '90s, there was a proliferation of technology, very small mobile technology, that could be placed on a countertop and allowed point-of-care testing to be initiated, particularly in physicians' offices, and there was concern about the quality of that testing as well.

Congress passed the CLIA law in 1988, on Halloween, so it looks like we're approaching an anniversary. CLIA regulates all testing on humans for health purposes using minimum quality standards. That means that any test that is done in any location, whether or not the entity is billing Medicare or not, no matter how many tests or how few tests that entity performs, regardless of where the test is performed. We regulate testing on ambulances, the type of testing that's done on the way to the hospital, to the emergency room; we regulate testing in schools where children perhaps are diabetic and the school nurse does a glucose test. So any type of test, not just your traditional hospital independent laboratory type of testing. Insurance testing is covered as well.

This includes research where the results are returned. So no matter what you call yourself, if you return those results back for use to a patient, to a caregiver, that testing is then covered under the CLIA regulations.

The intent of CLIA is not to put people out of business or to over-burden them with regulation. These are minimum standards. They are not rocket science. They are intended to ensure accurate, reliable, and timely testing.

The regulations to implement CLIA were published in February of 1992. Interestingly enough, it's near my birthday and about two weeks after I was employed by CMS to do this position. So I have a long history, needless to say. There are essentially five quality standards in CLIA. The regulations themselves are based on the complexity of the test that the laboratory performs. So the more complex the test, the more stringent the applicable requirements. Under CLIA, most genetic tests are high complexity because they are, number one, usually not categorized by the FDA, and they usually require a lot of training, they are very technique-dependent, and also require interpretation.

Under CLIA, the laboratory is required to have a certificate, and usually it's one per site. However, there are some exceptions for hospitals and universities. Where there are ancillary testing sites, the entity has the choice to have one or multiple certificates for multiple testing sites. The CLIA program is also unique in that it is entirely user fee funded. We do not get appropriations from Congress to operate the program. So it is our responsibility to utilize the funds that we receive from the laboratories prudently. The fees are pretty straightforward. They are based on the laboratory's test volume annually.

The program is actually a shared responsibility, and that provides us an opportunity to get the best of the best. You get the perspective of each different agency and the expertise of each different

agency to hopefully produce the best decisions and requirements. CDC is responsible for the scientific and technical expertise provided to the program. They do a lot of the research. They coordinate the CLIAC or the CLIA advisory committee. The FDA conducts test categorization responsibilities. CMS is responsible for disbursement of funds and also for all the administrative and operational aspects of the program.

Because of the impetus for CLIA being cytology, obviously there are very detailed and specific standards in CLIA for cytology.

Let's talk about very briefly the complexities under CLIA. As we indicated before, the more complicated the test is to perform, the more stringent the standards. We begin with the waived category. These are tests that basically have no quality standards except to follow the manufacturer's instructions. They are essentially simple tests that should be very accurate, and again where there is no routine oversight, only unless there's a problem or a complaint against the laboratory. These tests include tests done on a glucose meter, urine dip sticks, those types of tests that are very simple, and usually the point-of-care types of testing, cholesterols in the malls, those sorts of things.

Moderate complexity is actually where most tests reside. These are usually automated types of testing, the chemistry profiles, the CBCs, the immunology types of testing. The laboratories that perform these tests have to meet all the quality standards under CLIA and be routinely surveyed.

A subcategory of moderate complexity is provider-performed microscopy. That's kind of a mouthful. These are tests that are done by reading a slide under a microscope, usually by a care provider or a physician during a patient visit. So this category was created specifically for caregivers to allow them to provide instant information about a patient so that they can take appropriate action. They are usually specimens that are labile and don't require a lot of processing. The laboratories that provide those tests must also meet all of the quality standards and have no routine oversight, except again if there is a complaint.

The highest complexity is high complexity. These are typically tests that are more technique dependent. Oftentimes they are manual tests, like microbiology. They require more training or expertise. Usually there is a result interpretation. These are the most stringent standards, and these laboratories are also routinely inspected.

The quality standards themselves are very straightforward. The first is personnel qualifications and responsibilities. Under CLIA, the laboratory director does have the overall responsibility for quality in the laboratory. There are some additional required positions. For high complexity, where genetic tests usually reside, the laboratory director qualification is an M.D., D.O., or Ph.D. with board certification. Usually the laboratory director, if they choose to, can meet all the other positions if they care to or don't have enough staff.

Under CLIA, there is a unique additional aspect. Besides having the appropriate education, training, and experience, the laboratory director also has responsibility to ensure quality, so that each aspect of the laboratory is also under that qualification. The second quality standard is quality control. This just means that the laboratory needs to do something on a daily basis to check to see that the test is actually working before reporting patient results.

The third is called patient test management, which is really just the laboratory's audit trail, what kind of record-keeping system do they have, what do they have in place to ensure the integrity of the specimens, to ensure that patient specimens are identified correctly, to ensure the confidentiality of patient information throughout the entire testing process, and also protocols for referring tests to other types of laboratories to be performed.

The fourth is proficiency testing. This is really just external quality control. This means that the laboratory receives a specimen from a private organization with a known result in which

they test it to see if they can get the correct answer. If the organization -- for example under genetic testing, there is not a lot of proficiency testing available from private organizations. So then the laboratory is obligated to check the accuracy of each test that they perform twice a year in lieu of purchasing from the private organization.

In that case, the laboratory can split specimens, they can compare results from a reference standard, or they can have patient specimens for which they have known answers that they can reconfirm. Or I know a lot of the genetic folks do share specimens where you send samples back and forth between labs. That's perfectly acceptable in this case.

The final one and probably the key aspect of CLIA is quality assurance. It is now called, under the final regulations just recently published, quality assessment. These are the same requirements, just with a more quality system type of terminology. This is really the laboratory's overall plan to assure quality on a regular basis and to communicate with the providers, with the employees of the laboratory, and to resolve problems.

Just as a point of information, CMS recently published final CLIA regulations, actually in January of this year, and these are quality system regulations. So we have taken these standards and basically reorganized them so that they follow the flow of a patient specimen through the laboratory. That way it's very easy for the laboratory to identify which standards and which phase of testing the laboratory needs to meet. We have not made a lot of significant changes, but we feel this has streamlined the requirements to a great extent.

In addition in this final regulation, some of the CLIAC recommendations that were made to the tri-agencies who oversee CLIA were incorporated into this regulation because it was felt that they actually had general applicability and were not just specific to genetic testing, things like ensuring that the confidentiality of the patient's information and specimen results were carried through the entire testing process, other pre-analytic specimen identification and processing issues, as well as post-analytic test reporting information were also included in this final regulation. So we've already taken steps to incorporate some of those initial CLIAC recommendations, and Dr. Boone is going to tell you a little bit more about what else is being worked on.

For the CLIA survey process, I think folks always have a lot of anxiety about what are they going to do, here come the feds. The surveys themselves are required to be biennial, and they are announced to be sure that the appropriate people are there and the laboratory has an opportunity to get their records in order. So we feel that it's more important that we announce and schedule the survey, particularly in smaller laboratories where there are very few people available.

The routine surveys include only the laboratories that perform moderate and high complexity testing. Others are for complaints or to gather information. The laboratory actually has a choice under CLIA whether they can have an inspection by the state agency who is contracted by CMS to do the inspection -- these are medical technologists with extensive laboratory experience -- or by approved accrediting organizations that have been approved by CMS as having equivalent standards to CLIA. An example is CAP, the Joint Commission, the American Association of Blood Banks, the American Osteopathic Association, and so forth.

CMS uses an educational approach for CLIA, feeling that it's more important that the laboratory does the right thing. So we have always used an educational approach with an outcome orientation, outcome in this case being test results. Since we often don't have a patient there, the outcome is whether the test result is accurate and a quality assurance focus.

We have data. We have been doing this for a while. We have 11 years of data, and we have indications that starting in 1993 when we first began visiting laboratories with CLIA, approximately

35 percent of the laboratories had quality issues. At this point in time, we are happy to say that about 5 percent of the laboratories we visit have quality issues. We feel that part of the improvement is that, yes, they were afraid of us, but we also feel that by providing insight to the laboratory to give them resources and ideas about correcting problems has helped improve their performance as well.

Just some general information for compliance for genetic testing. Labs need to enroll in the program. That's the first step. The application is located on the website that's included on my slides, so you can download it very easily and send it in, whatever means you have. You need to meet the five major quality standards that I just talked about. But there is flexibility permitted to the laboratory in how and when the laboratory meets the standards. We realize that for a new laboratory, that may be an overwhelming task, so we give the laboratory an opportunity to meet the requirements incrementally.

The priority obviously depends on the quality impact. That's how we do this program. Everything that impacts the quality of the laboratory testing is the priority. There are no penalties at this point in time for non-enrollment. However, if you are doing testing and you know you are, you need to enroll because if we find out that you're not enrolled, then we can obviously take some action. So only after notification and refusal to comply would we take some action.

Again, I think it's most important that CMS is willing to provide technical assistance to any lab coming into CLIA.

Some survey facts. The first survey is always information sharing so that we can kind of get to know you, you can kind of get to know us and what the requirements are about. The survey process again looks at outcomes or results, again the problems that we are looking for. If you didn't dot your i or cross your t, we're not going to be overly concerned, or you missed this temperature on this particular day of the week, it is not a problem. However, if you have serious problems where you are not evaluating the quality of your tests, then we are going to be citing deficiencies.

However, again, we offer customized guidance to help the laboratory fix the problems. We will set priorities based on that laboratory's operation. It's really important. We basically look at every laboratory as a unique operation. They're not one size fits all by any means, and our experience has certainly taught us that. Again, we will suggest resources and time frames for which the laboratory can correct their problems, and where there are small problems that we see, we'll provide verbal recommendations rather than citing them on a deficiency report. Most of all, the lab is given credit for what they do right so that they have a starting point.

The survey process itself is pretty straightforward. We come into the laboratory and schedule what we call an entrance interview. We meet with the laboratory director and key folks to talk to them about who we are, what we're going to do that day, about how long it's going to take, and what they should expect. Then we're going to tour the lab, and a lot of this occurs concurrently. It's not like a step by step sort of thing. We tour the lab, and that's including the storage areas, the collection areas, all the areas in the laboratory where testing is performed.

We will look at some testing to see whether or not folks are actually following the procedures that the laboratory has for that particular test. We would interview personnel performing testing and in different types of positions, doing different types of testing in the lab. We are going to look at QC. We're going to look at instrument maintenance. We're going to look at other data and information in the laboratory. But the key is not to sit in a closet and read the procedure manual. The key is to see what the lab is actually doing to perform quality testing.

Again, we're assessing outcomes, and we're going to determine whether or not the laboratory is in compliance with CLIA. When we're all said and done, we're going to ask the director to come back and the folks involved in the laboratory and talk to them about what we saw, what we found,

what we think is good or not, and it also provides a last opportunity for the laboratory to provide additional data or information to the surveyor based on any findings that they may have had. Then the laboratory will receive subsequently a report of the findings for which they will need to develop a plan of correction, and that's just not saying, oh, I'll fix it later. We need to have specifics: "I'm going to take these particular actions, and here's the invoice for this quality control material I'm going to buy, and here's the records that show you that I'm actually doing it now." So that's the kind of evidence we need to show that the problem has been corrected.

CLIA state surveyors. I think it's very important that you know that they are medical technologists. In fact, we just recently concluded some training for our final regulations for them, and I was looking at the amount of experience. We have folks who have 20 and 15 and 10 years of experience in the laboratory prior to coming to be inspectors. So they're not bureaucrats. These are laboratorians, so they're people that you can speak to who are professional and knowledgeable about CLIA and laboratory practices, and especially quality assurance.

They're going to look at the lab's overall ability to provide accurate results. So if we can see from our initial reviews that the laboratory is providing good quality, we are not going to increase the depth of the review. Once we start to see problems, however, we're going to dig and dig and dig and dig until we can find the source of the problem. The root cause is what we're looking for. We don't want to fix the symptoms. We want to fix the cause of the problem.

The inspectors do receive periodic training by CMS, and where there is new technology or technical science that we are not familiar with, we will engage experts to assist. We have guaranteed on multiple occasions to this committee and others that we will provide very specific detailed training with any CLIA genetic testing regulations and use experts that are nationally recognized.

However, it's important that you know that these folks are intelligent folks. They can still come into a genetic testing laboratory and even though they may not be familiar with the precise technology, there's a lot of stuff they can look at to determine whether or not that lab is doing a pretty good job. They obviously need to look at the laboratory director's qualifications, determine whether that director is meeting his or her responsibilities. They can look at QC data to see whether the QC is in or whether it's out and whether they've taken appropriate action to fix it.

Instrument maintenance, reagents, supplies, analytical test validation information, PT data, PT performance, interview testing personnel, look at testing to see whether procedures are being followed, look at specimen integrity and so forth. They are going to look at what kind of plan the laboratory has in place to assure accurate and reliable testing and whether, again, the lab is resolving its problems, communicating appropriately with its patients and clients, and then assist the laboratory to meet CLIA requirements.

We've had some experience already with genetic testing research laboratories, and we have found in most cases much of what that laboratory has done to verify that a brand new test works and the results are correct will facilitate meeting CLIA. So it's not like you have a separate process that has to be met. Existing documentation in the laboratory and data that the laboratory may have already produced are very useful in this case. Again, organizational materials that are available are also acceptable, things like job descriptions. So you don't have to rewrite responsibilities if you've already got job descriptions. If you have a safety plan in place, that's fine. All we need to see is that it's available and that it's being followed.

So I can tell you for sure, and they're still alive and breathing, that there are genetic testing research laboratories that have CLIA certificates.

Again, CMS considers every laboratory unique. But just as a point of information, if

you needed a priority order, I've provided you one where personnel is most important. You need to get a director in place who can pull that place together. Quality control we think is the next most important piece that the laboratory needs to meet. Proficiency testing is next, and finally quality assurance, because we found that people can't do QA if they don't know what QC is, because QA is basically taking all the CLIA requirements, putting them in a box and wrapping them in a bow with the quality assurance, because that's your overarching standard. So that's basically the sequence that we suggest that you might follow.

I thank you very much for you time, and Joe is going to segue into where we're going from here.

DR. McCABE: Thank you very much.

I think we're going to defer questions until the roundtable.

Can you please join us at the table here?

So now Dr. Joe Boone is going to update us on the agency's plans for augmenting CLIA to address genetic testing issues. I know you've been involved in this for the duration of discussions about genetic testing, so we appreciate you making this presentation, Dr. Boone.

DR. BOONE: Well, thanks very much. It's a pleasure to be here this morning. I want to tell you a little bit about where we are and also try to answer the question why is it taking so long? That's one of the questions we constantly get asked, and I think as I go through this presentation you'll be able to see why things do take time, perhaps more time than most people would like to think.

This issue is complicated, and we're not the only ones that are trying to address it. I just recently returned from the Office of Economic Cooperation and Development. The European Union was considering some of the same issues that we've been debating for some time. They were very anxious to move ahead with the oversight of genetic testing laboratories. Part of this was driven by a recent survey that they conducted which showed that 63 percent of the laboratories throughout the world were receiving specimens from other countries. So specimens are crossing international boundaries, and they don't all have the same standards for laboratory practice. So that was of concern.

Judy has already talked about this three agency group that has the oversight responsibility for CLIA and what each of the agencies' roles are. I am reminded that one of my colleagues, when they found that this was the path that the U.S. government was planning on taking, told me that a troika didn't work in Russia and it won't work here.

(Laughter.)

DR. BOONE: However, we've been really trying, and I think we've been successful in many ways. We do have different focal points, but we are really trying to make these three agencies work together in an effective manner.

You're not the only advisory group to the Secretary. We have one ourselves, the Clinical Laboratory Improvement Advisory Committee, called CLIAC, and the members are appointed by the Secretary. There are 20 voting members, there's one industry liaison, and there are three ex officio members. The CDC provides support to that committee, and much like Sarah Carr, sometimes people think of it as being a CDC committee, but it's really not. It is a committee for the Secretary and we report directly to the Secretary for our activities.

Let me kind of go through quickly the standards development process so that you can understand what the process looks like. I think it's important to understand that this is a very open process, and therefore it turns out to be fairly time-consuming because we're trying to get input from as broad a spectrum of individuals as possible, and organizations.

The first thing we look at is what the federal laws that we have to do, and then we look at the voluntary standards and guidance that's available, state requirements, accreditation standards that

might be available, what the industry has to say, what the public has to say, and what our advisory committees have to say. Then we develop a proposed set of regulatory standards.

In this particular instance with the genetics, we actually went through another process and we developed a notice of intent which described what we obtained from our advisory committee, what they thought some of the practices should be, and based on those recommendations we circulated a notice of intent and we got comments on that. So we had an additional input to consider in the overall oversight process.

The next step is a notice of proposed rulemaking, which we're not yet at. We're close to it, and that's a proposed set of regulations which again will solicit comments. We'll collect the information, we'll do an impact analysis, and then we'll develop a final rule. Those will then be the CLIA standards that will be in force.

As Judy pointed out, the current requirements do apply to genetic testing laboratories, as do all the general requirements for non-waived testing. There is especially a clinical side to genetics that is already recognized which has specific QC requirements and qualifications for the personnel. In addition, the quality systems rule that was published in January incorporated some language that our advisory committee had been telling us we needed to have for genetics testing, but we realized that it needed to be applied across the board to all other kinds of testing as well. So we incorporated that language into the systems rule, but there were some specific requirements that we did add in that applied to genetic testing.

For example, molecular amplification procedures. We talked about the facilities that need to be available for that and the confidentiality that Judy mentioned earlier. However, there are still some areas where there's nonspecificity that we feel like needs to be addressed in the final rule.

Mike Watson, I think in 1992, told us that we needed to be including genetics in our proposed rule. We didn't do that, and that's maybe part of the reason we're not there yet. But we did have the NIH/DOD task force report which indicated that CLIA needed to be augmented. We've had recommendations from CLIAC. We formed a workgroup, and that group met four times to try to develop a set of requirements. We shared those with the former group, the Secretary's Advisory Committee on Genetic Testing. We supported those recommendations. Then we published those recommendations in the notice of intent, and quite frankly they weren't all widely accepted.

There was some concern about some of the recommendations that were being made. Some people thought they were too stringent, some people thought they weren't stringent enough. So we're having to address those comments, and we had CLIAC actually review the comments and make some suggestions to revise their recommendations. As I pointed out, the quality systems rule has incorporated a few of the changes that were recommended in this process.

So what are some of the issues? Well, the definition is one of the key issues. How do you regulate something unless you know what the definition is? One of the challenges is to try to define what genetics testing is, what the scope of it is in terms of regulatory oversight. Perhaps it doesn't matter as much since CLIA applies to whatever is out there, and so the definition may not be quite as important as some are trying to make it be.

Clinical validity was a concern. It's been a concern of this committee about when is a test ready for use, and the answer to that is still an issue. Who should be authorized to actually be able to order a test, what the informed consent process should be, and whether the laboratory should be part of that informed consent process. Confidentiality results we've already talked about. Whether there should be genetic counseling required for certain genetic tests. Then there are a number of pre-analytical/post-analytical kinds of issues, as well as analytical issues that we felt like needed to be addressed.

Let's just quickly go over some of the comments that we received on the big three, I

think, in terms of controversial issues related to rulemaking in this area. One is the definition. I just mentioned that. About 50 percent felt like that the definition was too broad. The definition really encompassed both the heritable kinds of conditions as well as the non-heritable kinds of conditions, and there was strong sentiment among some of the comments that we should not include both of those in the definition of genetic testing. So the determination of what is a genetic test is a little bit problematic.

Some people thought we ought to base that definition on the intended use of the test. That didn't seem to always work, and as the FDA knows, sometimes things don't get used for their intended purpose. Subspecialties' definition of what should be included, and a number of other areas about whether they should be addressed or not in this overall definition.

In terms of clinical validity, again we had about 50/50, and what do you do with a 50/50 comment? They disagreed with the notice of intent proposal which was developed by the CLIAC committee and was fairly prescriptive in what they thought ought to be done by the laboratory to document clinical validity. There were, as I said, different positions that were sustained. Some people thought it was impractical and out of the laboratory's purview to develop clinical validity for their test. Others really felt like strongly that it should be required, but only required for certain types of tests.

There were concerns about how would it be monitored, what would be the criteria, where would data come from, how many samples would you have to test in order to document clinical validity for the test that you were offering. No easy answers in this area.

Informed consent. About 60 percent felt that laboratories should not be required to ensure documentation of informed consent. The recommendation to CLIAC was basically that there ought to be a checkbox on the requisition form that would indicate whether informed consent had been obtained -- fairly simple, fairly innocuous to the laboratory. But the questions, of course, are, well, what happens if the box is not checked? How do you verify it? Do you have to verify it before you perform the test? Lots of questions, more questions than answers in this area. Most felt that the oversight should be deferred to the states, not a federal responsibility, but the laboratory should be required to establish policies and procedures, and there was controversy, as I said, on the extent of the responsibility of the laboratory.

So we're left with the same major issues that we need to consider in our final rule -- our proposed rule, I should say. This is a proposed rulemaking -- what the definition should be and what subspecialties should be recognized, how do we deal with informed consent, test validation, proficiency testing, specific requirements for each of the subspecialties, how do we deal with the retention and use of specimens, what should we require.

At the same time that OECD meeting was going on, there was a meeting in Paris by UNESCO in which they were talking about a human rights declaration, and one of the provisions in that human rights declaration was that once a patient received the results, the laboratory or care provider was required to destroy the background information. They had to destroy the specimen, they had to destroy any data that was behind that result. Of course, that violates a lot of our state laws and other requirements that we have in the U.S., so we were quite concerned about that.

But everybody is taking off from this on different pathways, so it's really a little bit difficult to kind of steer the ship, if you will, in the right direction.

In terms of CLIA itself, we really do follow some basic principles in terms of how we develop a rule. We want to make sure that we ensure quality in all the phases of testing, not just the analytical part of testing. So we're really concerned about the pre- and post-analytical issues. We want to provide flexibility to those so they can accommodate the different testing environments. Judy talked about the wide spectrum of places that genetic testing might be done, and we have to make sure that we are encompassing that whole range of activities.

We have to ensure that there are appropriate personnel to do the test and that it is available, that there's access to the test. We don't want to inhibit that process and the development of new technologies.

So what will the NPRN look like? It will contain a preamble which will explain and clarify what the proposed requirements are. We will address all of the comments that we received in the notice of intent and provide responses. We will describe the sources of information that we had in our rulemaking process, and we will provide everyone with a regulatory impact analysis about where the data came from, what are the cost/benefits for this proposed rule. That's all standard. Then we'll have the proposed requirements.

We just completed the regulatory impact analysis for this proposed rule, and in so doing we did try to identify all sources of information that we had. In some instances we're working with inadequate data. No one really knows what the test volume of genetic tests is in this country. We wish we had that number, that magic number, but we don't have it, so we had to estimate how much genetic testing there was in the country.

We also are concerned about the availability of people who have the specialty training in genetics. Are there enough genetic counselors? Your committee has talked about that as well. Do we have the right kinds of personnel to implement the requirements? We had to project this over a five-year period and what the costs and benefits were going to be, and this will all be in the proposed rule.

So where are we in the development? I described a notice of intent that we sent out. We've got the revised recommendations from CLIAC. We've looked at all the different inputs, and at this point we've got something that we're transferring to CMS for them to begin putting the final touches on the rule. So we are making progress. She's got it on their regulatory schedule, I believe, so we can report progress for this. I hope I've given you some indication of why it's taken so much time to develop this, because it's not where you have black and white answers. You have to really take into account a broad spectrum of use.

We have to clear this through the Department, which means that we have to get concurrence from all the other agencies. CMS, CDC, FDA, the HHS sister agencies all have to concur with this proposed rule. Then we also have to get it through the Office of Management and Budget, which takes a very close look at the rulemaking process, decides whether or not there's a benefit here that outweighs its cost. Congress can even weigh in on this if they think this is a significant rule. I don't know that they would on this; they don't do so very often. Then finally we get to the Office of Federal Regulations.

This Judy didn't say, I don't think, but this isn't the only thing in CLIA that we've got to work on. We've got a number of other areas that require our attention that haven't been addressed since the final rule in 1992 when you go back to them and update them. So we're getting hit by a number of groups that say these are really out of date, you need to change them. So these are some of the areas that are big areas for us to try to address for the future.

With that, I think I will close. Thank you.

DR. McCABE: Thank you very much, Dr. Boone. If you could join us at the table here also.

Before we begin the roundtable, let me first express my appreciation to Dr. Winn-Deen, Dr. Leonard, and Ms. Zellmer for agreeing to serve as facilitators of a roundtable discussion. Their role is to help amplify the oversight issues and focus our discussion, but all members and ex officios are also encouraged to please join in and raise questions and issues. We want to be sure that we cover all of the salient points.

So, Dr. Winn-Deen, I'll let you take over now. Thank you.

DR. WINN-DEEN: So I guess what I'd like to do first is to ask if there are any specific questions that anyone on the committee has before we sort of kick off our discussion, or any of the ex officio people as well.

Hunt?

DR. WILLARD: Just a question for clarification, at least for me and I suspect for some others as well. It is not clear to me to what extent your purview on genetic testing and the range of questions you're considering exactly parallels what you would do for, for example, in the case of a new imaging test that the radiology community was bringing forward, or whether you are truly considering genetic testing in a totally different light that brings in and raises questions that you'd never consider when MRIs came along or some new imaging technique came along. Depending on your answer, I may have a follow-up.

DR. BOONE: Well, I think you're raising what are sort of the horns of the dilemma that we've been facing all along, which is is there enough specificity in CLIA at present to deal with genetic testing, or do we need to add some specificity to encompass genetic testing? I don't think the answer is completely clear on that. I do think that it would be awkward, since we have no genetic heading/category under CLIA, for the rest of the world, if you want to take it from the world view, for us to have a major clinical laboratory oversight that doesn't have a specialty for genetics, just from the perspective of the public. They would expect something to be -- to have some specificity about genetics in a rule, I would think.

The other side of this that also is affected is the payment side. If you have some specific categories for genetics in a rule, then CMS has a little bit easier time of paying for those specific tests as well. So it's not just the black and white issues of whether or not there is something unique or exceptional about genetics, but it's also that you have to take into account the overall regulatory process and what effect that process has on a specialty area.

DR. WILLARD: Let me try to focus the question so that we don't get spread that thin. From the standpoint of CLIA -- or let me phrase it in terms of this new hypothetical imaging test -- would you just concern yourself with the analytical procedure of imaging or would you be equally concerned about the pre-analytical, the post-analytical, the equivalent of genetic counselors, how people would charge for it? Is that all within CLIA's purview for every test that's done on human subjects or on human patients?

MS. YOST: Right now, the umbrella oversight for CLIA is obviously the CLIA law, which is fairly broad. It certainly didn't anticipate the type of technology that's available today back in 1988, and so it doesn't really cull that out. However, because of the issues that came up with the notice of intent that Joe just articulated, we have actually asked general counsel from CMS to evaluate those issues to determine the extent of the authority of CLIA regarding those issues. So that is actually under review at this time, the clinical validity versus analytic validity, the informed consent, the counseling process.

What is the extent is actually where is that line, and it's not clear from the statute or from our reading, so we need to have attorneys review that and make a determination for us, and that will then help to determine the focus of that proposed rule.

DR. WILLARD: Let me ask one more focus question and then I'll be quiet. So informed consent is a great example. Does CLIA worry about informed consent for the other thousands of tests that you regulate?

MS. YOST: Not at this time. It does not.

DR. WILLARD: So what is the motivation for considering for the first time ever informed consent as being under the purview of CLIA when it's never been there before for the previous 10

or 15 years?

MS. YOST: I believe that the CLIAC had very good intentions and also felt that part of the pre-analytic phase of testing could include informed consent. So they made a recommendation that there at least be some connection within CLIA, not total oversight because clearly that resides elsewhere, but at least to be considered as Joe indicated, perhaps just a box on the laboratory requisition, which is covered under CLIA, that the informed consent was obtained and that there was documentation about why it was not.

But at this point, again, that issue is one of those that is with our attorneys under review at this time.

DR. WINN-DEEN: I think we'll take a question from Ed, and then Reed, and then Arden.

DR. McCABE: Ed McCabe, and please, if you could, state your name for the record.

I have two questions. One was raised. Joe, you mentioned about specimens crossing international boundaries, and my question is is there a responsibility of the individual who is ordering the test, the health care professional, if the specimen is being sent to Canada or to Europe, where there is no CLIA, if I'm ordering a test, what are my responsibilities toward that test?

MS. YOST: Any testing that's performed on specimens from U.S. patients or clients, the facility that provides it, regardless of its location in the world, must have a CLIA certificate. So it is the prerogative of a provider to order a test. However, when it's a U.S. patient, the facility that provides the testing, regardless of where it is, is required to have a CLIA certificate.

DR. McCABE: But in genetic disease, there are a lot of rare diseases, and there may be labs where there's only one lab or two labs and they're not in the U.S., and they aren't CLIA approved because they don't feel that they have adequate volume to seek CLIA approval. So then we should not be ordering those tests.

MS. YOST: No. The laboratory should have a CLIA certificate. I'm not going to say don't order the test. I'm going to say the laboratory needs to have a CLIA certificate.

DR. McCABE: But this is a problem for rare diseases.

MS. YOST: I realize it is a complex situation. We've dealt with it in the past, and I guess it's really most important that individuals ordering their tests search out or seek out laboratories that could provide that service that have a CLIA certificate for their patients. I mean, we're talking about a safety issue here too.

DR. McCABE: But I'll just point out that I saw a patient with Hershbaum's disease a couple of years ago. The only laboratory that I could find that was offering clinical testing at that time was a laboratory in Canada, and as a result and because I was aware of this issue, we were unable to get testing for that family because there was no lab in the U.S. that was providing the testing. So it basically prevented that family from having testing from a reputable academic center. I mean, we just have to recognize there are issues.

MS. YOST: It's a double-edged sword. I mean, there's a quality issue on one side, and then there's an access issue on the other, and I think certainly we're willing to work to resolve that. I don't mean to take a hard line, but I need to tell you what the requirement is at this point. That's my responsibility.

DR. WINN-DEEN: Judy, can I take the chair's prerogative and just ask a follow-up question here? This is Emily Winn-Deen.

MS. YOST: Sure.

DR. WINN-DEEN: What are the barriers when you go out to these small research

labs? What do they perceive are the barriers to getting a CLIA certificate so that they could offer that kind of testing for real patient service to anyone from anywhere in the world who might need it?

MS. YOST: There may be a couple, one of which is perception. It's an unfortunate thing that people think it's a big bureaucratic requirement to have to meet CLIA requirements when more or less they are very straightforward. They are implemented -- you know, I gave you the whole spiel this morning, so I won't go through it again. But people feel that it's a huge, huge monster to have to deal with, a paperwork nightmare, and it creates a lot of work, and it also requires a lot of personnel with specific qualifications that perhaps they don't have available at an additional cost. I think those are some of the major concerns that I hear. But part of it is really just not understanding how the program works and what its intent is and getting correct information.

We do our best to get the word out. We're hoping that this committee will assist in getting that word out so that people can understand that it's clearly not as complicated or difficult to meet CLIA as it may appear on the surface. If you get the federal regulations from 1992, it's 200 pages worth of requirements and you think, oh my God, I'll never do this; or you get the CAP checklist, which is hundreds of pages of questions, and that's not CLIA. CLIA is really the very simple things that I explained, and that's what it's intended to be, and then whatever somebody else makes of it obviously is different. But I think that's part of the difficulty, that folks understand.

The costs are relatively inexpensive only because we have very, very low fees that don't even cover our costs for the smaller laboratories, both for their inspection cost and their certificate. We intentionally kept those low because we realized that there would be not just small research labs but small doctors offices, small clinics where it would be prohibitive to be able to meet CLIA. The idea again is to help the laboratory be able to meet the requirements.

DR. WINN-DEEN: So could you just tell us if you were the lowest volume, anything out there, what's the bottom of the fee schedule?

MS. YOST: The bottom of the fee -- it sounds like the bottom of the whatever. But anyway, the lowest certificate fee is $150 every two years, and the lowest survey fee is $300 every two years. So that's $425 a year, and that's for up to 2,000 tests a year.

DR. WINN-DEEN: Thank you.

Reed?

DR. TUCKSON: Two related questions. Reed Tuckson, by the way, and thank you both for those excellent presentations.

Joe, I get the sense that this is going to be a while, and there's no question it's going to be a while, a long while. In the interim, based on Huntington's point, today people are doing things, there are tests going on today. I guess the question we need to be -- at least I need to be comfortable about is how comfortable are you today in assuring the American people that the testing for these diseases in normal medical practice today is adequate, that the public is protected in the interim while we wait for all these extra things to occur? How do we know the quality of the protection of the health of the American people in this area today?

DR. BOONE: Well, that's a very difficult question to try to answer, but we do have the New York State information, which if you want to look at the most heavily regulated area where they actually do look at the test validity of all the tests that are being done on New York State citizens, one of the actions that they've taken -- and about 50 percent, I believe, of the laboratories participate in the New York State oversight activity, so it's a fairly substantial part of the overall testing group that participates. They actually did withhold the ability of one laboratory to provide testing to New York State citizens. Because we don't have as much specificity in our law right now, I think that it could be a little bit

problematic for us to go that far.

Then you've got the international community that's going to drive this as well. So I do think that there's a lot of concern that's being expressed. We don't have any hard evidence that real harm is being done, but we've got a lot of anecdotal kinds of information that would indicate that we could.

DR. TUCKSON: Well, Joe, let's do this. Maybe in the interest of time because we probably can't drill any deeper, and also I don't want to put you on the spot for this kind of question, but I think what I would appreciate as a supplemental set of material is if you are the head of the CDC or you are the head of the FDA, or you're the head of CMS, somebody somewhere must have a checklist that sort of says how do I know whether or not this system that is designed to protect the health of the public in this area, whether it works or not? Because clearly we've got rules that all these people are meeting because they're worried about making sure something doesn't go wrong. Great.

The question that I don't understand is what would be the checklist that they're looking at to determine whether all these zillions of regulators and all these people and everybody out there doing all this work, how do they know whether or not it's effective? I'm just curious what the criteria would be that everybody is using as a yardstick for whether or not this thing works or not.

The only other question I have is -- and I really appreciate you putting it up there as a question mark on your last slide, and I know probably that under the constraints of government you're unable to answer this. But do you all have the resources to do this job? Do you have the resources today under your present definition of CLIA, and then what will it mean going forward? Because I don't know how anybody will be able to evaluate the budgets that are submitted by HHS in this area to know whether or not they're adequate or not, and how important it is in terms of your resources.

So I don't know the way we begin to look at that, but again our job, as I understand it, is to begin asking these questions and thinking about protecting the public in this regard. So I just don't know what criteria we can take from your presentation to know whether or not you've got the resources.

DR. WINN-DEEN: I think Muin is going to answer you, behind you, from CDC.

DR. KHOURY: This is Muin Khoury from the CDC. Reed Tuckson always asks the right questions. I've known that for a while now. He asks questions that have no immediate answers, unfortunately.

If you all recall back from the discussions during the SACGT years when we discussed the issues of oversight of genetic testing, the previous committee recommended essentially a three-legged approach to the issue of genetic testing. One is an FDA approach. The other is a CLIA approach. The third one is essentially a non-regulatory approach to try to collect data on what's going on in the real world. So based on those discussions we had in the previous committees, and also the essentially non-regulatory nature of CDC as an entity, we began developing approaches to deal with those issues that Reed is asking about, what's going on in the real world.

Unfortunately, with the issues of resources that are not coming to bear on genetics per se at CDC, and some of the barriers that Joe mentioned, it's very hard to collect that kind of data in the real world, but we've made some progress. I think what's going to happen based on the discussion of this committee, we're willing to give you a more detailed briefing on the non-regulatory approaches that CDC and also other agencies have been engaged with to try to collect data on the full range of parameters of genetic testing, from the analytic performance in the lab all the way to the clinical utility and the ethical issues in the community, as well as utilization rates.

But we don't have answers to what you're asking, Reed, but we have begun developing approaches to try to come up with those answers in the long run, and these approaches are also equally difficult and they would take time to implement. But we'll be happy to give this committee a fuller briefing

next time.

DR. WINN-DEEN: Arden Bement?

DR. BEMENT: Arden Bement, Department of Commerce.

My question is to Judy Yost. On your slide 6, under your quality standards and under proficiency testing, you require an external test for accuracy for a private organization. Is this private organization certified? Is there a chain of conformity in the program?

MS. YOST: Yes. There are specific regulatory requirements that the private organizations need to meet, and they actually go through a wonderful annual approval so they can provide this testing by CMS.

Since you brought that up -- I thank you, actually -- there is an answer to Reed's question. There is one small measure, actually, that CMS has in place already. If you recall, I said that with laboratory testing it's a little bit different in many cases because you don't have a patient. It's one step removed from a patient. You have a provider ordering a test, the test result going back to that provider, and it's the provider who takes the action with the patient. So we don't have a lot of outcome information. If you remember, I said the test result is the outcome that CLIA is authorized to measure under its analytical purview.

However, there is one measure that we have, and that is the proficiency testing, because that data is collected and maintained and evaluated, and we use that data currently. Again, it's not for where there is not an organization that provides this on a regular basis to the laboratory, so that a lot of genetic testing isn't measured by this process. But for those tests that are, and there are about 84 different representative analytes under CLIA that do have structured proficiency testing, we actually look at that data to look at laboratories' performance on an ongoing basis to determine, number one, are they enrolled in proficiency testing correctly and are they performing appropriately under proficiency testing.

So there is one measure that we have maintained over the last five years, actually, to evaluate laboratories' performance, because proficiency testing is well documented in the laboratory community as a measure of accuracy of testing. It's a long-term measure of the accuracy of the laboratory's testing. So we have been monitoring that over time, and I am also pleased to tell you that from the data that we have collected, something that almost pulled the entire CMS data system down, it's that much data, because if you realize proficiency testing is five specimens three times a year to every laboratory for each test that they perform that's regulated, so it's a huge amount of raw data that has to be compiled and synthesized into these reports, and we are looking at about a 98 percent threshold whereby every laboratory that's supposed to be enrolled is enrolled; and secondly, laboratories' performance has improved significantly since CLIA began in 1993, and we actually began measuring this more in 1995 when we had our act together a little bit better, until the present.

So that information is available and it is made public actually every year. It's called a Government Performance Review Act that was passed by Congress.

Thank you.

DR. WINN-DEEN: We'll take one more question from Deb Leonard before the morning coffee break.

DR. LEONARD: Debra Leonard. I actually have two quick questions, one quick. Can CLIA create relationships with other quality monitoring programs internationally, and are you working to do that? Because I'm sure the laboratory in Canada was monitored by some program if it was a clinical laboratory.

MS. YOST: Yes, very much so, and actually we are in the process of working with that now, because we do have a number of foreign laboratories already enrolled in the CLIA program in

our database. Most of those are actually accredited already by a private organization, so basically we've assumed that they're fine. We are going to set up a more formal process, however, but we have not determined exactly what route we will take for that. We're looking at various options, one of which is an agreement with a private organization.

The other is to use the -- there is an international laboratory quality standard that was recently published, I believe it was last year. It's an ISO standard that is cross-referenced to the ISO 9000 documents. It's one specific for laboratory medicine, and we may use that standard as a possibility whereby if a country would adopt that standard as its national regulation or quality standards, that we would accept that as equivalent to CLIA. So we are working in that direction as we speak, yes, and that might help some of this international problem, because a lot of countries, at least 30, have indicated, that I'm aware of, that they will adopt that standard as their national requirements.

DR. LEONARD: The second question is how many problems, even anecdotal, are with CLIA labs as opposed to those laboratories that are not trying to meet the CLIA standards, and what mechanisms are there for identifying those laboratories and bringing them under some sort of regulatory process?

MS. YOST: I'll start and Joe can finish. We have certainly seen -- I think all of us have some great horrible horror stories anecdotally of problems that are not necessarily documented of laboratories that do not understand the importance of doing some sort of routine check on a daily basis that their testing is working, that they have not evaluated the validity of the types of testing that they're doing, the accuracy, the precision and so forth; or they have not reported the tests in a timely fashion where it's useful to any kind of caregiver.

So we have a number of pieces of information like that. Obviously, data from our surveys from those that we do overseas, we've got plenty of background information on those laboratories. But for those that have not, when we find them, we have found some fairly significant problems in labs that do not have oversight because they just may not be aware of the importance of meeting some basic quality standards.

As far as efforts, we don't have a formal program, partly because of resources I guess, to go out and beat bushes and really to do some sort of ground-level encouragement of people to come into the program. We certainly have a plan in place to talk about how we might accomplish that, by working with entities that we typically do not, such as university organizations and genetic testing symposia and those sorts of things, where the folks who might be the ones we're looking for might be attending so that we can do this in a very non-threatening way to folks, because it's very important that they understand that there is no penalty. If you're not enrolled, we give you the benefit of the doubt one time around. Everybody is given that allowance.

So again, I have a plan written. It's just because of resources and being overtaken by other priorities that I've not been able to follow it through.

DR. LEONARD: So you seem to be confirming -- are the egregious problems that you're talking about, were those in CLIA labs or non-CLIA labs that then when you went into there were problems and they got identified, and they got corrected --

MS. YOST: And they got corrected. It's both.

DR. LEONARD: -- through the CLIA process?

MS. YOST: Yes, yes. It's both, actually. There are many that are doing just fine. I mean, some of the initial laboratories that we visited that were doing specific genetic testing research actually had done so much work in the preparation of the test that they had developed that they had gone well beyond what CLIA would have required to meet QC, PT, and QA. So we were very happy with that.

Then there are other places that do not recognize, as I indicated, the importance of just doing some very simple things just to check on the accuracy of their testing. It was just a little less careful. So in those cases, then, we have serious concerns. But we have always said that CLIA is an incremental process. You start out with the very basic, simple things. You make sure you have qualified people, you make sure they do some quality control, and over time they then recognize the importance of having some overall systems process in place to ensure accuracy.

So that's basically how it works. You start out with problems, but you find over time that we've helped people improve.

Have I answered what you're asking?

DR. LEONARD: I guess my question is are we regulating more stringently where we're already regulating and not doing anything to capture the problem areas, the problem laboratories?

MS. YOST: Well, we do focus our resources. What we do, as I indicated, our process is intended to visit people routinely. But for those folks who are doing a good job, it's kind of hi, how are you, and checking --

DR. LEONARD: But those are the CLIA labs.

MS. YOST: Right, those are the CLIA labs. For those that are not, if we don't know where they are --

DR. LEONARD: You can't get them.

MS. YOST: -- we can't get them, because we'd have no way of finding them. Oftentimes we have the old report on your neighbor -- "If I have to do this, so do you" -- and we get some of that. But we don't have at this point the resources to go out and dig up where there might be places where folks are unregulated that might need a hand in meeting the requirements.

Go ahead, Joe. I'll stop.

DR. BOONE: Well, I think there are two areas that this committee needs to consider. It's not just the regulatory agencies that have responsibility here. It's a societal concern, and so we need to be aware of what the professional organizations are doing and what their commitment is to identify the fringe areas, because that's really what you're pointing at. I think most of the problems that you're talking about and that this committee has talked about and that CLIAC has talked about are in the fringe areas, direct access testing kinds of concerns, laboratories without validated tests that are being offered.

Those kinds of things don't occur within the College of American Pathologists programs, and they don't occur to a wide extent, at least as far as we can tell, within the CLIA-certified laboratories. It's the group that's not under that umbrella that we're concerned about. I think the most aggressive, if you want to look at it from a regulatory standpoint, the most aggressive program is the New York State program. They would also point out that they don't encompass everything that happens in that state or to residents of that state.

So the outreach of the regulatory effort can only go so far, and we are only looking at minimal requirements. We're not looking at the level of requirements and expectations that a professional organization would look at. So I think it's very legitimate for them to set higher standards and to have those adhered to, but I don't think you should expect the federal government to take care of every problem.

DR. TUCKSON: What's the answer to Ed's question? I'm sorry to break in. But let's say that it wasn't Canada that he went to to try to get his test, but it was in Wyoming, and let's say he knew that lab didn't have a CLIA certification for that test. Would it have been illegal for him to have still ordered the test and used it, even if there's no exchange of insurance money and all that? It's just you and the patient who are doing this deal, the patient is getting the test and paying for it themselves. Is it illegal for him to do that? Is it unethical for him to do that? Is he required as a physician or an academic center to

report that he is aware of this lab doing this that isn't CLIA certified?

MS. YOST: The ultimate responsibility under CLIA resides in the laboratory, with the laboratory where the test is performed. That's how CLIA operates. So I won't qualify what Dr. McCabe is, but I will say that it is his responsibility as a physician to report it to somebody. You can do that completely anonymously. I mean, you can just make a phone call to the state agency, to us, to our regional office and just let them know that, oh, by the way, I'm trying to get this test done, but I noticed that this laboratory doesn't appear to -- I mean, I think it's every citizen's responsibility, whether you're a patient or a physician, if you're going to have a test done on yourself or on your patients, that you should ask do you have a certificate.

I think that's the first and foremost question. That's what we teach folks who are looking for laboratory services. That's the first question. That's what Medicaid does to any laboratory that's going to bill them for any kind of testing anywhere. The first thing they want is not only tell me your number but send me a copy of that piece of paper that shows that you're certified, and not only are you certified but it's effective and that it's for the type of testing that I'm going to have done here. That's a very simple, baseline ground rule to use when selecting a laboratory for services.

DR. McCABE: Thank you very much. Thank you, Emily, for facilitating that, and thank you to Judy and Joe for your presentations and for answering our questions.

We'll now take a 10-minute break. We will shorten it from 15 minutes to 10 minutes. For the SACGHS members and presenters, there are refreshments here. For the ex officio members and members of the public, refreshments and beverages are available in the Starbucks Expresso Bar, the hotel gift shop, and the eateries at the Metro level. Please be back in 10 minutes. Thank you.

(Recess.)

DR. McCABE: In addition to requesting presentations on the FDA's role in the regulation of genetic technologies and its efforts to enhance oversight of genetic tests, we also requested a briefing on how the agency is addressing pharmacogenomics and is -- can we please have the doors closed in the back and have the conversation cease? We also requested a briefing on how the agency is addressing pharmacogenomics and its potential to enhance drug development.

Dr. Lawrence Lesko is head of the Office of Clinical Pharmacology and Biopharmaceutics at the FDA's Center for Drug Evaluation and Research.

Dr. Lesko, thank you very much for being with us today and please proceed.

DR. LESKO: Thank you, Dr. McCabe, and good morning, everyone. I'm going to try to give you a perspective on pharmacogenomics and the FDA drug review process, and in particular some of the impact that this science has had on product labeling in the recent years.

The perspective is based upon what we've seen at the Center in terms of submissions either of INDs or NDAs. That's not to say there isn't a lot more going on in drug development that we're not aware of because companies have either not submitted it to us or they consider it to be some sort of exploratory experiment and they're waiting to see the outcomes of that information and so on.

But let me try to give you a sense of what is going on. Let me start off by saying when we use the terminology, I'll be talking about pharmacogenomics in a very broad way and I'll be referring to hereditary differences in gene expression profiles at the RNA level, although this could be at the mRNA level or protein level, or in nucleotide sequences at the DNA level. The purpose is to better understand variability in disease phenotypes, disease progression, and dose response. The data itself we feel can be used to either select a drug for a particular patient or select a dose for a particular patient.

Now, the two types of data that we have experience with in submissions include microarrays, which basically I think of as quantitative gene expression profiling at the RNA level using

target tissue or surrogate tissue. As you're well aware, this could be from a host, a patient, it can also be from a tumor, or it could be from a pathogen. In fact, most of the information we've seen is from the latter two categories, as opposed to the patient.

The goals that companies have in their protocols when they're using gene expression are any one of a number of the ones I've listed on the slide. But basically the ultimate goal is to identify a panel of biomarkers that can be used in a predictive way. That can be, for example, to diagnose a disease or a subtype of a disease on a molecular basis, to monitor disease progression as in a carcinoma, assess severity, predict clinical outcome a priori to see if a patient is going to be a responder, to give a drug and then look at gene expression changes dynamically as a function of drug response, and the ultimate goal if all works out is to develop a diagnostic or drug response predictive test.

The other technology that we see quite often is genotyping, and this comes in several varieties. It comes in whole genome scans when there's attempt to develop a hypothesis that's related to genotyping and clinical outcome, or it may be a candidate sequence that a company might look at using blood or some tissue sample as a surrogate. Basically, the goal of this research is to identify one or more single nucleotide polymorphisms or alleles, sometimes haplotypes, and this category includes what I would call pharmacogenetic tests, the commonly validated variants of drug metabolism genes which have been around for a good 40 years.

Sometimes it's a custom set of SNPs that's related to a specific issue in safety or efficacy, such as hypersensitivity to abacavir. Oftentimes this technique is used in population analysis to see if one could distinguish between responders or non-responders retrospectively. Sometimes this technology is used to include or exclude patients from treatment based upon what's known between the genotype and phenotype association. Sometimes it's used to guide dose selection a priori to improve the risk/benefit of a particular drug.

Now, one of the problems with pharmacogenomics has been the regulatory pathway for sponsors to submit the data, and at least the sponsors, from what they've told us, this pathway is unclear. Beginning about two years ago, we frequently would get questions from sponsors about what data needs to be submitted to the FDA. Because most of this data is exploratory and not suitable for regulatory decisions -- it's novel, it's new -- companies were unclear whether we want to see that data or not. The exception was the drug metabolism genotypes which are well established in the scientific community and there's a lot of public information on it.

Another question comes up, what formats can be used for submission? This is all evolving. Standardization of assays, standardization of reports, the level of detail that comes in is not clear. There are not standards that have been evolved. Then finally the companies would say what are you going to do with this data in decisionmaking? Are you going to hold up a clinical trial? Are you going to ask for more data? Are you going to interpret it incorrectly? There's this kind of uncertainty, and that of course is all dependent on the validity of what they're submitting. So there are a lot of questions related to pharmacogenomics.

Part of the problem was the regulations that were written 30 years ago did not think about pharmacogenomics, and as a result the regulations require interpretation in light of the new science. This is the current regulations that relate to the submission of genomic data during the IND phase, and you can see what I've highlighted in italics there. "Data should be submitted on the basis of which the sponsor has concluded that it's reasonably safe to conduct a proposed clinical investigation." What does that mean? What does "on the basis of which the sponsor has concluded" if much of this information is exploratory, so it's a gray area?

When you move from INDs to NDAs, submission of pharmacogenomic data, again

there's regulations that dictate what should be done, but they're not very clear. As this quote indicates, pertinent to the evaluation of the safety and efficacy information in application. So "pertinent" is open to interpretation on the part of a sponsor. How pertinent do we mean? Very pertinent, or what?

It was the regulations that created some problems in interpretation, so we had a public workshop on this question, on those three questions actually, back in May of 2002, and at that workshop the agency made a proposal to develop a regulatory pathway within the construct of the current regulations to facilitate the advancement of pharmacogenomics in drug development. We called it at the time a safe harbor, and the safe harbor was intended to get sponsors to submit exploratory genomic data to the agency for the purposes of increasing our understanding of the data, looking at the data, learning from it, and using that information to develop good regulatory standards.

That workshop led to an initiative over the past year whereby we developed a guidance for industry we call "Pharmacogenomic Data Submissions." It will be out in the public domain at the end of this month, and later on in November we're going to have a public workshop to get comments on this guidance primarily from the pharmaceutical industry and others that would be interested in it. So this guidance, then, we hope will clarify the situation and address some of the questions that companies had. So we hope it will address questions like this: When is a sponsor required to submit genomic data to the FDA?

We have three general principles that address the question. Whenever a sponsor uses genomic data in decisionmaking in animal studies or human trials. For example, they may use this data to include certain people or exclude certain people. Maybe this data will be used to support a claim by the sponsor related to safety or efficacy or dosing, use a different dose in a poor metabolizer genotype. That data we need to see. It supports a claim. Finally, if the exploratory data ends up providing information or recommended uses of genomics in product labels, we need to see it and evaluate it.

So these are the general principles of this guidance when it comes out, and hopefully this kind of framework will enable a sponsor to make the decision about what ought to be submitted.

We do talk about level of validity of biomarkers, which are a byproduct of genomics in this guidance. We talk about valid biomarkers as being those we're most interested in reviewing, and a valid biomarker by definition is one measured in an analytical system with well-established performance characteristics and described within the framework that establishes its significance either in toxicogenomics or clinical pharmacogenomics.

Now, let me turn to what we see at the IND and NDA level at FDA and show you the growth of applications that have come in. This is an incomplete picture. It's actually an informal survey that our review staff has conducted looking at INDs and NDAs and basically doing head-counting as to how many of them have proposed to collect samples for genomic testing. You can see the increase, and I think that increase is real. If we had everyone captured, I think the trend would be the same. But it shows an increasing interest in this science within the drug development process.

Now, the types of data in that survey, in those over 100 INDs and NDAs, include microarrays. When we see these data, we think about it as relatively new technology. There's a lot of heterogeneity in the techniques and test procedures across applications, frequently not really well validated because the intent of the sponsor is to use this information in an exploratory way.

When you go to interpret the data, it's often not confirmatory, but rather hypothesis generating. The studies are oftentimes small, whether they be animal or human, so that extrapolation of the findings are tenuous, and in the overall count from what I showed you on that trend, we have relatively few examples that involve microarrays. So most of those examples that I showed from the IND/NDA world are from genotyping experiments.

We've had more recently many informal meetings with companies where they talk about

hypotheticals: "What if I had a drug for this carcinoma, and what if I had this microarray?" These types of meetings are helpful and we encourage them because it allows us to have a dialogue about what might be coming down the pike later on.

The majority of those INDs and NDAs contain genotyping information. I think this is reflective of the maturity of the techniques and the test procedures, and the fact that there are several well-established biomarkers, particularly in the pharmacogenetic or enzyme activity category.

On the other hand, frequently the interpretation of these data is unclear if it isn't something we already know a lot about, trying to link a genotype with a clinical phenotype such as an adverse event or the absence of efficacy. The hypothesis for that link is often unclear. So these again are hypothesis generating, for the most part.

For the same reason, we have difficulty with what we've seen so far, extrapolating findings from these studies across patient populations. It's not uncommon to see a study with 95 percent Caucasians, and we know that certain alleles distribute differently among the different race groups, and thus to extrapolate this information on a global scale -- for example, into a product label -- is a challenge.

So most of the examples in the survey fall into this category. In fact, what I showed you there, that over 100 count of INDs and NDAs, 75 percent of those involved genotyping of the cytochrome P450 enzymes, this isn't bad. It just shows where companies are starting to focus on more intensively. The pie chart illustrates the distribution of the cytochrome enzymes, and the ones that are most interesting, the ones people feel are most associated with variability and dose-response are the 2C9, 2C19 and 2D6. They all have standard nomenclature, as you may know -- family, for example, of CYP2. There's a subfamily 2D6, and there's a gene indicated as *3. When companies do, for example, 2D6, they generally look at six to eight alleles of 2D6 and then categorize patients into extensive, intermediate or poor metabolizers for the purposes of interpreting those response data.

These are important enzymes because they account for such a large percentage of the metabolism of drugs in the marketplace, so it's not trivial by any means, and we're just beginning to get data on understanding the association between these genotypes of drug metabolism enzymes and clinical outcome.

This little cartoon illustrates the question that we're asking of sponsors in drug development. We're interested in dose-response, dose exposure as I call it here, and many drugs are metabolized through the liver by the polymorphic enzymes, and this shows what happens when one has a single change in a nucleotide in the sequence of the gene that encodes for enzyme activity. Imagine this enzyme is 2D6, so 90 percent of the population would have a sequence that would encode for high levels of enzyme activity. They'd be called an extensive metabolizer. If I give them the same dose as the other folks, they have a certain degree of exposure to the drug in their systemic circulation.

A change in one of the nucleotides in that sequence creates a poor metabolizer. The patient may have no enzyme to metabolize, or perhaps an intermediate level of enzyme to metabolize. We would refer to those as poor metabolizers. They obviously, given the same dose, would have a much different degree of exposure. So exposure leading to response, then, is influenced by the genetic state of the enzyme activity.

Let me just pick one example that's been in the news recently. It's serotonin reuptake inhibitors for childhood depression. The agency has approved two of these this year. There's a lot of clinical trials being reported in the Wall Street Journal and so on. Most of these drugs are 2D6 substrates. The drugs have a relatively narrow therapeutic index which I've indicated with the two lines there, indicating therapeutic response and toxicity.

So imagine I have a fixed dose for all comers who are going to receive this drug. If I

have an extensive metabolizer, they're going to have a certain level of exposure. I've indicated with that green, the little mark, and they're going to be happy. They're in the therapeutic window. Their efficacy endpoints, their clinical endpoints will be an improvement in their childhood depression rating scale, and this is composed of nine different symptoms.

Now let's imagine I give the same dose to another child that happens to be a poor metabolizer. Well, their higher exposure pushes them further out in their plasma drug concentrations. They're now on a plateau of the efficacy curve, so they don't get much more benefit from that drug in terms of efficacy. But as you can see from the relationship between safety and efficacy, those children may be at risk for CNS difficulties, insomnia, irritability, and there's some concern now about long-term growth and suicide potential.

So getting the dose right is an important factor in drug development and therapeutics, and knowing the genotype for a drug with a relatively narrow therapeutic index like this can be useful in optimizing the risk-to-benefit ratio, and that's why the agency is interested in it.

I'll share with you three examples to illustrate how this information on drug metabolism has impacted labels. The fact of the matter is we do not have a lot of examples where genomic information has been included in labels. We of course have Herceptin with the FSH test to identify those patients that are candidates for Herceptin. We have resistance testing genotyping in labels for some of the AIDS drugs. We have, for a drug like tamoxifen, in the label some information about receptor-positive or -negative nature.

But let me focus on some recent things dealing with the enzymes, and I'll go through this quickly to illustrate how it works. Voriconazole is an antifungal we approved in 2002. We knew that 2C19 is a major metabolic enzyme that controls clearacin exposure. We also knew from the clinical trials that visual disturbances and potential adverse events were of concern on the safety side. An obvious question would be if I give somebody a dose of this drug and they're a poor metabolizer, does that predispose them to these adverse events?

Well, typical in drug development is to look at genotype early on in drug development in the Phase I studies, and this is some data that shows the difference in exposure depending upon which genotype you happen to be. From a poor metabolizer I have a plasma concentration of 4. If I'm extensive, I'm on the other side and my plasma concentration is 1. So there's this four-fold difference in exposure that could have a bearing on the risk/benefit of this drug in therapeutics. We don't know that in the case of this drug because genotyping, while it was done in Phase I, was not done in Phase III, so there was no way to associate an adverse event with genotype from the clinical studies that were done to demonstrate safety and efficacy.

What often happens in drug labels is that we put information in the section called "Special Populations," where we look at covariates that affect exposure and dose adjustments. For this drug, there were several covariates that warranted a reduction in dose. As you can see, low body weight. If we didn't adjust the dose, they'd have a two-fold higher exposure. Hepatic impairment. People with hepatic impairment had a three-fold higher exposure to the drug, so the sponsor recommended reduction.

But as I showed you that data on 2C19 genotype, people had as much as a four-fold increase in exposure, and we did not in that label recommend a dose reduction, partly because of the fact that if we were to do that, we have to be assured that the test is available to physicians that want to use it, and it's available to patients at a reasonable cost as well.

The other problem is racial differences in phenotypes and genotypes. When a sponsor does this type of testing in drug development, they often will identify in advance what alleles of the enzymes they're going to consider to be poor metabolizers. If they happen to only pick only two of the alleles and

not four, that means that whenever the patient doesn't have the two genotypes that they picked, they're going to be classified as the other genotype extensive metabolizer, and that's going to be a mistake.

So it's important in monitoring these studies that we look at the alleles that are included in the study to make sure that the alleles are relevant to all of the major demographic groups that are likely to take the drug if it were to be approved, and this shows an example of that with the 2C19 where the prevalence of poor metabolizers is greater in Asians than Caucasians, and also the actual allele -- for example, the *3 -- actually doesn't appear in Caucasians but it appears in Asians. So you really have to have this information straight when you're reviewing this information.

Now, that was a case -- and I'll turn to a different case to give you a variety of the types of things being done. That case was where a sponsor looked at genotyping in the early phase studies and then did not do anymore in the clinical phases of Phase III. This was a different story. This was atomoxetine for attention deficit disorder. We approved it in January. It's a 2D6 substrate, so it has the same sort of situation as the 2C19, and you can see that a certain percent of Caucasians and African Americans are poor metabolizers. If they get the usual dose of the drug, their exposure based on this area under the curve goes up about 10-fold. Their clearance half-life is about five-fold longer.

This particular drug development program looked at the genotype in the Phase III trials. The numbers are on there. The prevalence of poor metabolizers was right on as to what we would expect, 7 percent in this population. That, in fact, is one way we assess the quality of these tests, is the prevalence consistent with what we already know.

Then when you looked at the clinical outcome data, what they did here was really have everyone double-blinded, and they looked at patients who discontinued therapy and then analyzed the genotype into either poor or extensive metabolizers. The data is interesting because clearly you can see there's a double-edged sword when it comes to genotyping. On the adverse event side, poor metabolizers had a higher rate of adverse events that caused them to discontinue the drug. That's because their exposure was too high. On the other hand, the extensive metabolizers had a different degree of efficacy. I'm not clear why that occurred. It could be related to an active metabolite or something like that.

So you really have to be careful about this type of data, but it does sort of raise the question if I had a patient going on this drug, would testing for their genotype in advance and perhaps lowering the dose proportionately have any benefit in improving the risk/benefit ratio? We don't have data to support that, so there was nothing in the label on that.

What we did put in the label is basically truth in labeling. We put in the label what we know and the evidence that's backed up by credible studies. We put information actually in seven different sections of the label in a hierarchical fashion. The most extensive information went where it was most important, and we had information in the four sections of the label that you see there, including laboratory tests to let the physicians and patients know that a test for this poor metabolizer genotype is available.

Just to mention that this is consistent with labeling regs, the label should describe the evidence and identify specific tests needed for the selection or monitoring of patients who need a drug, and we feel this kind of information is similar to liver enzyme function tests that are used to monitor drugs or blood levels of drug for TDM.

I'm going to finish with a third example. The first two were really talking about new drugs, new drug development programs. But what about drugs in the marketplace, drugs that were approved years ago before genomics was here? Why should they not be considered?

So we began to look at drugs that have narrow therapeutic indices and ask the question can the use of these drugs in therapeutics be improved on the basis of a genomic test? So we looked at 6-mercaptopurine as our example of this idea, and we took it to a pediatric oncology subcommittee in July, as

you can see.

Very quickly as a little backgrounder, 6MP is the drug of choice for childhood leukemia. The important part about using this drug is dose titration is critical. Getting the dose right not only affects long-term survival, event-free survival, but it also affects myelosuppression. Too much and you have a problem that requires a patient to go off the drug for three months. Going off the drug for three months affects event-free survival going out years. So getting the dose right is really critical.

It's metabolized by two pharmacologically active nucleotides by the enzyme TPMT. That's the key to this example. Now, TPMT genetic polymorphism is a well-established and well-documented situation, and through the literature and through ongoing research protocols there's a strong link between TPMT polymorphism and clinical effects, and in particular toxicity. On the left you can see the gene frequency of patients that have either normal to high, and then at the other extreme low to absent. 0.33 percent, one out of 300 patients, have no enzyme activity, and if they get the usual dose of this drug, 100 percent of them get toxic with myelosuppression and require hospitalization.

It follows, then, would the availability of a TPMT genotype test be useful in steering the physician and the patient to the correct dose that will have the appropriate risk/benefit? That was the question that we asked the advisory committee of experts.

PG tests for TPMT are fairly widely available commercially and in academic centers. Places like Mayo Clinic and St. Jude's have used them routinely for years to guide therapy, and more recently commercial laboratories as well. These are the three alleles that are measured showing the distribution. There is no difference between ethnic or racial groups, and all the commercial labs that I'm aware of operate under CLIA certification, and some of them operate under, in addition, GLP conditions. Academic labs operate under, in addition, research protocols for using this test.

So it follows, then, that there's a likelihood that the agency will look at product labels of approved drugs and advise those labels appropriately on the evidence that is out there.

So here's a summary. We think the technology in biomarkers from genomics is new, but the fundamental concept of using these markers to enrich populations or to exclude patients from studies or guide dosing, that's not a new concept. We've done it before with phenotypical markers, and all we have now is more precision in terms of a molecular basis for those phenotypes.

For co-development of a test and a drug that is intended for simultaneous marketing, let's say, I'm sure the FDA would recommend submission of complete information on both. The EGs are just examples. IDE shouldn't be the only way to think about this. It depends on the intended use and results of the test. As far as the analytical validity of these tests go, we're comfortable and we rely on the internal QC programs that you've heard about already this morning under the CLIA certification. We're also familiar with laboratories doing these studies that operate under GLP conditions, and this refers again to all the things that you heard about sample handling, the integrity of the incoming RNA and DNA.

Most labs put positive and negative controls. They do things in duplicate. We also look at the outcome in terms of the percentage of alleles being reported for a population to see if that's consistent with what we know, and then some of the laboratories are engaged in the voluntary proficiency testing.

So we tend to review this information like we review pharmacokinetic information or drug blood level information and bring a lot of the bioanalytical standards to this field that we've been applying to therapeutic drug monitoring and so on.

Thanks.

DR. McCABE: Thank you very much, Dr. Lesko. That was very informative. Please join us at the table here for the roundtable.

Our next presenter is Dr. Steve Gutman.

We're going to hold the questions until the roundtable.

Our next presenter is Dr. Steve Gutman, who is director of the Office of In Vitro Diagnostics.

Maybe not.

DR. FEIGAL: We pulled a switch on you.

DR. McCABE: Okay. Our next presenter is not Dr. Gutman, but it's Dr. David Feigal, who is director of the FDA's Center for Devices and Radiological Health, and the FDA is ex officio to this committee, and who will share with us the FDA's plans for enhancing the oversight of genetic tests. Thank you.

DR. FEIGAL: Thanks very much. I'm the warm-up act for Dr. Gutman.

(Laughter.)

DR. FEIGAL: This is a cover that occurred in Time magazine about two summers ago and made the comment that thanks to a patchwork regulatory system, perhaps a quarter of all research gets no oversight whatsoever. I don't think they actually had investigational diagnostic tests on their radar screen. I think they were talking about other kinds of research. One of the challenges this morning for you to consider that you discussed a little bit with the CLIA program presenters is what is required? What is investigational and what's the appropriate level of oversight in the different ways that diagnostic tests are offered?

It's appropriate to begin by saying what's FDA's oversight? FDA regulates manufacturers, not laboratories, not doctors, manufacturers, and we regulate the manufacturers of medical devices. This is the medical device definition, the part of it that's germane to diagnostics, and it's language that's almost 100 years old, so we still are trying to figure out what a contrivance is. But we regulate those if you make them.

(Laughter.)

DR. FEIGAL: But we do regulate in vitro diagnostics, components, parts or accessories, and products which are intended for the diagnosis of disease or other conditions, and things that are used diagnostically that are useful for cure mitigation, treatment or prevention of disease in man.

The basic kinds of consumer protections that FDA has been providing for almost 100 years can be sorted out into a couple of different groupings. One of the important ones is our role in risk/benefit management. We need to decide when is first human use safe, and obviously that's an issue if they're going to put something in your body. But sometimes information itself is important enough that it takes careful consideration to actually design how that new information is going to be used.

Consider, for example, if you're a young woman taking a test to see if you have early ovarian cancer. Since there is no recognized test that can do that already, the issue of how you're going to proceed from there if the test is positive is one that has a lot of implications. So there are times when, in fact, FDA requires protocols for the evaluation of new diagnostic devices and all of the protections of IRBs and informed consent and monitoring.

We have responsibilities for safe investigational use during product development. We control the access to market for some products but not all. We have responsibilities when products are in widespread use to monitor the use, the adverse experiences, and the corrective actions that are taken. We have the authority ourselves to do recalls when the situation is very serious. We and manufacturers issue warnings and alerts and monitor market withdrawals of products.

There's another grouping of consumer protections which is really what makes FDA different in this country than a lot of other countries. Many countries actually regulate their products in a

systems approach by assuring that there's an overall system that will assure quality, but they don't look at any evidence about the product per se. What happened in the FDA law, and it began to really have teeth for drugs in 1962 and for devices in 1976, was to actually set a standard for evidence. The standard for evidence for a new drug is adequate and well-controlled trials. A drug must be studied in humans in clinical trials that are adequate and well controlled.

The evidence standard for devices is more flexible. It's the phrase "valid scientific evidence," which includes clinical trials but also includes performance measures, and in fact most devices actually are studied at the bench and do not have clinical trials as evidence.

But there are many settings, including settings for diagnostic devices, where the only way you'll know it works is to test it in a clinical setting and get that clinical correlation.

There's a third part of our responsibilities which we won't talk about very much today. It's actually one of the more colorful parts of our job, which is integrity assurance, enforcement for fraud, for counterfeit products, for research misconduct, but that really isn't what we're talking about today.

It's helpful if we actually look a little bit at the life cycle of a product and look at where the regulation sort of fits in. So if you begin with an IVD concept, a glimmer in a laboratorian's eye, one of the early steps is to develop the reagents and analytes that make that test run, the brains of the test if you will, and that may be paired with non-clinical specimens that allow you to assess the performance of those analytes.

In fact, if you want to be a reagent manufacturer, this is where you go to market, and there's a special grouping of reagents called analyte-specific reagents which include genetic tests where FDA actually published a classification rule some three or four years ago that outlined manufacturers' responsibilities and labs' responsibilities, and at that time down-classified most of these products.

The default in the device regulations we'll talk about in a moment is that a new product is assumed to be a high-risk product until proven otherwise. What was said with the ASR rule is that if these responsibilities were met by the manufacturer and by the laboratory, then in fact most of these ASRs would be Class I-exempt, and Dr. Gutman, when he follows up, will actually talk in a little more detail about the refinements that we need to the initial approach we took with ASRs.

But the manufacturers must register, tell us who they are, what their products are, and they must follow quality systems regulations, sometimes called good manufacturing practices.

They can only be sold to a high-complexity lab. The labs must establish the performance and labeling. The manufacturer is only selling a reagent. Most, as I mentioned, are exempt from premarket review. The manufacturer, if they are aware of adverse experiences, must file medical device reports to FDA. It's part of a quality system to have such a program.

The laboratory has to be a high-complexity lab. There's no such thing as an off-label use of an ASR where the manufacturer can only sell it but if somebody else uses it, too bad. No, the laboratories must be high complexity. The laboratory is responsible for establishing the performance of the test and the label, and Dr. Gutman will go over what we expect in a manufacturer's label, and there are some things that we've said are mandatory in the labeling, some disclaimers about the test not having been FDA reviewed as a test, and then there are some things which we feel the laboratory should include but are discretionary.

Now, if you're going to actually make something more than reagents, if you're going to make laboratory testing equipment, if you're going to make kits, if you're going to make reagents and kits and equipment that all goes together, then you're going to have to actually show that the test actually has clinical benefit, and the benefit from a diagnostic test is the information it provides, and the risk of the information is that it may not be accurate. You may have false positives, you may have false negatives. If

you have to demonstrate that with clinical specimens, then there's a requirement that you follow good clinical practices, which include informed consent, investigational review board oversight, have a protocol, have monitoring of the performance during that time.

Many diagnostic tests do not actually have to submit their protocols to FDA. The ones we're particularly interested in seeing and that we consider not exempt from submitting to us are the ones where there is clinical reliance on the new information of the test. Ovarian cancer, the example I gave earlier, would be such a test.

If you want to go to the market as a completed test, you're going to have to scale up to GMP manufacturing, which means having a quality system, design controls, a CAPA system, which stands for Corrective and Preventive Actions, which means that you have to have a way of monitoring and tracking complaints, resolving complaints, recalling products, changing labeling, issuing alerts and so forth.

As you weigh the relative protections, consumer protections that are required of manufacturers, think back to the somewhat different approach of CLIA to the laboratories, and again when you get back to laboratories developing their own tests, how many of the things that manufacturers develop would be reasonable to expect to have their parallels, and in fact often do have their parallels in the laboratory system?

What do we look at with the premarket applications? Well, products have to be designed properly. You have to specify the design controls that identify how the test will perform, verify that, validate the device performance, and monitor that.

If you come to successful market, it will either be through one of three principal routes. About half of all devices are exempt from premarket review. That doesn't exempt them from all the manufacturing, quality and other types of reporting, but they can go straight to market. I'll talk about Class II and Class III in a moment, but those are the types of applications that FDA reviews, and you cannot go to market until we have done our review.

Then as you go through the life cycle of the product, you have the responsibilities of the product in use of reporting adverse reactions, recalls, labeling revisions, and so forth.

So in summary, if you look at FDA in risk assessment, there are different aspects across the whole life cycle of a product, and because we have products that have to get our approval to come to market, it's relatively straightforward to identify the investigational phase of a device that requires a 510(k) or a PMA. It's not so clear what the investigational phase is for a laboratory-approved test, and I think that's one of the challenges for us to all think about.

So we look at risk in the investigational phase. We review the performance before it comes onto the market. We review the production and the safety information.

Let me just say a little bit about our arcane review system, courtesy of Congress. This is their town, so we'll say nice things about them. In the beginning there were preamendment devices. In 1976 the law was passed to regulate medical devices, and at that time there may have been as many as half a million medical devices in use. When pharmaceuticals came on the market and required testing in 1962, the default was that the products had to actually demonstrate to review panels of the National Academy of Science that they were probably effective in order to stay on the market. Otherwise they came off, and tens of thousands of products came off.

With devices, the opposite was done. The default was that these products are safe and can in fact be the basis for the approval of future products. In 1979 or 1981, comparing yourself to a 1976 product wasn't so bad. Now, in fact, it works out somewhat differently, although it's still legal to come to the market on the basis that you're as good as something that was on the market in 1976.

The default in the law is if the product is new and novel, that you have to file a

premarketing application, which has many parallels in structure to a new drug application, and the standard is that the product must be safe and effective. For a diagnostic device, safe and effective refers to the usefulness of the information.

But one of the things that was done about devices, recognizing that there are between 25,000 and 50,000 new medical devices on the market every year, was that you couldn't require large applications for all of them. So a streamlined application was designed for lower-risk products, and then other products were exempt from any kind of premarket review at all. These are Class I and Class II, the lower-risk class products.

The basis of approval here, they can demonstrate that they're safe and effective, just like a PMA does, but the usual basis for their coming onto the market is to show that they're substantially equivalent to an old product, a product that's already on the market, a product that can go back to products that were on the market as far back as 1976.

This is a little different. It sounds like it's sort of a little bit like a generic drug program where if you're bioequivalent, you can come on the market. But with a generic drug, you want the generic drug and the originator drug to be freely substitutable, because that's how you're going to use them. With devices, it's actually that you have to be at least as good as, and the market pressures in the 510(k) area have worked that most products over time improve and are better than their predicates, but they only have to be as good as something already that was on the market.

Let me talk a little bit about in-house tests. That was all about the device manufacturers per se. In-house tests is a well-established practice with a long history and regulated by CLIA in ways that were described this morning. The analyte-specific reagents that I mentioned earlier when I talked about reagent manufacturers are the building blocks or the active ingredients for many types of in-house tests. The ASR rules and the supervision of manufacturers of reagents was designed to allow for in-house tests with incremental control based on the tests. As I mentioned before, the guidance that was published many years ago was actually a classification guidance saying that most of those products were going to be Class I exempt, there would be no FDA review prior to coming to market.

What's the regulatory gap with in-house tests? Well, the gap is that the CLIA intent and the FDA were designed to accomplish different goals. The CLIA system is oriented towards the quality of laboratories, and it looks at the whole system of how the laboratories work and the quality of that system, and it focuses on analytic performance and quality control measures. As I have mentioned already, there really is not a definition of investigational, although we heard today proposals to treat genetic tests somewhat differently.

The FDA focuses on devices and the device manufacturers, and it requires evidence of analytical and clinical performance. Sometimes the clinical performance can be implied by linking it to other tests that have already demonstrated clinical performance, and the basic FDA requirement is manufacturing quality standard device by device by device. So between these two standards, there is a bit of a gap. There are things that you have to do for CLIA that device manufacturers don't have to do, and vice versa.

So one of the things that we'll focus on a little bit in the rest of the time is to talk about some of the other FDA consumer tools. I've already talked about almost all of them except for the first one, and that's truth in labeling. This was actually the first FDA approach back in 1906 to providing consumer protections, to simply require that products be accurately described by their manufacturers. The language was that a product's label could not be false or misleading in any particular, and then later they added some additional requirements around fraud.

In summary of my part of the talk before I turn it over to Steve Gutman is just a

comment. I noticed this was an historic slide because I've still got HCFA on here. In the HHS, you actually have to pay Tommy Thompson a dollar every time you say HCFA instead of CMS. So I owe the Secretary a buck. Hopefully it won't multiply times all of you.

But if you look at diagnostic tests, one of the real challenges here is you're probably dealing with one of the most regulated areas of medical therapeutics, but it's an overlapping quiltwork as was described in my first slide. It doesn't cover everything, and yet if you'd ask a laboratorian whether or not they're regulated, they have responsibilities to us, to states, to the CLIA program and CMS, to their local IRBs, and not only the devices but the facility itself and each of the professionals in the facility each have a measure of regulation.

So the theme that we would like to develop is how do we get the right balance and how do we get the protections we need without being burdensome and without making a system that already has some redundancies even more difficult in an area where we expect quite a bit of benefit from the medical progress being made in this area?

So with that, let me introduce Dr. Steven Gutman, who is the head of our in vitro diagnostic office and who has responsibility for in vitro diagnostics throughout their whole life cycle.

DR. McCABE: Thank you. Again, we'll hold questions.

DR. GUTMAN: Good morning. As David has suggested, a fundamental tenet in our regulatory process is our regulation of labeling. So I'm going to surprise folks by sort of introducing labeling advertisement and future directions all in one fell swoop.

From our perspective, a label is a manufacturer's product monograph. It is what we refer to actually as a package insert, and it includes a wide range of both general and specific information about a device that allows the user to properly select and to properly use a device. The label is the basis for the approved promotion of the product by a manufacturer, and there is an important distinction here. Off-label promotion, off-label from the FDA-approved product, is not allowed, although off-label use is, of course, within the practice of medicine and at the behest of laboratorians or clinicians in fact is allowed.

FDA sets labeling requirements, monitors advertising and promotional labeling in the context of those labeling requirements, and watches to ensure that use is appropriate for its approvals. In vitro diagnostic devices are unique among medical devices in that we are so obsessed with labeling that we have our own regulation. We're the only product line with our own regulation. It appears in a glorious part of the regs called 809.10, which I suggest you all rush home and read.

(Laughter.)

DR. GUTMAN: It has 15 components, the most important of which is the intended use or the indication for use, since that particular component will determine the classification of the product and will determine where in Dr. Feigal's scheme a particular product will belong. The intended use may allow it to be Class I exempt, may require a Class II premarket notification or 510(k), or may be interesting and high risk and novel enough that it might require a Class III or PMA. So the intended use and the indications for use are really critical.

The IVD labeling regs are so brilliant that I intend to share them in their entirety with you this morning, albeit I will be mercifully brief and try to give you just a quick overview. They include the requirement for the proprietary name and establishment name for the product; the intended use or uses; a summary and explanation of the product and the principles involved in the device function; when appropriate, they require that there be information on reagents, information on instruments, or information on specimen collection, processing, storage, handling.

They include requirements for an outline of the procedure to be followed, an explanation for how results are calculated, and for us a very important feature, information on limitations

of a device, either analytical or biological limitations. Then last but certainly not least, they include information on the expected values, on the heart and soul of the test itself, the performance characteristics, and then as icing on the cake a bibliography, name and place of business, and a date of labeling so you know whether it's a contemporary label or not.

The FDA act itself does not define advertisement, but FDA interprets that term to include supplementary or explanatory information in relationship to the label, and products can be found misbranded if either the advertisement is false or misleading or the labeling is false or misleading.

The agency does watch to ensure that off-label use -- although perfectly appropriate by labs and physicians, we do watch to make sure off-label use is not promoted in device ads or labels. We have partners in crime, in particular in competitive areas, where in fact the manufacturers help us watch. We do not exert, as I think you already know, authority over laboratory ads or over laboratory reports, with the exception that in the ASR rule there is a requirement for a disclaimer clarifying who is taking responsibility for the performance of the in-house test made using the ASR, and there's also an opportunity for explanatory language explaining that you haven't grown a second head and you're taking advantage of a perfectly legitimate mechanism for generating a lab result.

The FDA, in fact, does not have direct authority over ads, does not have authority over marketing patterns, direct to consumers, and in fact the most interesting and strongest hook we have in this area is in the area of the ASR rule where we specifically note that an in-house test built with an ASR cannot be sold over the counter. The notion is that it's too complex a beast to be sold over the counter. As you'll probably hear more this afternoon, FTC has primary jurisdiction for over the counter devices, and it relates to an historic agreement, sort of like the Warsaw Pact but dating to 1954.

(Laughter.)

DR. GUTMAN: FDA does have guidelines for pharmaceuticals that are based on the requirement for truthful and balanced presentation of facts, and in fact if in that area there are violations identified, it could lead to misbranding charges. Those actually don't apply directly to diagnostic devices, but a lot of the principles are similar. So if one is looking for reasonable advice on honest labeling, that's probably as good a place to go as any.

There are two general important themes at FDA. They're not new but they're certainly prominent in the life of our center and the life of our agency. The first is an increased flexibility in regulatory approaches and an increased menu of regulatory tools, and I won't dwell on them because they're somewhat an arcane and parochial taste, but in fact there are alternatives now to the 510(k) process that provide opportunities for more streamlined submissions, there are alternatives to the PMA process that allow for administratively more controlled patterns of interaction with the agency, there are new mechanisms for making classifications simpler so that we can classify important novel devices with more facility than in the past, and there is, of course, as a result of the modernization act, a commitment on the part of the agency, and certainly on the part of the center, to be least burdensome and to make sure that our premarket review process is focused on relevant endpoints and doesn't wander into interesting academic escapades.

The second equally important theme and a slightly newer theme is derived from senior management in the Center for Devices, and that is the strategic plan which emphasizes the notion that we as regulators should take a very broad view of regulation and we should, in fact, approach regulation from a pan-regulatory standpoint rather than some kind of segmented, separated, pre- and post- and safety patient piece, that we should really bundle that together into what we call the total product life cycle, an entity which charts products -- and Dr. Feigal showed you in glorious graphical form -- charts them from birth to obsolescence and watches as you build on existing knowledge, so better knowledge management.

What has happened that is certainly unique in IVDs -- I would contend lots of things are rather unique about IVDs, but certainly what's happened that's unique in IVDs is that we have in the center under Dr. Feigal's charge crafted a single office in which all regulatory functions are now subsumed. So the Office of In Vitro Diagnostics is responsible for premarket review, it's responsible for compliance activities, it's responsible for postmarket surveillance, and you have truly for internal and external stakeholders an organization which is in the pursuit of providing one-stop shopping.

As you are all aware from the last meeting, or maybe from previous meetings, the Secretary's Advisory Committee on Genetic Tests, your predecessor committee, put forth a challenging menu of ideas for HHS to consider for enhancements and oversight by, frankly, all of the involved regulatory parties -- CMS, FDA, and even CDC, which isn't exactly a regulatory party.

FDA in this scheme was charged with considering increased oversight of new genetics tests, and although SACGT was bold, they weren't completely crazy, so they in fact suggested that this ought to be risk based, that this ought to be posited in a way that would be non-chilling to technology, and that this be informed by professional societies. Whatever else, I do know it's certainly the intention of the agency as it explores this area to follow those central tenets.

Probably one of the most interesting work products of the Secretary's Advisory Committee was a data template generated by the data collection subgroup that was chaired by Wylie Burke. I think it is well known, but if it's not then I will make it well known that that template was explored in the context of a professional roundtable and that the Association of Molecular Pathologists were in fact the sponsors of that roundtable, and Dr. Leonard in fact was the chair of what turned out to be two merged committees that created a data collection template that was designed to try to tame this data set.

What the agency has done is it has simplified and modified that template and in fact is now using an FDA model for that template in the course of its routine reviews. So perhaps one size does or perhaps it doesn't quite fit all. So I'm not sure what we gave to SACGT, but I am quite certain of what we took away from SACGT, and what we took away from SACGT was the notion that there ought to be some kind of streamlined and standardized way of presenting data about laboratory tests.

We in fact adopted a review template. It has essentially the heart and soul of the FDA review process subsumed in that template, and it has replaced our final review memos, and most recently it is now being made public. So if you bother to go on the OIVD webpage and look at products that have been cleared, you'll see some have the decision template and some don't, but hopefully in a month or two they will all have that decision template.

What we settled on was a template which included key administrative information, like the 510(k) number, the analyte, the type of test, who was submitting the test and what its names were; the key regulatory information, which includes intended use; device description; the charting of the critical element, which is substantial equivalence, which Dr. Feigal mentioned; any standards or guidances referenced to help make that decision; the heart and soul of the review processes, which is looking at the scientific information to see if it does what it says it does, so looking at test principles and performance characteristics. Performance characteristics is the single longest part of any subcomponent of this template, as you might gather, since it attempts to encompass all the features of performance. A conclusion, and I guess not entirely scientific but supporting information and contact information.

The future is now. So although it's a tool that we'd like to explore in the future, we are now using it to try and tame our process, to try and standardize our process, to try and streamline our process, and certainly to make our process of premarket review transparent.

We view this review template as an IRS 1040, as the final report, and it is our intent at

some point to steal from TurboTax or TaxCut the idea that they are probably making lots of money off of -- I hope so, since it was a great idea -- the idea of an electronic format that would streamline input from manufacturers and streamline the review process for FDA. So we have a -- I wouldn't call it long term, but certainly I also would not call it a short-term project to try and craft an electronic format that would allow this data template to be based on Schedule A and Schedule B and Schedule C and all kinds of special forms, when appropriate.

In the interim, we actually have as a short-term project -- that's three months, but of course in the FDA that really means six or seven months -- the intention of producing a paper-based version. So we're going to create our 1040 the old-fashioned way, using paper, and we'll fool around with that before we actually generate electronic signals. I spend a lot of time in this review because I love this template. It is a gift that SACGT gave to the agency, and it may or may not be useful for future genetic regulation.

The most interesting development on the sidelines, as I suspect many of you know, has been in recent months commercialization of microarrays and other technologies which may challenge the definition of the ASR, and certainly challenge the definition of Class I ASRs. In the light of those technologies, and in the light of revisiting the ASR rule as a fundamental tenet, we in fact are doing a great deal of policy and legal analysis to try and figure out how all this sorts out. Under the statute, all new devices actually come to life as Class III products. That's the natural default. The ASR is one type of new device, and if a product in fact fits into that category, the ASR has historically, with a few exceptions as David pointed out, been viewed as a Class I exempt device.

Some of the new technology, some of the microarray technologies, whether ASRs or not, may not be Class I exempt, particularly if they fall outside of the description of what we would consider a Class I product, and in fact what I may not have shared with this group before because it's actually a relatively new discovery on my part -- you see, all devices have limitations. Those limitations are in fact visited in the law, and if you're really perverse you can actually look it up. It's 510(l) of the law. They are present in the regulations, and if you really have a pension for joy, it's in 864.9 of the regulations.

What they suggest is that some new technologies may not fit the description of ASR classifications or of Class I exempt classifications and may trip the limitations, and I'll give you two examples that might trip the limitations. The limitations of an exempt product might be tripped if you had a startling new technology, or it might be tripped if you had interesting new intended uses.

So we are exploring that, and it's certainly our intention, once we have more clarity on exactly what those words mean, to try and communicate that to both the laboratory and the manufacturing communities.

We are revisiting the ASRs, and it's been tougher than I would have hoped, certainly tougher than I would have guessed, but that revisit follows some of the tenets that we've always expressed, which is that we want this to be collaborative with other parts of HHS. I don't remember if I've expressed it or not, but in fact the revisit of ASRs is not focused on genetic testing alone. That is, we went back and looked at the issue critically. We in fact concluded that there actually was a good argument to make for not treating tests that were genetic-based in some exceptional way, that all tests ought to be created and treated equally, and they ought to be treated in the context of the risk they pose.

So the one really big change as we revisit the ASRs is not focused only on genetics tests but on any test, frankly. And it's likely as we struggle forward with this that we will be emphasizing the Commissioner's goal of risk-based and cost-effective regulation that will likely emphasize the Commissioner's goal of informed consumers. That certainly is at the heart of the data template we're now posting, and it is, for better or worse, likely to take time. It's likely to take time because if there's anything

that we have learned, it's that these issues are challenging.

The central issue is trying to develop a risk-based approach towards the ASRs. That was a challenging issue for SACGT. SACGT, in fact, drew back after a number of efforts to try and craft a variety of very rich and nuanced risk schemes. That turns out to be a challenging issue for FDA in spite of our experience, and we have lots of experience classifying products and lots of experience with risk management. It is harder than I would have guessed to sort through and craft a non-chilling, a risk-based, and a user-friendly mechanism for dealing with this challenging problem.

We are expecting input from professional groups. I'm personally going to nag some of those professional groups at the break today. Input is still welcome, and any help in trying to move forward with an intelligent, well-crafted regulatory scheme that informs public health would be welcome.

Thank you.

DR. McCABE: Thank you very much. If you could join us at the table.

Before I turn the floor over to Dr. Leonard, I would ask that we try and maintain the questions around the issues of regulation and labeling. Advertising is something we'll take up this afternoon and we'll have an opportunity to discuss that at that time. So for now, if we could focus on regulation and labeling.

Dr. Leonard.

DR. LEONARD: Thank you. This is Debra Leonard. I will take the chair's prerogative and ask the first question, and then if others want to ask, I know Emily has already asked me to ask a question.

This is directed, I think, for Steve or David. The data template that you referred to that you're now using grew out of the SACGT process with a direction to FDA to provide oversight for laboratory-developed genetic tests. You're now using this, I think, for IVD submissions and review. Is it your intent in the future to move ahead with the laboratory-developed test mandate of providing oversight?

DR. GUTMAN: What you see is what you get, actually. The template has no broader design. We loved the idea, we subsumed it into our review program, and we think it fits our review program nicely, so we're grateful. The plan right now is for the agency to look at the ASR rules. So the plan is for us to look at manufacturers and look at reagents, and there are broader schemes on the table but there are other parties involved. There's CLIA. There's still the possibility that professional groups may weigh in. So I'd like to suggest, at least right now in the incremental picture of things, we are looking at a revisit to the ASR rule.

DR. LEONARD: And does that involve the IVAT guidelines/documents that are out there? I mean, is the IVAT related to the revisiting of the ASR regulations?

DR. McCABE: Could you explain what IVAT is, please?

DR. GUTMAN: Yes. The manufacturing community has put a model on the table in which they're suggesting that our premarket review be based only on analytical performance and that the clinical issues that we often struggle with and the clinical signals either be addressed through truthful labeling, which is that they're not clearly known, or that that responsibility be assigned to laboratories.

The IVAT is actually under legal review, and it's hard to say that there's no relationship at all, but it actually isn't directly being plugged into the thought processes about the ASR rules. It could be, I suppose, but it's being treated as sort of a separate entity.

DR. LEONARD: Thank you.

Emily?

DR. WINN-DEEN: I wanted to ask Dr. Lesko a question about what you feel -- you mentioned in one of your slides that before you required testing in a product labeling, that that testing had

to be available. Certainly for 2D6, for example, there are commercial, CLIA-certified laboratories offering that testing. Does that mean that the agency doesn't feel that that meets their definition of "commercially available" and we're waiting for actual IVD products to be available? What is the thinking of the agency about tying the requirement or even strong recommendation for a test in conjunction with prescription of a drug?

DR. LESKO: To continue with the 2D6 test -- can you hear me? My mike isn't working, but I'm speaking into it. I think our preference would be to have these tests approved by the agency, including 2D6 and some of these polymorphic enzyme tests. I think the problem in terms of availability when you move from laboratory to laboratory is the alleles or polymorphisms that are being tested for. There are some laboratories, for example, that do offer a 2D6 test for identifying certain alleles, but it may be limited to, let's say, a *3, 4, and 5. On the other hand, if we had a new drug in development, we'd be much more interested in about seven or eight of those alleles, which would be the *3, 4, 5, 10, 16, and 17, because these are the alleles that predominate in the ethnic populations of Caucasians, Asians, African Americans, and Hispanics or Latinos.

So I think it's an issue of coverage. When we say available, it needs to be available so that the results are generalizable or extrapolatable to the population that's going to get the drug, and it doesn't help to have a test available that's only targeted to a specific group and excludes others, because the absence of a test then becomes the assumption that this individual would be the most predominant allele, which would be extensive metabolizers.

DR. WINN-DEEN: So could you handle that by just making specific recommendations that a test covering the following A, B, C, D, E alleles is recommended and allow the community to decide if that's an IVD or "home brew" from a CLIA-approved laboratory? Or are you still really thinking that the only way that we're going to really see this happen is through the IVD manufacturers stepping up to the plate and starting to take IVD kits into the agency?

DR. GUTMAN: Well, there is another choice, and I can't speak for CDER, but I know that CBER uses that, and that is when they're looking at a therapeutic trial and there's a home brew-linked diagnostic, because there is concern that they actually have insight into the diagnostic beyond what might be normally seen in the CLIA program, that CBER will frequently ask for information about the test. It's not quite like a CDRH device review, but it's probably a bit more information than might normally be seen.

So I don't know that CDER does or doesn't do that. I would encourage them, if they don't, that they probably should. In-house or home brew or a CLIA test comes with a wide spectrum of expertise, and when it comes from Debra's lab, I'm really, really comfortable, and when it comes from my old lab, I might be a little bit less comfortable. I can't quantitate that because I favor Debra over myself, but I can quantify that by saying, gee, you need to provide us information about the home brew test. It makes sense to support this product as a whole.

DR. LEONARD: I didn't pay him to say that.

(Laughter.)

DR. FEIGAL: There's already been one precedent, though, where a drug was approved that suggested a laboratory test for monitoring that was only available for several years from central labs as home brews, and that was therapeutic drug monitoring for FK506, a tacrolimus test. It took about three years for that test to become commercially available. So we've already sort of crossed that bridge of having had a drug that was useful and a test which was only available from central labs and approved in that setting.

DR. LEONARD: Right now I have, just so you know and don't keep raising your hand, Reed, Ed, Brad, Barbara, Muin, and Francis and Arden.

Reed?

DR. TUCKSON: I'll try to be short. This is Reed Tuckson. This is in the same area that Emily Winn-Deen was sort of getting at.

Dr. Lesko, you presented a number of cases of drugs that it may make sense to have some more precise specificity of use if we could use a test that would give us that information. Steve mentioned cost-effectiveness as part of the FDA's mandate for this particular Commissioner. Do you see, then, the responsibility of the FDA, given how expensive drugs are today and how everybody is worried about how we're going to handle that, do you see a responsibility of the FDA, then, and can we expect the FDA to provide clear guidance around the use of tests to be able to better monitor/titrate/use expensive pharmaceuticals that will ultimately be a cost/benefit tool? And will you be clear as you all make your recommendations so that those who have to pay for all these things, pay for the drug and pay for the test, will understand that cost/benefit ratio?

DR. LESKO: No. I think it's a good point, but I guess I don't think of that as being part of the mandate that we have when it comes to testing. I think the way I would look at it is that the role of the test is based upon the level of risk management that it might bring to the table, so to speak. I think the decision to put information in a label is dependent on the clinical benefit that can accrue from using that test, or at least making that information available.

DR. TUCKSON: Well, if you've got that database and you're doing all those analyses, who in government, or where would you expect somebody else to reproduce that? If you're not doing that, who ought to? And if some other part of government is going to do that, or are you going to be able to make that stuff transparently available in the literature or in some other way so that everybody else can use it? Otherwise it would be redundant and wasteful, wouldn't it?

DR. LESKO: Yes. I think we have information that can be provided, but the decision on cost/benefit or a cost/benefit analysis would fall more into the area of third-party payers or CMS reimbursement, I would think.

DR. LEONARD: So can you give that to CMS? I think Reed has a very good point.

DR. LESKO: To an extent we can. I guess it would depend on the Freedom of Information extent, what's in the package insert and things like that. I think it would be case by case. I think one can do a decisional analysis type of simulation, if you will, to figure out whether the cost of a test is going to be effective in terms of what happens with adverse events and not having a test available to guide dosing, for example. I mean, some of that has been done and published in the literature already.

DR. GUTMAN: This is really a big problem, and there actually have been some seminal efforts to try and make better connections between NIH, FDA and CMS on an informal basis or a semi-formal basis. Some of the working groups have connected in imaging and cancer diagnostics. There was recently an AHRQ-sponsored or an AHRQ/CMS co-sponsored activity to try and figure it out better. So it's on people's radar screen, but you're dealing with different agencies, different cultures, and different regulatory missions. So it's harder than it seems, but it's not being ignored. It may not be going as fast as you would like, but it's not being ignored.

DR. LESKO: Just to add to that, I think many of us have been up to, for example, CMS, and they've provided educational programs that would lay out what we do know about, say, pharmacogenetic testing and clinical outcomes. The other side of that is, at least with some of the older pharmacogenetic tests, the literature, the published literature, the publicly available literature is quite extensive and can, I think, be used to make a case for or against testing in terms of cost effectiveness.

DR. TUCKSON: Well, there are so many people in line. I think it would be helpful if you could teach us more about whether or not this is a promising area. Do you believe -- and don't answer

because we don't have time -- is there any future in this kind of being able to actually more precisely dial in a test for a drug? At the end of the day, is that actually going to have any impact, do you believe, on the cost of drugs in this country that the American people have to pay? If this has any promise, we sure need to understand something about it so we'll know whether we should spend any more time on it.

DR. LEONARD: Thank you.

Ed McCabe?

DR. McCABE: Actually, my question was already answered. It had to do with the home brews. But I notice that somebody from the audience wants to make a comment. I would just point out that we, by tradition, hold those until the very end, and if there's not time when we get through with the people around the table here, then I would ask that you submit your comment during the public comment period. Thank you.

DR. LEONARD: Next I have Brad.

MR. MARGUS: I'm Brad Margus, and I wear several hats, but right now I'm speaking as a consumer rep. I'm questioning the connection between the actual content of the test and how it affects whether there's a gap or not, so let me give you a scenario.

If there's a team of researchers doing a genetic association study and they found a clear connection, a genotype/phenotype correlation between a couple of markers and an important disease or a trait, and then they wanted to provide this test for people but they're not selling a diagnostic test or a kit or anything, this morning from what I heard about CLIA it sounds like as long as they get CLIA approved for being able to reproducibly do that test with qualified people and all that, it can be a CLIA-approved lab.

Then when it comes to the FDA, my question is how much does it matter if -- does it fall through a gap there where it's not really going to need your approval to be provided to people? And I assume that if someone would assign them the reagents to do that test, it sounded like it could get caught. But if it's just that the lab could make or order some primaries to do the genotyping, it doesn't sound like that in itself would get caught.

And then to go one step further, let's just say that that test had been reproduced in other labs, and we all feel good about the science but what it predicts is intelligence for athleticism or tendency toward criminal behavior. Where does it get caught in the FDA, or doesn't it?

DR. FEIGAL: The reproducibility of the test and the ability of the test to measure what it says it's measuring in terms of the genetic information it's looking after is the kind of thing that CLIA would provide, oversight over how the laboratory performed that, and Judy Yost mentioned this morning some of the proficiency testing that's done when the same test is offered by multiple labs.

Some genetic information speaks for itself. If you have the sickle cell gene, we know exactly what that means. If somebody wanted to offer a sickle cell test, they wouldn't need new clinical studies. The literature tells us exactly what it means. They would just have to show us they could accurately measure the genes.

The challenge is the information that is more speculative, and in fact for a CLIA test, there doesn't have to be any clinical evidence. You mentioned that they had clinical evidence that the test meant something, but there are tests that have never been shown to have any clinical correlation, there's no literature, there's no research, and people are offered the test saying that the results speak for themselves, it's up to you to interpret the test. Dr. Collins I think showed some of those results before.

There's a gray zone where there's some preliminary results that suggest there's an association and there isn't much confirmation. When that kind of test is brought to us, that's a very difficult situation. There was recently a meeting sponsored by Duke looking for risk factors to predict cardiovascular risk, and they had sample sizes of 2,000 high-risk pairs with 2,000 controls in a typical

study. It included groups like Framingham, groups from all around the world. All of them found markers of predictive cardiovascular risk, but none of them found the same markers. All of the markers that each group found were highly statistically significant. It had five zeros in front of the 1, the P value. So they weren't occurring by chance and they were marking the individuals in that sample, but they weren't reproducible, and that's one of the difficult situations for us.

The venture capitalists estimate that there's about a million genetic tests done a year in the United States now, and it will increase to 200 million over the next five years. Currently there are less than a dozen tests that are FDA approved. So right now you're looking at a CLIA-supervised world.

DR. LEONARD: We'll move on to Barbara.

MS. HARRISON: I'm Barbara Harrison. I had a question for Dr. Lesko. We've talked a little bit about the importance of including people from different populations other than Caucasian, particularly in these genotyping studies, and I think it's particularly important given the admixture that's happened in the African American population at several loci. We just have many more alleles than would be found in a population of just Caucasians or just Asians, just because again our admixture is so much higher.

So I was just wondering if there's expectations for these companies when they do these tests. You mentioned that most of the studies involved 95 percent Caucasians. Are there any expectations, is there any way to stop companies from just basing it on a population like that? Is there any regulation on that?

DR. LESKO: I think the answer is yes. There's an interesting report, and you can look at it on the FDA webpage if you put in "ethnicity" as a search term, and it's a study that was conducted over 1995 to 1999 that looked at clinical trial enrollment as it was broken down by race and ethnicity, and it shows the distribution of different populations in the different phases of drug development. At that time, the distribution of different groups in early clinical development paralleled the percentage in the population in general. So if we're talking about Phase I and early Phase II studies, there was good representation.

Things broke down when you went into the Phase III trials to demonstrate clinical efficacy and get the bulk of your safety data, and that's where the limited enrollment occurred. That was 1995 to 1999. Since then, things have improved. The agency has near final a guidance to the industry on the enrollment of racial and ethnic groups, and it's also on the webpage in draft form. The guidance is intended to encourage this type of diversity in the enrollment in clinical trials consistent with the target population, the disease state, and so on. I think the impact, the hopeful impact of that is that things will change in the clinical Phase III efficacy/safety trials to mirror what already has occurred in the earlier studies. But that guidance will be finalized fairly soon, I believe. That's available for public review on that same website under "Guidances."

DR. LEONARD: Does that mean that a drug could not be approved because they didn't have the breadth of ethnic diversity in their clinical trials information that they're submitting to you?

DR. LESKO: I think the answer is no. It could still be approved. It's going to have perhaps a different label than it might have otherwise, but I don't believe the agency could not approve something based on the enrollment of different patients in a clinical trial. I don't think there's a regulatory mandate to do that. The way we encourage companies to do that sort of thing is through guidances, and a guidance is non-binding, non-enforceable, but a company is obligated to address the issue of why didn't you do something that might be recommended in the guidance.

DR. LEONARD: A follow-up from Ed.

DR. McCABE: So in follow-up -- this is Ed McCabe -- there might be labeling like "a drug has not been tested in children," there might be labeling to specify what populations it has been tested

in and that there's limited knowledge beyond that ethnicity. Is that what you're telling us?

DR. LESKO: Yes. That's kind of routinely put in the labels now in terms of what not only is known or what was studied but what also is not known or what wasn't studied, and there is a proposal now, a new physicians labeling that creates specific sections for that type of information under "Special Populations" and other places, depending upon how important that information is to know.

DR. LEONARD: Next comment from Muin.

DR. KHOURY: This is Muin Khoury, CDC. Just want to come back to what Reed Tuckson was talking about a couple of hours ago now, about the issues around pharmacogenomics and cost-effectiveness analyses. This is really where the rubber meets the road. At the end of the day, there's going to be an expansion of many, many, many tests that are going to be used in conjunction with either treatments or prevention, like the TPMT with acute leukemia, et cetera, et cetera.

As I was listening to Dr. Lesko give the presentation on the few cytochrome-based available genetic tests, what came to my mind was the wonderful analysis which was a framework that was done by David Veenstra from the University of Washington a couple of years ago on the cost-effectiveness of pharmacogenomics, and he used specifically TPMT as an example. I don't want to take too much time here, but it's a complex set of factors that come into play.

One of them is the frequency of the allele itself, or the trait. If it's rare, like 0.3 percent of the population, as he showed, it may not be cost-effective to test the whole population, especially if you have a phenotypic test or a measurement that can follow or track the levels of the drug in the body to assess the body burden of the disease. So the value added of a genetic test, whether in the context of pharmacogenomics or prevention or screening a whole population, is much more complex than the analytic validity of the test, which could be wonderful, the clinical validity of the test, which could be wonderful because there is genotype/phenotype correlation, but the clinical utility is a complex scheme of factors that involve economics.

For that to happen, it's going to require working hand in hand with the regulatory paradigm and the practice of medicine and the professional organizations coming together and reviewing the evidence for or against different uses of technologies. It's sort of an objective way, using technology assessments. There are processes that already exist within the government, like the U.S. Preventive Services Task Force that's housed at AHRQ, and the Community Preventive Services Task Force that's housed at CDC, and a whole variety of other existing mechanisms that can complement the regulatory paradigm to come to bear on the actual utility of genetic information and practice.

DR. LEONARD: As a follow-up to Muin, I was a little disturbed to look at the table for 2C19 genotype for voriconazole and find that there is no dose reduction recommended because the test was not broadly available. It would help physicians to know that if they could get the genotype, what to do in response to that, and I would encourage that when these things are done, that even if the test is not available, that there be some recommendation that if it were available, this would be an appropriate response, because that's the only way that physicians are going to be able to move forward, and many times laboratories will not develop tests unless physicians will use them, and this would drive that motivation and more appropriate use of drugs.

DR. LESKO: To clarify the situation on that example, I had mentioned on one of the slides that there was no testing in Phase III of that development program, so there was no evidence to point towards a risk factor of a genotype predisposing somebody to an adverse event. There was no evidence pointing in that direction, so there was no way to label the product. What we did know is that genotype does increase exposure to the drug. What wasn't known was whether the increase in risk associated with the higher exposure warranted a stronger language statement in the label.

So I think that was a case of basically what we knew about the drug was put in the label in terms of descriptive clinical pharmacology, but there was no evidence upon which to recommend a test or any other measure other than somebody reading that information, putting two and two together and figuring that maybe a test might be beneficial in figuring out, for example, why a patient might have an adverse event when it wasn't expected.

DR. LEONARD: Thank you.

Francis Collins?

DR. COLLINS: Francis Collins from NIH. I actually have two questions. One is a more specific, practical one, and another is more of a broader policy issue.

The practical one really follows up a bit on the question that Brad Margus asked. Having had the good fortune to interact with my fine FDA colleagues over many years, I still find I get lost in the arcana sometimes. So I wonder if you could help me here in terms of what was proposed now as far as the use of ASR oversights in terms of how that would play out.

So I am a laboratory that is CLIA certified, I have a good track record of doing good analytical validity, and I have decided that I would like to market to physicians an in-house home brew test on the gene CETP, a gene involved in cholesterol metabolism which has some very interesting data associated with it in the published literature. In one way, it seems to be that variants in this gene play a role in risk of heart disease. In another way, variants in this gene seem to play a role in predicting response to statin drugs, whether you're going to have a beneficial effect on progression or non-progression of coronary artery disease. Of course, last week this publication indicated that a variant in CEPT is associated with exceptional longevity. So a lot of things sort of focusing in on this gene.

I can set up my highly validated method to determine whether there's a T or a C in a particular nucleotide position, and I think there are three indications here that might make this a useful test in certain clinical applications, and I would like to put this out there and expect that physicians will figure out the appropriate way to use it or not.

What is FDA's interest, if any, in my doing that if I have gone through the CLIA approval part? What does your oversight of ASRs have to do with whether or not this test is going to easily find its way into the hands of a physician for application?

DR. FEIGAL: So you're making your own ASRs? You're making your own reagents?

DR. COLLINS: Yes.

DR. FEIGAL: We currently say you are supervised by CLIA, so you can advertise anything you want, you can claim anything you want. The FTC may have issues with you, but from FDA's standpoint --

DR. COLLINS: I'm not marketing to consumers. I'm just marketing --

DR. FEIGAL: Physician advertising also has to be -- that's this afternoon. But essentially that's CLIA supervised under the current scheme. The gray zone is whether or not any reagent manufacturer is under FDA jurisdiction or whether that reagent -- it has to be someone who sells reagents to others.

The area that we decided to focus on when we felt there were already a number of products was the -- if you looked at a test that was developed with that ASR, irrespective of whether it was an ASR or a kit, that you'd say this is not an exempt product, this is a product that has issues that require review. Originally, we actually specified that ASRs could be Class I, Class II, or Class III products. So part of where we are starting from is to take a look at the ASR manufacturing and ask what's the most appropriate way to do risk classifications within ASR.

The original rule said the default would be that they'd be exempt and gave some

examples when they would be II's and III's. But for the in-house test where everything is developed in-house, currently that's just between you and CLIA.

DR. COLLINS: So let me then ask my second question. I gather from your response that this is sort of this regulatory gap that you referred to in one of your presentation slides.

DR. FEIGAL: Yes.

DR. COLLINS: Obviously, there has been an ongoing debate, it seems, about whether or not FDA has the legal authority to take a larger role in terms of their oversight of in-house testing of home brews. Earlier conclusions four or five years ago seemed to indicate that yes, the law would in fact cover that kind of authority if FDA chose to exercise it. More recently we understood there was a review of that going on, and I don't think there was ever a clear answer provided as to whether FDA currently feels they have that authority or not, not getting into whether FDA wants to use it right now, but does the FDA actually have that authority.

Is there anything new to say about the status of that legal review?

DR. FEIGAL: No. It's an issue that hasn't been settled, and unfortunately some of these issues don't get settled until you take a stand and then go to court.

DR. LEONARD: Arden?

DR. BEMENT: Arden Bement, Department of Commerce. In the near future, the EU will require mark for IVDs, and this is a practice that may also carry over in the future to other regional economic blocks in the world. This brings a new international dimension to mutual recognition arrangements, harmonization of regulatory pathways, and perhaps labeling in order to minimize barriers to trade.

My question is how is the FDA anticipating or preparing for these new challenges, and what do you see that needs to be done in addressing these international dimensions?

DR. GUTMAN: I can start. I have a narrow picture, and I know David has been involved in global harmonization on a much broader base. But in the area of IVDs, there actually is a standards group, ISO 212, that is trying in a proactive way, racing as quickly as they can to keep up with the changes. Some of the things that they've done are crafted IVD-specific standards that could be used across continents, and probably the most important single standard, and it's one that's now right in the heart of the development process, is an international standard for labeling. If that international standard for labeling is in fact concluded with a reasonable outcome, which I actually believe it will be, then the FDA can recognize that standard and then can have its review process parallel the requirements for whoever else would recognize that standard.

There are, at least in terms of the regulation of IVDs, some interesting differences. In Europe they have the IVD Directive, and it is actually in some ways -- it's administratively a little looser than our regulation, although scientifically it's quite a different process and in some ways a stronger process. Instead of being founded on the notion that you'll find a product equivalent to a product which is equivalent to a product which might have been marketed in 1944, what they require is that you actually find that the product can be properly made in relationship to a higher-order reference material or method. So they actually require a standards-based approach.

Now, they don't have a tough regulatory scheme or a lot of experience. It may be a great regulatory scheme but not a lot of experience and oversight of that. So there actually are some differences that are cast in the laws that will make, at least for IVDs, make complete harmonization challenging. But we obviously are quite interested in trying to learn and trying to exploit synergisms between processes.

DR. BEMENT: I think you bring up a very good point, that in some of these regimes

the ISO is going more toward performance-based standards, which used to be the U.S. approach. In some cases we're a little bit behind, and it may be in this area we're somewhat behind as well.

DR. FEIGAL: Well, it's a statutory difference. The U.S. requirements for manufacturing are less rigorous for middle-class products, the Class II products, the 510(k) process, than they are in Europe, or Canada, or Japan, or anyplace else in the world. So currently, for better or worse, we've really evolved into two systems, a U.S. system which is tougher for the highest-risk products than anywhere else in the world, but we've taken a different approach with the middle-risk products where we do not even require that a manufacturer have even begun manufacturing in order to get their market clearance. In Europe, Canada, other parts of the world, you actually have to have certified that your manufacturing is up and running and meets quality standards, and there are strong economic reasons to maintain the two systems.

So I think there will be some things we'll harmonize and some things where industry will work with the two systems.

DR. LESKO: I just can add to the issue that from our center in communicating with the European Union, the EMEA and CPMP, we have agreed on a terminology for samples that might come out of a genomic or genetic study, which has helped the informed consent process a bit by having common language between studies done here and studies done in Europe. That guidance has been put out by the EMEA. It's available on their website. We worked on that more or less together in getting the terminology harmonized, along with industry.

The other connection is more informal. When we talk about workshops like in May of 2002, or there's one coming up in Europe next week, the agency participates in those in Europe, and they participate in the ones being held here domestically. As part of those workshops, we're trying to exchange information on where each of the respective regulatory agencies are, where they're going, and in addition to that just some offline discussions about what's going on. So there's a communication link as things evolved that I think is being established.

The final thing is all of the regulatory agencies around the world are involved in a WHO initiative on a pharmacogenomics working group that consists of perhaps 35 to 40 people representing the three major regions -- Japan, U.S., and Europe -- both industry as well as regulatory agencies, and that's another forum in which to discuss common issues.

DR. BEMENT: Thank you.

DR. LEONARD: I think we'll have Hunt and then Chris, and then we'll wrap it up.

DR. WILLARD: Hunt Willard. I want to make sure I understand the issues of FDA purview. It in part follows up on Francis' question, but I actually had come to it before that.

I certainly understand the issue of the FDA wanting to know whether a test or a device or reagents that underlie that test, whether it's valid and it's clinically meaningful. That makes sense to me. However, to what extent is it the FDA's purview to then ask questions about when that test might be indicated, whether it's available broadly -- that's the part that jogged the question -- and/or whether it's cost effective in terms of it really truly being value added and therefore clinically useful, as opposed to just clinically meaningful?

Maybe I'm more of a believer in the open market approach here, which would, to me, say that all those questions can just be left to the open market. If no one wants to buy a test because it turns out not to be clinically useful even though it's clinically valid, well, so be it. So to what extent does the FDA think that everything I just described is in the purview either for tests in general, devices in general, or for those within the realm of genetic and genomic tests?

DR. FEIGAL: The phrase "cost-effective" has to be linked to the cost-

effective regulation, not cost-effective products. The marketplace will determine whether the products are cost-effective, as you point out. We don't consider the cost of the product, but we do realize that what we require does increase the cost of development of products, and that will eventually have to be paid for by the consumer. So the Commissioner's mandate is that we develop regulatory mechanisms that are as least burdensome and as least costly as possible.

So that's the context there. But we're actually forbidden from considering cost when it comes to a product. If you want to charge a half a million dollars per test, if somebody will pay for it, great.

We also don't have any particular opinions about how broadly the test is available. Where breadth comes into the matter is whether or not you're selling reagents or creating them for your own use, and that's where there's this sort of distinction between the in-house test where everything is manufactured in-house versus where you purchase the reagents. We clearly have the authority -- it's in my first slide, in the statute -- to regulate people who sell reagents and those reagents.

The standard for medical products is not let the buyer beware but is that the products have to actually be safe and effective. A product isn't effective if it provides information that is of no known use. So that's where it comes back to having to actually look at indications for use and some evidence for that. Sometimes it's completely evident from what's known from the literature and longstanding experience with the information. Other times we're on the frontier where it's difficult, and that's where the judgment calls are difficult, and that's sometimes where the cost of developing an FDA-approved use, as opposed to just saying this is an analyte that measures the following genes, make of them what you will, which is sort of the analyte proposal, is a different standard. The FDA is a higher standard. It was a standard intended by Congress for medical products.

DR. LEONARD: Chris?

DR. HOOK: Chris Hook. First just a comment and follow-up to Dr. Khoury's comments about approaching the question of the parameters you use for cost effectiveness. Certainly frequency is important, but oftentimes in these analyses it's the severity of perhaps that rare side effect, and when you might have 15 to 20 percent mortality because of neutropenic sepsis and death, I still think that that should weigh very heavily, not just the frequency in the calculation.

My question, perhaps to Dr. Lesko to begin with, you were showing these very good examples of the knowledge that we're learning from the pharmacogenomic data, but at the present time the FDA can only report what it is provided in this regard. Since we're finding more and more, perhaps in some of these instances with antidepressive agents, SSRIs and others, that 10 percent may be significantly and adversely affected depending upon their ability to metabolize the drugs, shouldn't the FDA be requiring pharmacogenomic data in order to even approve a drug at this point?

DR. LESKO: It's an excellent question. Again, requiring and encouraging are two different things.

DR. HOOK: I understand.

DR. LESKO: Requiring anything is hinged on the evidence, and I think we're fairly early in the game with many of the things we're seeing. The evidence has to come from studies that are prospectively designed to answer the questions. I think what we have in many cases is evidence that might be more retrospective analyses, circumstantial, as opposed to something that's prospectively designed to answer the question.

The other thing that we've seen, I think, is the distinction between an at-risk patient and one not at risk. They're not clear distinctions. This is a probability, an odds ratio type of thing, and the distinction between those if they're not necessarily clear becomes difficult to make the case to mandate

something like that.

So it's a moving target right now, I think, and we have to see how things play out going forward. But I think it would be difficult to mandate unless we had the evidence appropriately established.

DR. HOOK: To assist you in getting that evidence, then, should we not require that drug studies that are being sponsored by the NIH or the NCI have as requirements for that sponsorship the collection of pharmacogenomic data to help provide you that additional evidence that you need?

DR. LESKO: I think it's an excellent idea.

The other aspect of drug development would be other things besides genetics that may play a role in outcomes, and it would seem the absence of information generally we've dealt with by the appropriate labeling, which is basically what we do know and don't know, for the most part. But what you point out as far as having more information in an appropriately designed study would be great. It may not necessarily come from the drug development process in the future.

DR. McCABE: Well, thank you very much, Dr. Leonard. Thank you to our guests and our ad hoc from the FDA. This has been very informative to me and I'm sure to the rest of the committee.

At this point we will take a one-hour break for lunch. We will begin sharply at 1:30. Just to let you know where you can eat, there are hotel restaurants. The American Grill and Old Dominion Brew Pub are located downstairs in the lobby. Seating has been reserved in the American Grill for members, ex officios and presenters to try and facilitate your getting through the lunch. There's also a food court on the Metro level.

We'll be back sharply at 1:30. Thank you.

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

AFTERNOON SESSION (1:38 p.m.)

DR. McCABE: Well, welcome back from lunch, everyone. Let's go ahead and get started again, please.

We're very pleased that Matthew Daynard could also join us today. Mr. Daynard is senior attorney in the advertising practice division of the FTC, and he will be explaining the Federal Trade Commission's role in regulating the advertising and promotion of consumer products, including genetic technologies.

Mr. Daynard?

MR. DAYNARD: Thank you, Dr. McCabe, and I want to thank you, Dr. McCabe, and the committee for giving us the opportunity to come here and talk about what we do and how it might apply to the marketing of genetic testing in the future.

That little blurb you see in the lower left-hand corner is supposed to say that these comments are my own and not necessarily those of the Commissioner, but don't believe it necessarily.

(Laughter.)

MR. DAYNARD: I hope that's not being recorded.

DR. McCABE: It's just being webcast.

MR. DAYNARD: Oh, is that all? Okay, no problem.

(Laughter.)

MR. DAYNARD: It will come back to me. After 32 years, they can't touch me.

(Laughter.)

MR. DAYNARD: I'll give you a quick overview of our jurisdiction, our advertising principles, our work in the privacy area which is also important here, and our work in health fraud, in

particular with respect to home test kits, which are sort of analogous.

A big part of what we do is consumer and industry education. We have to get the most bang for the buck. We're a very small agency. I think our budget would run FDA for about 10 minutes, maybe 11 minutes, and we do get big bang for the buck. We do a lot of law enforcement, but at the same time we do industry and consumer education because the best offense is good prevention, a good defense. So I'll talk about that a bit.

Our jurisdiction is very broad, as you can see. We have a single statute. I love it. It says, "Unfair or deceptive acts or practices affecting commerce are prohibited." That's it. Boom. There isn't anything else, no subsections, and we have a 70-year history of what that means. A nice little addition was added by Congress to make sure we don't step on the FDA's toes, Section 12, the second one there, "False advertisements for foods, drugs, devices and services are prohibited," and what that does for us, it just gives us an extra allegation in our federal district court litigation, I suppose. It's helpful.

The jurisdiction includes ad claims by anybody for anything, which would include marketers of genetic tests, including off-label uses. This is one area where the FDA and the FTC can often get together. As you were told this morning, off-label uses for ASRs can't be promoted. They can do it, but they can't be promoted. If what they say about it is not substantiated by competent and reliable scientific evidence or is false, we might want to get involved, so we'd work with the FDA.

Our main heart and soul is deception, and here's the definition of deception. You can read it. It's very simple. "If representation or omission is likely to mislead consumers and it's material" -- that is, consumers would find it important -- "it's deceptive." In the context of a genetic test, I suppose something like "We've developed a genetic test that will give you a 90 percent surety of whether you're going to contract a particular disease or not." If that's not true, that falls squarely within this definition of deception.

The other part of our unfair acts or practices is unfairness, and this is more particular in that it has to be a widespread injury, there have to be no other countervailing benefits, to use the FDA's cost/benefit analysis, and most of all I guess it's not reasonably avoidable by consumers themselves. I guess, for example, if a test had some inherent safety problem for a certain population of patients and consumers had no way of knowing that, we could charge that not only was the representation a deception but it was also unfairness.

I think as Steve alluded to this morning, we have a longstanding liaison agreement with the FDA, since 1954. They have primary responsibility for the labeling of devices, we have primary responsibility for the advertising. What does that mean? That means they go after manufacturers, we go after retailers, and we often get together and do coordinated actions. It does mean we can have dual jurisdiction for ads, for example, for unapproved home test kits.

Now, I have to make a caveat, of course, here, an admission and a concession that we haven't taken any formal action in this area as of yet, but everything I say is applicable to the marketing of genetic testing, so keep that in mind.

For us, true and substantiated health claims are an important part of the FTC mission, and we have a number of people working this area. I've been doing it for a couple of decades myself. We're concerned, among other things, that the injury to consumers can be serious should they use the wrong product or service or forego other treatment. But on the other hand, we don't regulate "the practice of medicine," which means if a doctor wants to encourage a patient to have a certain genetic test, we're not going to say, well, you might have said the wrong thing there. We leave that alone.

I guess there was one case, though. It had to do with infertility. It was a Dr. Jacobson in Virginia. It was an in vitro fertilization case, and he was telling women patients that they were pregnant

when in fact they weren't, and that then the fetus had resorbed into the uterus or something like that. That was a doctor-patient relationship, which we'll usually stay away from, but that was just so far over the line that we got involved. We sued him in federal district court, and the AG in Virginia eventually put him in jail and took his license away. But generally we're not going to get involved in what doctors say to their patients or what therapies they encourage.

These are basic advertising principles that we tell marketers. They're very simple, at least in theory. Tell the truth. Don't mislead consumers about efficacy or safety. Tell all the truth. Make sure you haven't omitted anything that consumers would find important and that would keep what you say from being deceptive. Make sure it's the truth, meaning you have to have substantiation at the time you make the claim -- before, not after.

Advertisers are responsible not only for express claims but also for implied claims. I suppose you can all infer what implied claims are. If the net impression of an advertisement, taking into account the text, the product name, the visual images, are that a test is going to give you a surety that you are or are not going to get cancer, even though it doesn't say that expressly, we can challenge that claim.

If there's qualifying information that's necessary to be disclosed to prevent deception, that's important. For example, as was discussed this morning, if there's some preliminary information that a genetic test works and works for some people some of the time, but it's only preliminary information and not definitive testing, then that ought to be disclosed and qualified, or the claim itself ought to be something less than this is going to apply to everybody. And those disclosures can't be in fine print at the bottom, and they can't be three clicks away on a webpage. They have to be clear and conspicuous and prominent.

Our substantiation standard is very important. As I said, you've got to have the substantiation before disseminating an ad, but the standard is flexible. We don't always require the gold standard of double-blind human tests. It depends on the claim, it depends on how that claim is presented, how it's qualified. The point of how we regulate is the substantiation standard has to ensure consumer access to information about even an emerging science or service, but at the same time it has to ensure that that information is accurate.

So we have a flexible standard, and it depends, again -- it's always an ad hoc situation -- it depends on what the claim is and what we think consumers are going to take away from that claim.

The standard, though, is rigorous. It's competent and reliable scientific evidence, and since we're not scientists, what do we do? Well, we call you folks. We call the FDA, the NIH, the experts around the country, the grandfather, if you will, of genetic testing if it came to that, and we'd ask them what do you think is adequate and competent and reliable scientific evidence for this particular claim? If they tell us double-blind, randomly controlled human studies, we say fine, then that's got to be the standard. Then we go back to the marketer and say, well, have you got these? If they say, well, no, but we've got 3,000 anecdotes, we'd say, well, anecdotes are just that, they're anecdotes and they don't suffice under the FTC Act.

Consumer tests. I don't know how big an issue this is going to be in genetic testing. Maybe it will be. It's big everywhere else. Just look at your weight loss ads in the paper every morning. The point here is that unsubstantiated claims can't be made indirectly through testimonials. A testimonial says, well, I had this genetic test 50 years ago and it told me I wasn't going to get this disease and, by gum, I didn't get that disease. The underlying claim is this test will tell people whether or not for sure they're going to get this disease. So the anecdote doesn't work. You can't hide behind the testimonial.

Third-party literature is also an interesting subject. We don't regulate content or accuracy of books or articles or non-commercial literature. That's not our charge. But if in a doctor's office a study or a book is given out in furtherance of a commercial scheme, then we do have jurisdiction.

If the primary purpose of using that literature is to propose a commercial transaction and not just to sell the book or the article or the brochure, then we have jurisdiction, and that's come up several times in the medical area.

We've also been involved very heavily since 1995 in the privacy area. You may have seen things about the FTC and privacy online -- "Do Not Call" for instance. That's another issue. But that's got to be of serious concern here also, it seems to me, and even though HIPAA may apply certainly to the caregiver, it may or may not apply directly to the laboratory. If there's an indirect relationship between the laboratory and the consumer, it's unclear to me at this point how it's going to apply.

So we might be interested or we might get involved with OCR at HHS also, and it could come into play. For example, if a laboratory says we're going to keep all this information confidential, when in fact they either don't have security adequate enough to make sure it's going to be confidential or they sell the list to somebody or sell your health information to somebody, the FTC could be concerned.

Whether it's a privacy case or a health fraud case, these are our case criteria. We have to pick and choose. We're a small agency, as I said. So what we look at are products and services that represent a significant safety concern. For example, we brought actions in the dietary supplement area for comfrey, which is toxic to the liver; for ephedra, which you all know about; for St. John's wort, which has interactions with other drugs, and it's an important issue for us, although it's not our charge. Our charge, again, is to protect the public from unfair and deceptive acts and practices, whereas the FDA's charge is to protect the public health, but we overlap when we can. It's important.

Also, unfounded treatment claims for serious diseases, as I've been talking about -- heart disease, multiple sclerosis, AIDS, diabetes, anything that you would consider a serious disease, we would consider a serious disease. Also, we don't get involved in local doctors, for example, or maybe even local laboratories marketing a test for a local or even a small region. We are charged to protect the public interest, and that means national to the extent possible. So we look for national advertising campaigns, infomercials, websites, direct mail that goes around the country, the freestanding inserts in big newspapers around the country. Put these three together and this is what we look at.

So in the genetic testing area, I suppose that if and when the Commission gets involved, it will be a large campaign, advertising campaign for false or unsubstantiated claims that involves a serious disease and that might have a separate safety component.

This is an old slide. I just left it in here because it shows that consumers are obviously concerned about genetic testing. I don't have to tell you folks about that.

These are privacy cases. I guess I'll do this pretty quickly. It just shows that the Commission is very serious about privacy. These were our first cases in the privacy area where we settled some charges where a website misrepresented the purposes for which it was collecting personally identifiable information from kids and from adults. With Liberty Financial, we challenged false representations on a site that claimed information collected from children and an online survey would be maintained anonymously when that wasn't true.

Here was a bogus pharmacy online. They paid a doctor $10 for each application they looked at, and they said they had a network of pharmacies around the country, and that wasn't true at all. It was this one doctor who was giving a cursory review to an application and getting ten bucks each time. But they represented online to consumers that the information the customers provided would be encrypted and used in SSLs, secure connections. None of that was true. They represented they would use personal information only for medical consultations and billing for prescriptions and consultations when that wasn't true.

Our order -- this was really our first big order -- prohibited all these representations and required the defendant to establish and maintain reasonable procedures to protect the confidentiality and security and integrity of personal information, and required a number of other things, including clear and conspicuous disclosure of the privacy policy covering these areas and information.

Eli Lilly got itself in trouble, to use another privacy case, where it unintentionally disclosed the health information, the fact that consumers had gone online to Prozac.com to all their mailing lists. So all the consumers on the mailing list got information about everybody else on the mailing list who had gone to this website, and it was unintentional. But nonetheless, we challenged them because they had represented that they had a secure, confidential website when, in fact, that wasn't true. There were holes and they made some mistakes. It was a quick settlement.

Microsoft, too, can have problems. Surprise, surprise. Consequences can also be of potential harm rather than actual or realized harm. Microsoft's Passport services actually had far less security than they represented, so the order requires them to implement a security system, prohibits misrepresentations and that sort of thing.

Guess? Online had false and misleading representations about the security of the personally identifiable information collected through their online store, and we alleged that they had misrepresented that the PII obtained and stored encrypted and unreadable format at all times, when in fact it was a pretty easy attack on the security system and anyone could get the PII.

I guess we're semi-sophisticated. We have a web online lab, an Internet lab, and we go after folks that do metatags and page-jacking and mouseovers and all the stuff where you come up with little claims that weren't there before, but still it was very easy to hack into this, a commonly known attack. So they weren't secure enough, not as secure as their representations led consumers to believe.

These are privacy resources the FTC has, and these are all in your handout, so if you have any interest in them you can go to them. I guess the most relevant area that we challenged were HIV home test kits. We had several cases like this. Here's one where the defendant falsely represented that their HIV home test kit accurately detected HIV when the test really didn't have a clue. So it was a slam dunk in this particular case in federal district court. The order bans the defendants for life from marketing any HIV home test kits. It may sound Draconian, but the FTC, as I said, has to get the most bang for the buck, and if we can convince a judge that a remedy is warranted in a particular case, we can get it. In this case it was pretty Draconian but warranted.

The defendants also had to pay back the money they received from the sale of their kits, and if they sell other medical devices, they're required to post a half a million dollar bond.

As I said, consumer education, industry education is equally paramount to law enforcement with the FTC, so we have a number of items on our website that deal with advertising and what's required. When I get a call from a marketer, I give them the URL of this online "Rules of the Road and Dietary Supplements: A Marketing Guide for Industry and Facts for Consumers" on these other issues, because it generally answers most questions that folks have about what the law is and what you need to do, and we've gotten excellent feedback from industry about it being helpful and helping them comply with the FTC Act. It would apply equally to genetic tests. I'm not familiar with the industry members yet in this area, but I expect I will be.

That's me. That's my phone number. That's my email. Feel free to call me anytime about any of these issues. I wanted to make this brief to have more time for questions, so I hope that's cool with everybody.

DR. McCABE: Thank you very much. Please join us at the table, and Steve is going to join us. Steve actually covered the material from the FDA regarding advertising this morning, so that

will give us even more time to discuss this afternoon.

So, Ms. Zellmer?

MS. ZELLMER: Mr. Daynard, thank you for your information. Again, I have a few questions myself, and then I'll turn it over to those of you who have questions.

You had mentioned at the beginning of your presentation that as of this point in time, there had been no actual actions taken on claims on genetic testing. How does something get on the radar screen of the FTC? I mean, does there have to be a complaint? Is this something that you actively monitor? I guess there are a couple of other parts to that question, then. Do you have people at the FTC who are physicians or who have the training that they would -- how do you know if there are deceptive claims, and is there the funding to pursue these?

MR. DAYNARD: Well, to answer your second question first, no. Sometimes I feel like I'm a physician because when I get heavily involved in something, I can at least talk sensibly with the scientists. But, no. We have economists at the Commission who look at studies to see whether they're methodologically sound, but otherwise we call the experts. We call you, we call the FDA, the NIH, and I have contacts with all of those folks. It's my coming to events like this that gets it on our radar screen.

So what's going to happen in the future? I really can't say. I expect that as this area evolves, there will be more and more marketing, and that's what will get it on the radar screen of my superiors at the FTC. Plus, I've been telling them about this for a while, so they'll be expecting it also.

MS. ZELLMER: Reed?

DR. TUCKSON: Well, first of all, it is just terrific that you're here.

MR. DAYNARD: It's my pleasure.

DR. TUCKSON: And I'm glad that it's on the radar screen. I think one of the questions is that it's sort of between FDA, Steve, as you sort of indicated I think in your comments earlier, that you all do not regulate or look at -- you don't have authority over laboratory ads or labels or direct-to-consumer advertising in this area. So it sounds like you're out of it completely. Does that mean, then, by inference, that the only folks who are in it is the FTC?

MR. DAYNARD: And states, I presume. Well, like other areas, I expect I'll be getting a lot of ads from my friends at the FDA saying what about this, what about this? That is, in part, what we rely on. We also rely on competitors and rely on watchdogs at the state level, consumer medical watchdogs.

DR. TUCKSON: The other thing would be that at our last meeting Dr. Collins, who presented not as a decision of a particular example being, in his mind -- I'm trying to be very careful -- he didn't present it as if it were over the line, but he presented a case of interest which I actually have a copy of with me, and I'll share it with you. I'll leave the manufacturer moot, but it was the one that had to do with do you think your child has a genetic predisposition to bad behavior or alcoholism, whatever? Just take this little swab and swab the inside of your mouth and put it here and send it to us, and we will study this and prescribe the right nutriceutical that is just perfect for you.

Obviously, I remember it and I've used it because it's driven me nuts as an example. The point I'm getting to with this is the notion of egregiousness of this, and I wonder does egregiousness, if there is such a word --

MR. DAYNARD: There is. We use it all the time.

(Laughter.)

DR. TUCKSON: Does it relate on an individual by individual basis, or can you look at an emerging class of problem, like direct-to-consumer advertising preying on genetics as an emerging issue and say that that becomes important enough to sort of get order in the world early on so that each

individual case may not be -- this company may sell only $12.22 worth of product, but it starts to become an example that you want to set?

MR. DAYNARD: That can happen and has happened in the past, but typically we'd like to nip things in the bud if it's possible to nip things in the bud. You're absolutely correct. The FTC, generally what it does is it uses its law enforcement authority to set examples for the rest of the industry. So we get a quick consent without having to go to litigation. It's out there and we press release, and we have at the same time a joint statement with the FDA or NIH or somebody about here's what you should look out for. With a quick-fix genetic test, if it's too good to be true, it probably is kind of thing.

We have consumer ed people who are wonderful with sound bites. But at the same time, it's got to fit within our resources, because as I said, we're small. In the last few months, for example, since the beginning of the year, we've gone after dietary supplements that have safety concerns that amounted to a billion dollars in product sales, and this is one division. We've got a full plate. So I would have to convince somebody that we're going to nip this in the bud.

Now, if that had been a genetic test for some serious disease, it would have a better shot.

DR. TUCKSON: One last thing, and just as we think about the role for our committee, maybe that's one thing we can do as a follow-up.

The other thing as an afterthought is the idea of educating consumers about what to look for when they read ads. It would be terrific if you have any campaigns or activities that are going forward that are designed to educate the public in this regard, or if you're anticipating such, perhaps our committee, as we make recommendations to the Secretary, could suggest some things, especially given that we have a lot of patient advocates around the table, and others. Maybe we could do something there in terms of our energy.

MR. DAYNARD: That would be great. I mean, we've done things both ways. In the past typically we bring a number of cases, and then in a final push, so to speak, we'll issue a Facts for Consumers kind of thing. But we've also done it the other way around. For example, in the LASIK area -- you all know what LASIK is -- I issued a joint statement with the American Academy of Ophthalmology called "Basic LASIK" about you have to go into this with your eyes wide open, not your eyes wide shut, the movie notwithstanding.

(Laughter.)

MR. DAYNARD: It was terrific. And then I brought two cases, because then I could say, well, you guys all knew what was coming down the pike here and you kept making these unsubstantiated claims, and you threw your glasses away when I told you directly that you can't make that claim. So here you are.

So that's a great idea, and again all I'd have to do is, one, get to know the science a little better so I can talk with you intelligently about it, which I will; and second, convince folks that this is something that's going to be very important to do. So we'll keep in touch on that one.

MS. ZELLMER: Francis Collins.

DR. COLLINS: Francis Collins from NIH. I want to follow up on Reed's question. I actually have the ad in front of me that he's referring to, and yes, it is pretty amazing, not only the fact that the test is completely without foundation but the nutriceuticals that they are marketing to you, and this is all direct-to-consumer marketing, also without foundation as far as I can determine.

I appreciate your being here and your willingness to consider looking into this area. I just wanted to comment that while it may still be the case that, compared to the billion dollar market that you're wrestling with of another sort, this is clearly an area of growth opportunity, and this may be a case

where a little bit of prevention will save you and consumers a lot of trouble down the line if you could basically enter the fray in a fashion that puts a line in the sand to direct-to-consumer marketers for genetic tests and says basically if you cross over this, you're going to hear from us.

Right now, it's pretty clear that the marketers don't perceive that they're particularly at risk because one can simply, by googling under "direct to consumer genetic tests," appreciate that the number of offerors is going up month by month. There are two published articles in the peer-reviewed literature that have surveyed this, one of them in JAMA. So the information is out there about what exactly is going on in the field. They are certainly able to document not hundreds but certainly quite a number of websites that are doing direct-to-consumer marketing of tests which a trained geneticist would tell you really have no scientific foundation, and it is a growth arena.

So I appreciate your being here and your willingness to consider looking into this. I would argue that it may be your time well spent, as well as good protection for the consumers, to try to jump in on this before it gets a lot worse.

MR. DAYNARD: Well, you make very good points, and I'd be happy to see the ad. Is it a national ad?

DR. COLLINS: It's on the web.

MR. DAYNARD: That does it.

(Laughter.)

MS. ZELLMER: I have Debra Leonard, Chris Hook, Ed McCabe, and Hunt Willard. Debra?

DR. LEONARD: Debra Leonard. So this is an instance where it's clear that there's no scientific basis, but eventually we're going to be able to understand the genetic basis for all sorts of what are now called personal characteristics, and so there would be truth in being able to do these things. It wouldn't be deceptive, and then I don't know whether the unfair part comes into this and whether it's ethical. But who in the government or which regulatory agency is going to decide what it's okay to test for and what it's not okay to test for? Because then you don't have the deception problem.

MR. DAYNARD: Well, it wouldn't be the FTC who decides. We don't regulate the quality of care. That's not our charge, as I said. So if the claim -- I mean, you could have a claim that has some truth to it which is also deceptive because it goes over the line by saying something else. Yes, we'll test you for predisposition to breast cancer, but then it says something else that goes way beyond its real efficacy. So it's always an ad hoc situation.

But no, the FTC doesn't -- there's no censorship, if you will, involved. We get involved in ethics, but it's a murky area. And lawyers, we don't like ethics. But the FTC is on the right side, so I'm not terribly concerned about that. But on the other hand, we do talk with ethicists. In fact, I remember I was on a panel at the AMA once on ethical medical advertising, not just deceptive or unfairness. So it depends on the claim, it depends on what the experts around the country think. In fact, if a test has some downsides, even if it truthfully can be done, and depending on what those downsides are, if those downsides are injurious, then maybe the claim does have a problem under the FTC Act.

DR. LEONARD: What would the FDA do with an IVD that was for a happy person gene or something?

DR. GUTMAN: Well, if it was offered by a laboratory, it would not be under our purview.

DR. LEONARD: No. I'm talking about a company that has an IVD, they're bringing it to the FDA and they can prove their claim.

DR. GUTMAN: Boy. Well, there's no predicate, so that's a PMA.

(Laughter.)

DR. GUTMAN: But the issue would be if you could establish safety and effectiveness. I actually don't know. I mean, being happy is really a good thing, so you have to establish the public health benefit --

DR. LEONARD: That was just an example. There are lots of personal characteristic kinds of things.

DR. GUTMAN: Everything with us is framed in terms of claims and in terms of risk/benefit analysis. The closest -- I have not gone even near where I think this might go, so I have no experience to draw from. The closest place where we carefully model risk/benefit analysis in this way is when we're looking at over-the-counter tests and we look at a test and we try to figure out the risks and the benefits and try to make a profile. If we're not certain, we'll call a panel of experts in the field together to give us advice or do homework assignments. We have actually no experience to draw from, so the people who are lucky or unlucky enough to be on our panels are likely to help us chart that course when we get that first product.

MS. ZELLMER: Chris Hook?

MR. DAYNARD: There's one other thing I want to say in response to Dr. Collins. There's another thing I can do, and I do it in the health care area and other areas if we don't have the resources to actually sue them or go into federal district court or administrative court, and that is a voluntary advisory letter sort of thing. It harkens back to the days when the Commission used to have an insurance for voluntary compliance, which just meant you promise and I promise, and hopefully you'll do what you say you're going to do.

But it seems to have worked in the LASIK area. I get ads all the time from competitors about LASIK, local doctors saying throw your glasses away, or Wavefront is the best thing since sliced bread and you'll never have a problem. So I send them a letter that says we haven't determined if you've violated the FTC Act, but for health-related claims you need a competent lab with scientific evidence, and if you don't have it for this claim, give me a call because you may want to change your advertising, and it works. It works. They don't want to hire a prestigious thousand dollar an hour lawyer from Washington. So I get them to change their advertising voluntarily.

This also should not be recorded.

(Laughter.)

MR. DAYNARD: But that's another possibility if I can't get the resources to actually do a complete investigation and bring a case.

DR. HOOK: Chris Hook. I feel like I'm being redundant to Reed and to Dr. Collins, but I want to go ahead and share these just because I think it's important to emphasize again the prospective nature of intervening.

In addition to the one that you have recognized, I ran into another site. It was brought to my attention by a friend who was doing a visiting scholar program at Oxford this summer, and in a pharmacy there, right off of the little metal rotating rack was this 10-pound packet kit that said send this, give us the buccal swab, we'll send you a complete genetic analysis, we'll tell you all of your risks for cancer, what you can do to live longer, to have a happier life, and it was a company from the United States that was actually producing this product.

I ran into another site that may not have been promising the world in terms of we're going to make you younger and able to live longer and all this, but they again claimed that they would provide a complete genomic analysis, which they can't do. And even if they could provide a partial genetic analysis, the things that they were claiming they would tell you about would require significant appropriate

genetic counseling in order to interpret appropriately. Yet they are sending this directly back to the patient. The patient believes that they understand how to use this information when clearly I'm sure they don't, and that to me is a major health problem.

MR. DAYNARD: There are two issues there, because we can't deal with the mind problem so much. The way we might normally deal with that is some failure to disclose an important point like that, that science has shown you need counseling when you get this kind of information. But we wouldn't bring a case probably based on that alone. So the first point would be what we'd look at, that there is no test that does this. We could be interested in that kind of thing, sure.

MS. ZELLMER: I just have one comment to sort of expand on what you said, Chris. Certainly I think deceptive advertising is a problem, but I think to me an even greater problem that Chris brought up is having direct consumer access to this information without having a health care professional involved. I think that if someone is going to have genetic testing, I think that a large part of the problem is that a consumer can order on the Internet home genetic tests without having a physician involved, and it sounds like, at least at this point, none of the agencies would address that issue. I assume it would be the FDA, or perhaps CLIA would dictate who had access to the test results.

DR. GUTMAN: Yes. I actually think that the FDA could investigate that circumstance, and if that circumstance was a lab that was completely doing the practice, creating the reagents and providing the assay within its own location, then we probably would not touch it. But if they were using the ASR rule, if they were purchasing reagents, they can promote to consumers but they can't actually market the product without a prescription.

MR. DAYNARD: The FTC can't require that, but the FDA could.

MS. ZELLMER: Dr. McCabe?

DR. McCABE: A couple of comments, one to Matt and then the other to Steve. I want to follow up on this issue about trying to nip this in the bud when it comes to genetic testing, a follow-up on what several people have talked about. You were saying you would have to get up to speed. I would think that you could get help from professional organizations, from consumer groups, and from the industry groups as well, groups like BIO. Mainstream groups I think would want to get involved proactively because it's going to give everyone a bad name if these things proliferate. So I would encourage you to approach a variety of groups, and I'm sure people would be happy to help you out there.

MR. DAYNARD: One comment on that is that at least in some other areas, nipping things in the bud doesn't always work depending upon how many bad guys there are out there and how really bad they are, because the bad guys aren't going to care about crossing the line until they get caught. They're not going to stop until they get caught. I don't know, and I suppose you don't know yet, how many bad guys you're going to have out there. I presume and hope it would be far less than, for example, the magic diet pill that you see in your paper every day. But I don't know.

So that's something that my folks at the FTC would be considering. I expect, though, that if they're going to nip things in the bud, they might want two or three cases right off the bat with different kinds of folks in different kinds of testing, and that means a significant commitment of resources. I'm not saying we're not going to do that, but I haven't talked to anybody about it.

DR. McCABE: But what I was talking about was really issuing educational materials for the consumers.

MR. DAYNARD: Oh, great. Sure, sure.

DR. McCABE: So it's a way of educating consumers so that they will be more cautious and so that they'll know the questions to ask.

MR. DAYNARD: That's a great idea.

DR. McCABE: I'm sorry, I wasn't making myself clear. But I think it would be good. You could easily get these kind of individuals together, professionals, consumer groups, industry groups, to help you develop those materials.

MR. DAYNARD: Great idea.

DR. McCABE: And then for Steve, a follow-up on what Dr. Leonard said. If there are no health benefits, so it is just simply a characteristic, if there are no health benefits, does that fall under FDA?

DR. GUTMAN: That's actually a legal question. I'm not sure I'm in a great position to answer that. If there were no benefits? I guess if there were risks associated with it, health risks, there would be, and actually, the fundamental question would be if you could link it to the definition of an in vitro diagnostic device to diagnose a medical condition or a disease. I suppose if it didn't and you were evaluating something from a narrow legal standpoint, I suppose it's possible to imagine something that wouldn't be a device. But as soon as you move into risks or benefits, I think you start moving towards health conditions, if not actually disease states, and I think we would probably be interested in the product.

MS. ZELLMER: Hunt?

DR. WILLARD: Hunt Willard. Two questions, both for, once again, clarification of turf and purview here. I followed everything you said about the FTC and agreed with it totally.

MR. DAYNARD: Terrific.

DR. WILLARD: But I see the distinction between -- there's a disconnect between what you said and what I see on television and in magazines, and it's the following kind of an ad which, if not being a misrepresentation, is certainly a non or unclear representation, and I wonder why that isn't deceptive, and that is the advertisements that advertise by brand name for a product that no one outside of the medical community has any idea what this thing is.

MR. DAYNARD: Are you talking about a prescription drug?

DR. WILLARD: Right. So it is a certain color pill, presumably, and all I know is that if I take it, my chances of running down the beach looking happy with my golden retriever goes up.

(Laughter.)

DR. WILLARD: And then it says call your doctor and see if that's for you. Now, is there a way out? You can't get it without going to the doctor, and hence at best all you're doing is busying the doctor's phone lines. But it isn't clear why that's any different from genetic testing where, again, we might say see if genetic testing is for you. We think as this comes along -- it's almost like marking your turf in genetic testing. Maybe today there's only a few things we can test for, but people are smart enough to know there's a lot more things coming down the pike.

So if you can build up an ad campaign that has people automatically thinking of you and Company Q when it comes to genetic and genomic testing, and you will not only live longer but the chance of running down that beach with your golden retriever goes up, then that's the company I'm going to think of once there are, in fact, five or six conditions that are worth testing for.

So what's the distinction there on these drugs that have no obvious --

MR. DAYNARD: I don't think we've talked yet about who has primary jurisdiction on consumer genetic testing advertisements. In the prescription drug area, it's clearly the FDA has primary jurisdiction over direct-to-consumer for all advertising for prescription drugs.

DR. WILLARD: But then my question, slightly off topic, is --

MR. DAYNARD: Genetic testing we actually haven't talked about yet. I'm not sure if that's a prescription drug or not. If it's a prescription device --

DR. GUTMAN: Well, there is guidance. I don't know if Larry is still here or if David

can bail me out. There is guidance on what's allowed. I frankly have seen those ads and also wish that I had that beach or that my animals were as well behaved as those.

(Laughter.)

DR. GUTMAN: I presume -- I can't say this for sure but I presume that people in the Center for Drugs must also see those ads. They're rather visible. So they must fairly or unfairly fall within the -- I know they don't pose the use, but I do know they always tell you about the diarrhea and the vomiting and the weight loss or the weight gain. They do it, of course, in two seconds, but they do it. So I make the presumption, although I'd be happy to go back and talk to people to make sure that they've seen those commercials --

DR. WILLARD: It just seems like a disconnect.

DR. GUTMAN: I think that that must fall within the -- they're too visible for me to believe that we just missed them. So they must fall within the borders of what is permitted by FDA.

MR. DAYNARD: Just on the FTC side, though, I don't think it violates the FTC Act or advertising a brand name. If we do have jurisdiction, and I'm not sure we do --

DR. FEIGAL: In the trade, those are called reminder ads, and they're legal.

MR. DAYNARD: Yes, or image advertising.

DR. FEIGAL: Yes. They're legal.

DR. WILLARD: But there's no question, bringing it back to our topic today, that image advertising from that perspective could be something that for genetic and genomic testing we'll see far sooner than we'll see very many ads that say absolutely we can predict your cancer risk or your Alzheimer's risk or what-have-you.

DR. GUTMAN: And I hope I communicated -- if not, then I will re-communicate that the FDA in the area of oversight of diagnostic advertising, its hook is somewhat indirect, through labeling and through intended use rather than directly aimed at the advertising.

DR. WILLARD: My second question comes again to this question that I raised for an earlier presentation on to what extent is genetic testing different from other kinds of testing, and where are we going to say it is different and where are we going to keep reminding ourselves that there really is no difference other than the fact that it's newer. That comes to the home kit question. There are pregnancy home kits that all kinds of people use. It's a successful industry, and if it isn't actually written on the package, since I've not used one of these, but if it isn't written on the package, the message certainly must be that if this test tells you you're pregnant, you should go see your physician.

Is genetic testing, home kits of the kind that have begun to appear, could those be handled any different? Would that be different from pregnancy? You'll get tested, we'll say your risk is now five-fold up or ten-fold up for Disease Q, we suggest you see a physician. Would that be any different in that respect?

MS. ZELLMER: But Hunt, don't you think it depends on the type of genetic test and whether the consumer actually has the knowledge to be able to interpret the results? I mean, pregnancy tests or a lot of the tests that are on the market, most people are very familiar with what it is to be pregnant or not pregnant. But they may not know all the implications of a specific genetic illness, or they may not know the implications of a positive result on a genetic test that may need further interpretation.

So in my opinion, and obviously I'm not an expert in this at all, but I think there's got to be certain genetic tests where maybe there could be home test kits. Maybe there are genetic tests where it's just as simple as saying you've got X mutation and here's the answer to your question. But I'm going to guess that most of them are much more complicated than that and that it is going to require some interpretation that you would need the help of a health care professional.

DR. WILLARD: Well, I'm raising the question. I don't know if you're right. Whether you're pregnant or not, everyone knows how to interpret that dichotomy. But all the downstream follow-up of being pregnant is every bit as complicated as trying to interpret a ten-fold increased risk of cancer in the next 10 years. So I'm not sure I see the distinction in those two. I see them as sort of parallel tracks. At some point in each case, one goes to the medical professional, but I'm not sure otherwise I see the distinction.

MR. DAYNARD: From the FTC's perspective, it's possible that for a given test, if it's important for one medical health reason or another that the explanation of the results be supervised by a physician, one remedy if we brought a case would be to have that disclosure on the label or the product package or whatever.

DR. HOOK: Can I respond to Hunt? I'm thinking of what if you had someone like Janet Atkin, who was Kervorkian's first victim, who did a test for Alzheimer's before she was symptomatic and chose to commit suicide at that point because of the results she got? Or a patient who is tested for Huntington's chorea and also chose to take their life because of that result without seeking medical intervention? I know some people might do that with pregnancy, but generally the tendency is not to do that because they have other means. They have abortion, they have other things they might do. So I think there is a difference of some degree.

DR. LEONARD: And also, a pregnancy test is positive or negative, and you and I both know very well that there are very few genetic tests that when they're negative they're absolute. So it's not like you can say when it's positive go see your physician. It's like whatever result you get, go see your physician, or a genetic counselor may be more useful.

MS. ZELLMER: Brad?

MR. MARGUS: I'm going to dissent from everyone by saying that I think the web is here to stay, and on average I would argue that consumers are smarter by being able to look up stuff on the web than only relying on their physicians and genetic counselors and all that. All the genetic counselors who are going to speak tomorrow are going to kill me, but I don't think you can avoid the web. Don't forget that everyone in this room is a consumer, and to assume that no one can handle the information themselves -- there's cholesterol testing being done now at a cholesterol (inaudible) or something, and a lot more people want to be tested for it than if they have to go to a physician for it.

So I think it's going to come. The one thing that's most discouraging -- well, before I go to the discouraging thing, the one thing I want to mention is I remember seeing a site a few years ago, I think on the National Cancer Institute webpages, but it was kind of along your lines. It was all the pitfalls or red flags that should go off when you hear claims about medical things. I think it was the NCI, but I'm not sure. But it was things like if the people who are making all the claims are also the ones selling it to you, and it kind of added up, if it was in nutrition, there was a whole list of things that should make you more suspicious.

It was pretty simple. I mean, I could understand it. I think that those kinds of efforts to educate people that way would be really, really helpful, just how to be a little more street smart about health claims. That being said, I'm a little discouraged by the whole presentation, and I assume the answer is going to be that the FTC only has limited resources. But you mentioned that it really has to be a -- what was the quote you had? -- unfounded treatment claims for serious diseases, so it has to be a serious disease, it has to be national, I think it kind of has to be complained about somehow or someone has to bring it up.

You mentioned that it can't be just anecdotal evidence, but then in the same breath you mentioned those ads in the newspaper for fat that we all see, which are anecdotal evidence. I know that from the beginning of time there have been snake oil salesmen long before any genetics or any webs or

anything else, so that's going to be out there, but it doesn't sound like we're really nailing a lot of the people who are out there. I mean, we're nailing the big ones and the ones where really, really dangerous things are happening right away, but there's an awful lot that we're not.

In fact, which agency regulates astrology? I mean, more people rely on astrology than will ever rely on genetics.

MR. DAYNARD: Not the FTC.

I'm sorry, but I'm not sure I understand your point, Brad. Is it that we're not suing everybody?

MR. MARGUS: Well, I don't think you can. Let me be clear. I'm not saying that the FTC is not doing its job. What I'm saying is that it seems like the whole world's out there making all kinds of claims. You have to pick your big ones that are really obvious or that are national in scope. You really have to pick the ones to make examples out of, but all of us can get on the Internet and find a million more claims.

MR. DAYNARD: Sure, but there's something else we do. I didn't think it would be so tough to toot my own horn. We do health claims surf days. I think the last one we did was a couple of years ago and we had 40 state AG offices and 30 foreign countries, and we got on the web for eight hours and did a surf for websites that were saying bad things about, in this case, dietary supplements for serious diseases. I think in those eight hours we came up with something like 4,000 websites. You don't have to be wealthy, you don't have to pay a sales force, you don't have to have an MLN to do all this. You just put up a website and your sales could be small.

But what we did then was we sent them warning letters. We sent out or emailed 4,000 warning letters, and we've done this several times now, and we got about a 45 percent success rate in folks either dropping their bad claims or taking their site down altogether. It's something we might consider doing here.

We can't do it all, and that's why we get involved with you folks and with the AGs and with Mexico and Canada and the UK. You're not going to get an agency with a $150 million budget to do it all by itself. It's not possible.

MS. ZELLMER: Cynthia?

MS. BERRY: Cindy Berry. Thank you for your presentations, both. The problem of Internet spam I know cuts across all kinds of products, services, industries, you name it, obviously not particular to the health care industry. But I'm wondering if there are specific barriers to cooperating with the Internet service providers in some of these issues.

MR. DAYNARD: We cooperate with them sometimes, and sometimes we sue them.

(Laughter.)

MS. BERRY: Are there creative ways to work with them to prevent some of this? Because it's one thing where someone goes to a website and seeks out information. Finding the websites might be a little bit easier than finding the needle in the haystack, which is these spam email messages directed to individuals that they get at home, unsolicited.

MR. DAYNARD: Well, we get spam. We have a database of spam at the FTC. We're really doing miraculous things. We've got a database of spam that comes in that's anonymous, and we've got a whole list of the biggest spammers in the country, and sometimes it's a good thing. If the bad guy doesn't show his head, how are you going to shoot him down?

One case we just brought against this company called Cecil-something, a liquid dietary supplement. They said diabetics could stop their insulin. This was not true, but the reason we found out about it, in addition to the health surf we did, was that one of our Federal Trade Commissioners got

spammed, and he goes "What the heck is this? Let's go after these bastards right away!"

(Laughter.)

MR. DAYNARD: So we are working with the providers, we're working with high-tech folks, we're working with the industry to do everything we can about spam. But when you have politicians spamming people, where are you going to go?

DR. TUCKSON: So what is his email address?

(Laughter.)

MR. DAYNARD: I ain't telling you.

(Laughter.)

MS. ZELLMER: Emily?

DR. WINN-DEEN: I guess one of my big concerns is in order to have the public believe in and reap the medical benefits that genetic testing we hope will offer in the future, not just for highly penetrant monogenic disease but for the common complex diseases where your genetic heritage is one component of your health management of your future, I have concern that if genetic testing is used for a lot of "junk science" and consumers lose confidence in its abilities and what it can really deliver because of junk science, then when the good science comes along they won't use it as they could and should to take better care of themselves.

We had an example in our previous briefing book of a company that was offering to take a cheek swab, send it in, and they would tell you which of several formulations of face cream was right for you. Now, there may indeed be something behind it, but they may just take this cheek swab, throw it in the trash and send everybody the same jar of face cream for $300 or whatever. I mean, it was very, very high-priced stuff. But it was purported to be customized for you. I can see in the area of let's call them beauty products, anti-aging, that whole thing, that there's enormous potential for some part of it to actually be based on real science but a lot of it to be based on just completely fraudulent kinds of claims.

So I guess I personally would like to see the FTC shine a little bit of light on not just the diet supplements, which are part of that, but some of the other health and beauty things that are going to maybe keep us from having the consumer confidence that we need in the medical applications.

MR. DAYNARD: Oh, we do, unless you're talking about genetic testing specifically. Bloussant is a breast augmentator pill that they sold 30 million dollars worth. We just had a big settlement with them. If you're talking about health care things in general, that's what we do, but we haven't done the genetic testing thing yet.

DR. WINN-DEEN: Okay. So we should forward you the ad on this one for the custom beauty creams?

MR. DAYNARD: Well, beauty creams -- you know, big deal. But if it's a beauty cream that's going to get rid of your extra fat or it's going to enhance your memory or it's going to get rid of all your wrinkles and make you look like a star or something. But the cosmetic thing, it's not going to fly too much with the Commission right now. We're into anti-cancer stuff, you know? How am I going to sell a beauty cream?

DR. WINN-DEEN: I guess I'm concerned that those kinds of things fall under the radar, and yet they can have more harm because they just erode confidence in what the technology can really do in a positive way.

MR. DAYNARD: Yes. Tell Congress to give us another $150 million.

I don't mean to be glib. I'm sorry.

DR. WINN-DEEN: Do I have to pay more taxes for that?

(Laughter.)

MR. DAYNARD: Yes. What's wrong with that?

(Laughter.)

MR. DAYNARD: I don't mean to be glib. It's just that we have to pick and choose, and it's impossible. I agree that if we can nip this in the bud, and if we can do it with a nice big fat serious disease case, that would be the way to go.

MS. ZELLMER: Does anybody else have anymore questions?

DR. SUNDWALL: My name is David Sundwall. This will be real quick. First of all, thank you very much. It was a very enlightening discussion. I represent the American Clinical Laboratory Association, but I also chair CLIAC, and I want you to know that in the last two meetings of our committee in Atlanta we have spent some time on direct access testing, been informed but perplexed about what is the role of the government in regulating this, if any. I think we've at the moment concluded that there's no role for CLIA per se, because in fact we've learned from the FDA that some of the most egregious claims are being promoted from CLIA-certified labs and CAP-accredited labs. So this is really kind of disconcerting.

So it's not the quality of the analyte per se, but serious questionable ethical concerns about what they're doing. So we are going to be inviting you to address our group because we have decided that the FTC probably has a role here that we haven't previously given enough time to. So thank you and I'm putting you on notice that we'd like you to address our committee.

Lastly, I'd just like to inform the --

MR. DAYNARD: Is that in Acapulco?

(Laughter.)

DR. SUNDWALL: Yes, right. Puerto Rico in January, right.

(Laughter.)

DR. SUNDWALL: No, unfortunately not. It's in beautiful downtown Atlanta, though. We've gotten away from the suburbs and moved into town, so that's progress.

MR. DAYNARD: I look forward to it. That's great. Thanks.

DR. SUNDWALL: Okay.

The last thing I think the committee, if you aren't aware of it, you might want to look at www.labtestsonline.org, a peer-reviewed, not-for-profit effort to put on the web absolutely honest, straightforward public information about lab testing, including genetic testing. I'm on the editorial board, along with Lisa Passaman, and I think some others who may be here, but it is professional organizations, consumers. We really try our level best to give as honest and clear and comprehensible information on testing as you can get, and it's won numbers of awards, and numbers of hits have gone up to 80,000 or 90,000 a month. So it's popular and been recognized for its validity.

In fact, with this committee and your expertise, we'd welcome your feedback on how we might make it better for information on genetic testing.

Thank you.

MS. ZELLMER: Any more questions?

Reed?

DR. TUCKSON: Just one comment that I thought was important between something that Brad said and something that Emily said which I thought sort of fit together. I think Brad's point is important, and I would think that all of us around the table on the committee would share that the concern in this area is not because we feel that consumers and the American people are not bright and that the inevitability for the movement for more consumer empowerment and more access to information is not only inevitable, as Brad has described, but also desirable.

I think that we, in our comments -- I want to make sure that we're at least clear on this.

I want to make sure that the sense of the committee -- and I'm looking for dissent -- is that we absolutely respect the intelligence of the American people and their ability to need to be able to take control over their own health. But as Emily I think rightly points out as well, what happens is that if we don't get on top of this, if people are provided with misleading information, it makes it hard for them to do what they're trying to do. If information is deceptive in this growing area, the natural distrust in this area could also lead to unfortunate decisions being made and an unfortunate level of distrust out there.

So I think the points go together, but I think Brad does us a service by making sure that we are able to say in the record that nothing that we have described before is to in any way suggest that the American people aren't capable or shouldn't be able to make the decisions they need to make.

MR. DAYNARD: Can I comment? That's terrific. I'm wondering if NIH or the committee has a website that gives good information to consumers. When people get online to ftc.gov or consumeronline.gov, we have a list of health-oriented websites, like HealthFinder and others where they can get proven and solid information about health care to help themselves, and that's obviously, it seems to me, the thing to do here as soon as you can.

DR. COLLINS: So in response to that, NIH's website I think is at the present time the highest hit rate of any government site, and certainly in the sites that people go to for health information, it routinely ranks number 1 as well. Now, whether there is a place on the NIH website along the lines of this consumer beware theme, here are the kinds of claims that you ought to worry about if you see them out there in the big worldwide web, I'm not sure that I know the answer to that, but it's easy enough to go and do a quick search and look.

DR. McCABE: Well, thank you very much. Thank you, Kim, for facilitating that. Matt, thank you for coming. Steve, as always, it's a pleasure to have you participate in these discussions.

We'll take a 15-minute break. Please return sharply at 3:00.

(Recess.)

DR. McCABE: Well, thank you, everyone, for reassembling on time. At this point in our agenda, we will take time to hear from members of the public. One of our functions is to serve as a public forum for deliberations on the broad range of human health and societal issues raised by the development and use of genetic technologies. So we greatly value the input we receive from the public. We set aside time each day during our meetings to hear from the public, and we welcome and appreciate the views that you all share with us.

We also have received a number of comments. I mentioned before that we received 20 comments in writing in response to a more targeted request regarding genetics education and training. Most of those written comments are in Tab 1 of your briefing book, and there are several additional ones in your table folders.

I have three individuals who we will be hearing from this afternoon. We would ask each of you to please try to keep your remarks brief, under five minutes. I would prefer that they be more like two to three minutes with time then for us to discuss them around the table. We will confine this to a period of 20 to 30 minutes maximum because then we want to move on to discuss what we've heard today and how that begins to help us set the agenda for the committee in the future.

So the three individuals I have in the order I have them, just so you'll know when you should be ready to speak, is Dr. Shirley Jones from ISONG, Dr. Veronica Feeg from the American Academy of Nursing, and Dr. Fred Ledley from Mygenome.

So we'll start with Dr. Jones, and if you could come to the podium please, up front here.

DR. JONES: Good afternoon, Dr. McCabe, and members of the Secretary's Advisory

Committee on Genetics, Health, and Society, fellow colleagues and concerned public. I am Shirley Jones, a founder, past president, and current member of the Ethical Issues and Public Policy Committee of ISONG, the International Society of Nurses in Genetics. ISONG is a nursing specialty organization dedicated to caring for people's genetic health through excellence in the provision of genetic health care services by fostering the scientific, professional and personal growth of nurses in human genetics.

The more than 350 members of ISONG reside and work throughout the United States as well as in Canada, Britain, New Zealand, Brazil, Israel, Greece, and Japan. On behalf of ISONG, I would like to offer the following comments in consideration of tomorrow's session on genetics workforce education and training.

Nursing is the prevention of illness, the alleviation of suffering, and the protection, promotion, and restoration of health in the care of individuals, families, groups, communities, and populations. Nursing practice encompasses the full range of human experiences and responses to health and illness without restriction to a problem-focused orientation.

The hallmark of nursing education at both the undergraduate and graduate levels is the acquisition of the knowledge and skills necessary to continuously integrate and apply scientific and technologic advances into the science and art of professional nursing practice. As such, nurses are well-grounded in the skills requisite to the integration and application of new knowledge.

A genetics nurse is a licensed professional nurse with advanced specialty education and training. Genetics nurses help people at risk for or affected by disorders with a genetic component achieve and maintain health. Genetics nurses perform risk assessment, analyze the genetic contribution of disease risk, manage genetic information, and discuss the impact of risk on health care management for individuals and families. Genetics nurses also provide education and conduct research in genetics. Recognition of this expertise may be obtained by acquisition of the advanced practice nurse in genetics credential or the genetics clinical nurse credential through the Genetics Nursing Credentialing Commission.

In support of the importance of the integration and application of genetics knowledge into the professional practice of nurses, ISONG developed, in collaboration with the ANA, the statement on the scope and standards of genetics clinical nursing practice. This document identifies and describes the integration and application of genetics at both the basic and advanced levels of nursing. ISONG has authored and adopted multiple position papers that address the diversity of issues that confront the role of the nurse, including informed decisionmaking and consent, privacy and confidentiality of genetic information, genetic counseling for vulnerable populations, and most recently access to genomic health care.

ISONG members are at the forefront of efforts to assist their nursing colleagues in the integration and application of genetic knowledge. Most notable are four well-established programs: the Genetics Program for Nursing Faculty and the Web-Based Genetics Institute led by Cindy Prows at the University of Cincinnati; the Summer Genetics Institute through the NINR, led by Drs. Mindy Tinkle and Francine Nichols; and the Practice-Based Curriculum for Nurse Educators developed by Dale Lea at the Foundation for Blood Research.

Annually, ISONG hosts an educational conference that is well attended by not only the members of the organization but also by nurse clinicians, researchers and academicians who reside in the geographic region in which the conference is hosted. The 2004 ISONG conference is dedicated to the assimilation and synthesis of the state of the science for genetics nursing and the establishment of a research agenda that will be strongly focused on the delivery of and access to genetic health care services for or by individuals, families, groups, communities, or populations.

However, there is a significant lag in the time it takes to move knowledge to practice

and apply scientific advances within the health care setting. As a consequence, there is inconsistent and irregular availability of genetic health care services as they become clinically valuable to the public. It is daunting to consider that at the present time there are 2.7 million individuals currently licensed as professional nurses in the United States who are in need of this knowledge. Therefore, it is critical and necessary that current programs continue to be supported and new initiatives identified and implemented to reduce the genetics knowledge to practice gap among the largest and most omnipresent group of health care providers, nurses.

At present, there is a national effort led by Dr. Judith Cooksey and her colleagues to identify and describe the issues confronting the development of an appropriately educated genetics workforce. The profession of nursing is the focus of the 2003-2004 effort. ISONG is actively involved in this effort, with many of its members serving on the advisory board of this federally-funded project. ISONG supports activities such as this and strongly urges the Secretary's Advisory Committee to recommend support for the identification, development and funding of such efforts so that the gap between identification and transfer of new genetic knowledge is significantly and uniformly reduced. Such action will strongly benefit those to whom we responsibly provide care.

On behalf of ISONG, thank you for the opportunity to provide public comment and for your courtesy in receiving these remarks. The International Society of Nurses in Genetics is eager to continue dialogue with the Secretary's Advisory Committee as you investigate and develop recommendations about these important issues.

Thank you.

DR. McCABE: Thank you for your comments.

Any questions or comments from members of the committee? Any of the ex officios?

DR. WINN-DEEN: I understand you're asking sort of generically for our support, which I could probably say on behalf of the committee you have. But is there anything specific that we could do to help move education through the nursing workforce in a more expeditious manner?

DR. JONES: At the present time, we have identified several programs that are doing very well in training nursing faculty, but there is limited resources to getting those faculty to the programs. So if there is a mechanism to provide funding and opportunity for the faculty who are going to be our principal way of reaching the most individuals, that would be especially important.

Additionally, I think it would be helpful to take a very serious look at the programs that are attempting to train not only nurses but all health care professionals who are in the practice level, not in academia or research, and see what has worked, what hasn't worked, and why it's not working. It is unsettling that we still have nurses who feel that their competency and confidence in providing genetic health care is lacking.

DR. McCABE: Emily, did that answer your question?

DR. WINN-DEEN: Yes.

DR. McCABE: Any other questions or comments?

(No response.)

DR. McCABE: Okay. Thank you very much.

Our next speaker is Dr. Veronica Feeg from the American Academy of Nursing.

DR. FEEG: Mr. Chairman, members of the committee, and distinguished guests and colleagues, I'd like to also focus your attention for the next five minutes on education and workforce issues that will be covered much more in depth tomorrow. Thank you for the opportunity to present public comment on behalf of the American Academy of Nursing Expert Panel on Genetic Health Care, whose members are recognized nursing leaders. The Academy's mission is to transform the health care system to

optimize public well-being. Members of the panel include nurse researchers, educators, and leaders in health policy related to genetics.

Education of the public and health care providers regarding implications of genome discoveries is an important priority for nursing. Nurses educate patients and the public on ways to protect and maintain their health. It is difficult to imagine any segment of our population who does not receive education on health-related topics from a nurse.

Nursing recognizes the need for basic and ongoing genetic and genomic education of the nursing workforce in order for professional nurses to fully integrate their knowledge into the nursing care provided to individuals, families and communities. The nursing profession is partnering with other health care disciplines to address workforce issues and nursing education regarding genetics and genomics.

Let me first address undergraduate education. Three documents provide standards for nursing education regarding genetics and genomics for entry-level baccalaureate nurses. You've heard from ISONG; you can also read in the document from the American Association of Colleges of Nurses, who recognize the importance of genetic knowledge for nursing practice.

Several associations also have produced documents. The Association for Women's Health, Obstetric and Neonatal Nursing, and the Oncology Nursing Service have issued position statements that describe the responsibilities of members of these organizations regarding nursing care for persons considering genetic testing. Educational programs and articles in nursing journals provide the members to fulfill these responsibilities.

Comprised of organizations representing the health professions, NCHPEG, the National Coalition for Health Professional Education in Genetics, with a membership of over 120 organizations, includes 16 nursing organizations. In 2000, NCHPEG issued core competencies for health professionals regarding genetics, and again you heard before from the previous speaker and will hear tomorrow more information about NCHPEG core competencies.

For over two decades, nursing educators have received funding from HRSA for the education of nurses in genetics. A recent example of this is also the program that is now web-based from the University of Cincinnati and has reached over 230 nursing educators throughout the United States.

Let me turn to advanced practice education for nurses. A second goal of nursing is to assure that advanced practice nurses apply an understanding of the influence of genetics on health care in their care for specific populations. Pediatric nurse practitioners provide primary health care to children and manage the health care of children with chronic diseases. Content regarding inherited factors that influence reproductive decisions in families is a component of family nurse practitioners and pediatric nurse practitioner competencies as defined by the organizations I've mentioned, as well as the National Organization of Nurse Practitioner Faculties, known as NONPF.

An innovative interdisciplinary program to educate faculty on genetics topics is ongoing at Duke University. The genetics education program is providing genetics education to 25 teams of educators who teach nurse practitioners, nurse midwives, and physician assistants across the U.S.

Let me focus specifically on education of advanced practice nurses with specialties in genetics. Advanced nurses in genetics provide nursing care to people who have genetic conditions or health disorders that have a genetic component. These nurses complete graduate-level education and training in Master's degree programs. The scope and standard document also defines the parameters of advanced practice nursing in genetics.

Now, what do nurses in practice do? Application of genetic knowledge into practice occurs in a wide range of health care settings. Nurses include a genetic family assessment when they conduct a health assessment for women who are anticipating pregnancy or who are seeking prenatal care.

Nurses provide education on healthy lifestyle practices prior to and during pregnancy, and education regarding genetic testing options. Nurses use genetic information in identifying persons at risk for inherited forms of cancer, and then use the information for promoting adherence of at-risk persons to surveillance and treatment plans. Nurses monitor the impact of genetic information such as genetic risk status, follow predictive genetic testing on the health and well-being of individuals and their families.

Let me speak very briefly to the development of scientific knowledge regarding genetics and health. The development of knowledge regarding the application of genomic discoveries to clinical practice requires a cadre of scientists whose research is based in the nursing and genetic sciences. As you heard, the National Institute of Nursing Research has hosted for several years a summer genetics institute that has produced 66 genetic nursing research scholars. Products of nursing research on genetic topics will increase the understanding of the impact of genomic discovery on aspects of health such as decisionmaking, psychosocial coping, relationships between ethnicity and risk for inherited diseases.

Let me summarize on behalf of the Academy. As a component of this mission, the American Academy of Nursing has taken a leadership role for several years in assuring that genetic content is integrated into baccalaureate and advanced nursing education. Last year their position statement integrating genetics competencies into baccalaureate and advanced nursing education was adopted with a statement that follows: "It is the position of the American Academy of Nursing that organizations or institutions that are responsible for curriculum development, curriculum standards, approval or certification of basic and advanced programs, and those that accredit hospitals incorporate and include NCHPEG core competencies as part of their continued competencies for health professionals, including nurses; and that jurisdictions that license registered nurses establish policies that acknowledge nurses with competencies in genetic care."

I'd like to conclude with the statement that nurses are increasing their ability to include genetics education in undergraduate, graduate, doctoral, and continuing education programs. This reflects an important contribution by the nation's 2.7 million nurses to clinical practice, public and health professional education, basic and applied research, and health policy in order to assure the genetic health of the public.

Thank you.

DR. McCABE: Thank you, Dr. Feeg.

Any questions or comments? Reed?

DR. TUCKSON: Yes, just a brief one. We'll hear more later around genetic counseling and the adequacy of resources for genetic counseling. Is it your position that nurses ought to be supported in an educational way to be able to help fill that gap in a particular way, or do you see that as being one of the competencies of the nurse of the future?

DR. FEEG: I believe I can safely say that the Academy's position recognizes a distinction but acknowledges that as first responders of sorts, nurses are asked questions and need to understand the limitations of their knowledge and when to refer. But I think that it requires the support of continuing education and support for programs that develop those competencies to know the distinctions. If your question is related to are they the same thing, I believe the answer is no, but I believe that there's a way of combining the clinical skills.

DR. TUCKSON: Then the other question would be if you do not specifically single out the counseling function as a special competence, what are the kinds of -- Huntington sort of asked these questions a bunch of times today, and I think if I understand his question, it gets to this idea that genetics is ultimately, if you transport to a few years from now, it's medicine. It's how medicine is practiced, just like everything else in medicine. So at the end of the day, what do you sort of see as being what it is that a

nurse would be doing in the genetic era that would be particularly different than what they do today?

DR. FEEG: I think if you're asking the who does what when, and if in fact changes on the horizon would change roles, I think the answer would be, to fast forward, that would depend. I think that the statement that the Academy would support is that nurses are in fact involved with health discussions. Whether you want to relegate those to specific counseling activities, I don't think I would be prepared to say they would become the genetics counselors. But I think they acknowledge that the role encompasses a broader frame of interactions with patients. Does that help?

DR. TUCKSON: Thank you.

DR. McCABE: Brad?

MR. MARGUS: I understand, and I think we all agree, that we'd like to have the millions of nurses be extremely well-educated on genetics in the frontline role they play, and I understand you were saying that there are already steps being taken to incorporate genetics into curricula at different levels, but what I don't have a feel for, and hopefully you can answer safely, is is it really inadequate right now? Is it pretty good? You would know this and we won't, so is it really a real problem right now, something outrageous, or it's getting up to speed and you'd obviously like us to support it and funding to be there to continue it?

But how bad is it out there? Have there been any kind of tests or studies or surveys done? I've heard of some with physicians that kind of try to measure that. But what's it like out there?

DR. FEEG: Well, I can say that through the NINR support, there are ongoing studies for the roles that nurses play in assisting with decisionmaking and in -- I don't want to call it counseling but in other psychosocial issues. So I know that the research is ongoing.

To answer your question safely, I think that the position would be that in the best world, where there were additional funding available, we certainly need more and need to do better. In general, I think we've established a track record of core competencies in those expectations of what every nurse should have and what those who are specialized in genetics should have, and I think we'd look for the kind of support the committee would give us.

MR. MARGUS: So if you made up a test, just a basic test of what you think or what we all would agree or what you would decide is adequate to acknowledge today -- and I understand the field keeps changing and you want to keep continuing to educate people, but today what you'd want a nurse to know about genetics, would most nurses pass that test today?

DR. FEEG: I think I'd have to say as a nurse researcher myself, that's a tough question to answer without any kind of information to support what I might ask you back, in what aspects do you mean in the different roles that they would play? I think in some fronts they're extremely well prepared. I think in others, as the previous speaker mentioned, there are adequacies that need to be brought up to speed.

DR. McCABE: Brief comment, Hunt.

DR. WILLARD: Very brief, because I just want to make sure I understand from your perspective what role you anticipate or hope for in the nursing community. Is this any different than your approach to kidney disease, for example? Obviously your hope is and we trust that the nursing community actually has been educated about the kidney and how to recognize symptomology that's related to kidney malfunction and how one might counsel, in the lower-case sense of the word, patients who have kidney ailments. Is this different from that, or is this simply as if we'd just discovered a new organ and it's called the genome, and the problem is that nurses in their education, because we hadn't seen the genome yet, were never really exposed to that?

DR. FEEG: I think that your analogy of being an organ or a disease is what makes this

different. I think genetics, as we've heard today, presents different kinds of issues. So I think I'd have to say that this is somewhat different. We've always looked to try to supplement education in whatever new things, in whatever diseases, or perhaps particular interests that large constituencies might want us to focus on. But the genetics changes that happen every day I think are presenting a situation that is different. So in looking for support for education for a workforce that would be competent, I think it's somewhat different.

DR. McCABE: Thank you very much.

Is Dr. Ledley here?

(No response.)

DR. McCABE: Okay. Perhaps he's coming tomorrow. I would point out in the packet that was at your place today, there's an article by Dr. Ledley from Nature Biotechnology, August 2002. There are copies out on the table outside talking about a consumer charter for genomic services. I think it would be important for individuals to look at that.

With that then as a background, I want to thank the speakers, the public for both their written and verbal comments.

Now we have about an hour and a half of discussion before we are visited by Ms. Kristin Fitzgerald from the House to talk to us about the House's plans for genetic anti-discrimination. How we're going to use this time is to return to our discussion from this morning and early afternoon regarding oversight of genetic technologies, the role of pharmacogenetics. We've had briefings from the federal regulatory agencies on their roles, activities and plans in regard to oversight, marketing and laboratories. You'll all recall, especially those who were involved in the Secretary's Advisory Committee on Genetic Testing, that our predecessor committee spent a lot of time and a major focus of the work was on oversight and a number of the recommendations about how oversight might be enhanced.

I think it's important, and I'll organize what I heard today into three areas. We heard about oversight through CLIA and FDA, we heard about FDA and pharmacogenomics, and we heard about oversight of advertising and promotion. One of the things we need to do now is discuss that further, and also discuss our future agenda and how we're going to focus our efforts.

Fundamentally, do we need to pursue oversight as a major agenda item of this committee, or do we feel that the FDA and CLIA are proceeding down a course that was set by SACGT and we want to monitor that? Are there other areas that we want to focus on now?

So I'll open it up to discussion by the committee.

Chris?

DR. HOOK: Chris Hook. Thank you, Dr. McCabe.

I go back to the end of our discussion this morning when we were talking with folks from the FDA about using pharmacogenomic information to understand the potential implications, negative consequences of certain drugs in various subgroups of the population, and the call or the need, the express need for more information to be generated. I think that should be a priority issue for us to consider.

As you said, perhaps the FDA cannot mandate those sorts of studies in terms of approving a drug, but if there are ways in which we can, through looking at the drug development process of Phase II and Phase III studies, through government funding as a means of requiring that type of investigation, we should at least talk about it, what would be the expenses that would add to the research overall, how can we provide them the information that they need. So I'd like to see that on the table.

DR. McCABE: Debra?

DR. LEONARD: Well, even beyond -- what you're talking about is prospective drugs. The Japanese government has mandated a pharmacogenetic analysis of all drugs that are out on the market being used in the Japanese population because the reactions there are different than the Western reactions.

So prospective is one thing, but what can we learn about the drugs that we have and some of the toxic reactions that physicians are well aware of that they might see? Is there a way to test for those? Also, for drugs that are even out on the market.

DR. McCABE: I think it was maybe you, Chris, but maybe somebody else mentioned that this should be funded by the NCI for cancer drugs, and I noticed that our NIH representative was taking notes since the National Institutes was mentioned. Alan Guttmacher is sitting in for Francis Collins from the NIH. Would you like to comment on that?

DR. GUTTMACHER: Sure. I think we certainly believe that this kind of testing is important to do. The question, of course, is that the NIH tends to fund fairly little actual drug testing in any aspect, including pharmacogenetics. It tends to be more drug companies and others. We tend to focus more on that basic science research that doesn't get funded by private industry, for obvious reasons. That's not to say we're not involved in any drug studies in any early drug development, and it's also not to say the NIH particularly -- supported largely by the National Institute for General Medical Sciences is a large pharmacogenomics group that's funded a number of institutes, et cetera.

So the NIH is clearly involved in these things and is interested very much in pharmacogenomics applications and pharmacogenetics, but I think that it would be false to think that NIH alone is going to be able to take care of this issue.

DR. McCABE: Chris, then Emily.

DR. HOOK: But isn't it true that through most Phase I/II programs, they have to receive NCI approval in order to proceed with human subjects trials in that regard? And couldn't the NCI mandate, if nothing else, the pharmaceutical companies pay for this? In other words, make it a requirement in order to do the Phase I/II testing?

DR. GUTTMACHER: I don't think the NCI -- I must say I'm not from the NCI, so I can't answer for them, but I believe that they don't have as much involvement as you're crediting them with.

DR. McCABE: Emily?

DR. WINN-DEEN: I think one of the issues -- so there's two issues in pharmacogenetics. I think we should probably address both of them. One is the issue of what to do to get the data from marketed drugs. Who is responsible for basically paying for the studies, designing them, paying for them, running them, the whole thing, so that the general public would have the information. Some of these drugs are generics. I mean, there isn't even one drug company to go to. So there's that issue. That's personally where I think somehow NIH could help with funding.

For drugs that are still in the pipeline, in Phase II/Phase III, working for a pharmaceutical company and also talking with a number of my colleagues who work for other pharmaceutical companies, there is still a big cloud over that whole process, and until FDA finishes its safe harbor guidance on what, if anything, it is or is not going to do with information that might be gathered and whether or not that information would be required to be submitted, I think that is still influencing the way trials are designed. That is, some trials are still purposefully designed not to include a pharmacogenetic component or to include it only in a blinded retrospective analysis should an efficacy or a safety issue arise because of fear for how the FDA would use that data and inhibit their ability to launch a drug.

So I think there are two different issues that really need to be resolved in two different arenas. But I do think from a public health point of view, if we're going to get to the point of really utilizing genetics and pharmaceuticals together, we're going to have to solve both those issues.

DR. McCABE: Steve, do you want to comment on the FDA? Steve Gutman from the FDA.

DR. GUTMAN: Yes. I'm not in the greatest position to comment on at least the drug

side, but I do know that they take this very seriously, and I do know that they're working on documentation to strengthen that, and I think that's on a fairly tight time line. So I think there's a reasonable ability to have a short-term expectation that they'll produce guidance that I think will be industry friendly and address exactly the issues that you've raised.

DR. WINN-DEEN: So my comment back is to just sort of encourage that to reach its logical conclusion, because there is a couple of year time lag, two or three years. People today who are designing a Phase II trial for a drug that will probably reach market in about four or five years are not going to do things until the FDA guidance is clearly there. So there's this time lag phenomenon. So we need to keep moving along on the FDA front so that we can see the benefit sooner rather than later on the drug front.

DR. GUTMAN: I do believe CDER appreciates that.

DR. McCABE: So is there a way now to focus this discussion? Is there a way that you wish this committee to weigh in on this topic? Is there something that you want other than an update in a year from the FDA? How do we stay involved, become involved again in the future on the topic of pharmacogenetics?

Yes, Debra?

DR. LEONARD: Well, we can have updates from the FDA. I don't know that we're going to move their process along for the new drugs any faster than they're going to move anyway, and they're hearing us say we want them to move as quickly as possible. But is there a way to explore funding mechanisms for, if you will, retrospective drugs on the market and that pharmacogenetic analysis through NIH, through an RFA? I mean, I don't know which part of NIH this would come under or be funded through, but is there a way to explore mechanisms to get funding for these types of research?

DR. McCABE: What we have done before, "we" being the Secretary's Advisory Committee on Genetic Testing, when we had questions about this was -- and I'll tell you, it's a huge burden on the agencies, but that is to ask them to explore what they are funding at the current time in these arenas. It is a huge amount of work on their part, but that's something that we could ask.

My impression is, having lived in academics and seen the flow of money, that once you get out of -- I know pediatrics, so once you leave the Children's Oncology Group, there's very little drug testing that's done in kids that's funded by the NIH. So I think we would find that there's a relatively small amount of money that's flowing. If we then say that we need to explore postmarket surveillance in terms of pharmacogenetics, that's going to have huge ramifications throughout the industry.

So I think this is a very large ticket item that we're talking about. What I would suggest is if other countries are exploring this in their own populations, like the Japanese government, one thing we could do is try and find out what other groups are doing around the world and see how they're supporting it and how they're going about it and whether any of the things that they're learning could have any effect on us. We've got some guests from the European community here. I don't know if they're prepared to comment on this.

Reed, do you want to --

DR. TUCKSON: I think that one of the challenges that we face here, and I think you're sort of getting at it, is that we obviously in this country have a -- whatever the trillion dollar deficit is. I think we all understand going forward what that's going to mean for the budgets of any of these HHS agencies.

So I think what we might want to try to find a mechanism to do is to -- if we're talking about retrospectively using new tools, what would be a grid, and who could help us to develop a grid that would say sort of where are the priorities here? What are we trying to achieve and what are the priorities

as you look back? I mean, if at the end of the day -- and part of this is my own naivete trying to get up to speed here. If we're saying that there are drugs that are in use today whose use could be made safer, give us better quality outcomes, and more cost effectively, if we had the ability to apply to them new knowledge around pharmacogenetics, then how would one make those choices of where you would look? I think that's what I'd be looking to for more guidance as to how to think that through.

On a prospective, going-forward basis, I think the thing that I'm most interested in from this morning's discussion is to assure that the data that is available going forward around pharmacogenetics and drugs is made available in efficient ways for the multiple constituencies that need to have it to make the most intelligent decisions regarding quality, cost and safety.

DR. McCABE: Before I call on Brad, I'll tell you what I teach when I teach about pharmacogenetics and pharmacogenomics. My Ph.D. happens to be in pharmacology back in my deep past, and so I get to teach this to the medical students. The people we need to have sitting at the table would be the American Bar Association. I really argue that it is the lawyers who are going to drive the development of this technology, because they're going to demand it for their clients, and that's why we will start to have testing.

Having had my nursery be threatened with a suit two to three years ago for Connexion 26 -- it turned out that the child who failed their hearing test did not have that mutation, the glycoside-induced hearing loss -- it made me begin to think about this.

So I think we will see a building of testing resources, and it will become a demand of the public, and it will be influenced by their legal counsel. Having said that, that takes us back to the question of how do we build the evidence base for this and how do we begin to try to protect the public and the professionals rather than just being reactive?

Brad?

MR. MARGUS: I talk to a lot of pharmaceutical (inaudible) pretty much daily about pharmacogenomics, and in fairness, so far, as of today, it's been pretty disappointing. The problem is there isn't a lot of great evidence yet that's driving this forward. I mean, the examples -- those of us who go to the conferences for these things see the same old examples of cytochrome P450 and HER2 and a couple of others, and then you run out of them. It's really been promised but it hasn't delivered. I think that will change because I really believe in the next few years there will be a lot more associations and markers, and that may drive a lot more.

I think if we could encourage the Secretary to encourage the FDA to continue working with industry in keeping up to date on what's happening so that they're ready for this onslaught, that would really be good. I think the safe harbor thing is obvious.

The other thing that we mentioned today is that we should also encourage that trials incorporate diversity. That's certainly important.

On the issue of how do you get people to do pharmacogenomics and find markers that could be valuable for either old drugs, drugs that are off patent in particular, or marketed drugs, for one thing if it's marketed drugs, the other fear is that no pharmaceutical company wants to cut their market size, so they're afraid of that. Obviously during development, they're worried about the safe harbor thing we discussed. And then on the drugs that are off patent, who in the world is going to pay for it?

I sit on a council right now at the NIH, and I can tell you -- it's the Neurological Institute -- they spend some decent money on clinical trials, but it's not going to go over really well if you tell them that you want to take out $100 or $200 million of R01 grants to do a few clinical trials. So what I was wondering, and maybe Alan could think of this, is there any other mechanism that would turn pharmaceutical companies on to revisiting pharmacogenomics in some of the old drugs?

For example, I have no idea what the mechanism is, but something along the lines of the Orphan Drug Act, how it provides some patent protection to encourage companies to work on it. Is there any way you could motivate pharmaceutical companies to revisit old drugs or off-patent drugs in exchange for doing pharmacogenomics that would end up actually helping the world?

DR. McCABE: Alan, do you want to respond to that before we move on?

DR. GUTTMACHER: Sure. It's a difficult question. I thank Brad for bringing up the reality that if one was to do retrospective testing, the multi-hundreds of millions of dollars that would be involved in that clearly just doesn't exist, even though the NIH has relatively deep pockets. It just doesn't exist. I think the question is how you would encourage those who are making profits from the drugs to use that kind of testing.

My -- I hope it's not cynical, maybe just reality-based kind of thinking about this is that that kind of testing, as much as it would be helpful today, probably will not become a reality until the cost of doing it becomes much less. The good news is I don't think we're decades away from that, but we're also years away from that. But I suspect that that kind of testing really needs to await the cost of genetic testing just becoming so much less that it becomes easier to do the research.

MR. MARGUS: Actually, the biggest problem I don't think is going to be the genotyping. The genetic testing is going to be. And for these old drugs, no one collected or banked any DNA, so even if you can get genotyping down to zero, you've got to still run new trials to go get the DNA.

DR. GUTTMACHER: That's right. It's going to be hugely expensive.

DR. McCABE: Emily, do you want to follow up on that point?

DR. WINN-DEEN: Yes. I just wanted to say one mechanism that we might consider is the cooperative group mechanism that's used in oncology today not for this particular application but for looking at best practices and combination therapies. Those cooperative group studies I believe receive a basic level of funding through NIH to create the cooperative group, and then the drugs that are involved in patient treatment are generally donated by the drug manufacturers. So it's truly a multi-funding source thing where everybody puts in a little bit and the patient community benefits.

Now, this is aimed at a different kind of best practices where no single pharmaceutical company really has the ability to combine its drug with a competitor's drug, so you need sort of a neutral venue where that can happen. But that's the kind of thing where maybe -- let's just take an example. Maybe all the manufacturers of statin drugs could contribute their statins and we could look for markers that predict response to statins, those kinds of things, and some of that is actually going on in the PROWESS trial, so I don't want to make it sound like that's not happening. But those are the kind of things that might be mechanisms for funding, where it's not on any one organization's shoulders.

DR. McCABE: Is this a follow-up, Reed?

DR. TUCKSON: Yes.

DR. McCABE: Okay.

DR. TUCKSON: In addition to the comments of my colleagues, I want to continue to be less ambitious than they. I'm still worried, quite frankly. I'd like to hear more, in an organized way, from the Secretary's subordinates, leaders in issues. They're too brilliant and wonderful to be subordinate, the people that run these agencies. I'd like to hear sort of the collective understanding from them about the potential value and when can we recognize the value of this new knowledge and this new science, and where are we with it.

Because, quite frankly, I keep having in my mind's eye the new report from the Census Bureau that just said there's another 2.6 million uninsured people, that the pharmaceutical costs are still continuing to go up and up and up. There are so many issues before us, and I want to be sure that

somebody in the government, and I think it should be the Secretary, should be looking at the cost effectiveness of these things, knowing how these tools can be applied in a responsible way to make sure that the American people get access to pharmaceuticals that they aren't getting access to now. There's a lot going on here, and I want to make sure that this is being precise.

So I would sure love to hear in a much more precise way from the presenters that we have available to us, the experts, as to where and when are these tools going to be available and how can they best be used, and I think we can then start to give better recommendations about how to go forward. But I'm not sure we know enough yet, and maybe others are just a lot sharper around these things than I am. But please keep in mind that there are a whole bunch of people who don't get access to fundamental digoxin, much less being able to start to do some of these other kinds of tools. So let's just make sure we know what we're doing as we recommend it. I'm not against it. I just want to know a little bit more.

DR. McCABE: Debra, and then Hunt.

DR. LEONARD: I have the impression from talking to pharmaceutical companies -- and Brad, maybe you can comment on this, and I was hoping Steve would be here but he's gone -- in talking to some people, medical directors and stuff at pharma companies, they say that there is pharmacogenomics and genetics going on at pharma companies up the wazoo, tons of it, but they don't let it out of the company.

So I don't know that it will be an additional cost to pharma, like they're waiting for the FDA to tell them that they have to do this. I think they're doing it because they learn a lot from that process, but they aren't submitting that information because it runs into the marketing issue of they cut down their market if they can identify who will benefit and who won't benefit from taking a drug with a particular disease.

So can anybody clarify that as to whether pharma is doing this?

MR. MARGUS: I will say that there's a lot of money being spent by pharma on pharmacogenetics right now, but the number of discoveries and associations where they've found a large enough percentage of genetic variants to have any predictive value, to have utility in a diagnostic test, a bar code that predicts drug response, either who is going to have adverse reactions or who is going to have efficacy, is really, really barren out there. There are very, very few examples of that, very few successes.

But the technology is moving along, so I think there will be, but I don't think they're sitting on things that would really help just because they're concerned about the market being shrunk.

Sure, some drug companies were thinking -- and it's changing, but were thinking why put money into this, why have these initiatives if it risks making a smaller market? But the flip side of that is that a lot of drug companies are hoping that pharmacogenomics will actually reduce attrition in drugs that wouldn't have made it to market will make it to market because of pharmacogenetics. So they're actually pretty high on it. But whether they're high on it and spending a lot of money or not, so far there isn't a lot of useful stuff coming out, I think.

DR. LEONARD: But part of the issue is that that's not transparent. I mean, it's not out there so that someone other than the pharma company itself is making that judgment about whether it's useful or not.

DR. WINN-DEEN: Debra, I think one issue is that a tremendous amount of the money being spent -- I'm going to be very careful in my wording -- in pharmacogenomics is aimed at finding new targets for drugs and then taking those drug targets forward. This is very different than having a test, a diagnostic test that would predict either response or safety. So the vast majority of that pharmacogenomic spending is on the way, way upstream part of things, and that's where it's been spent for the last four or five years, sort of during the heyday of the Genome Project.

Now we're starting to see some of the things from that effort coming forward, getting to Phase I/Phase II, and now you're starting to see companies having maybe a little more pathway knowledge. Instead of just having a drug that somehow works, they actually have some idea of how that drug might be having its effect. So potentially things are coming along, but I agree with Brad. From what I've seen in my interactions with pharma, the biomarkers to predict safety and efficacy are just not there. There's just not proof enough, and it's not that they're hiding it. It's that they just don't have them, and they're not motivated.

Let's be honest, they're not motivated to do a huge amount of searching unless there is some issue with the drug. If the drug is efficacious in 90 percent of the people they try it on and there's no apparent safety issues, there's no reason to spend a lot of money on those kind of studies.

DR. McCABE: Hunt?

DR. WILLARD: Just as a quick follow-up to that, and then to my original point, Debra, my understanding is exactly yours, but Emily makes a very important point. They're not going to release the data because it's their competitive edge at the early, upstream end in terms of how they figure out which darts are going to be the most likely darts to stick. But you hear it at meetings all the time, that there's tons and tons of data at the front end of this and that the concept is there. So I'm not sure there's much we can do except perhaps bring a few folks from pharma and figure out at what level they can share some of that information with us.

But let me move to my other point on other people we can hear from. It in part reacts to what Reed said. One group within the government to hear from would be CMS. Their pockets may not be as deep as the NIH's, but on the other hand they have an incredibly vested interest in trying to figure out how to best improve the efficiency of health care delivery and reduce health care costs. So it is certainly in their best interest to think about funding, even at the level of pilot projects, albeit large pilots, a few large pilot projects, whether, in fact, this is going to reveal a data set that's going to be of some value. So bringing someone from CMS I think might be useful for the committee.

But also the other group that has an incredibly vested interest is the health insurance industry, not that I'm so naive as to think they're going to voluntarily spend their money to allow us all to collect those data. But nonetheless I think they certainly have a vested interest in trying to reap the benefits of genomic medicine downstream even if they're not ready to do it today.

DR. McCABE: Does CMS wish to comment on this?

DR. SULLIVAN: Yes. I'm sitting in for Dr. Tunis. I'm Dr. Bill Sullivan, the Deputy Chief Medical Officer for the Centers for Medicare and Medicaid Services.

We're very cognizant of that. I've been at these meetings. We're going to other meetings. We're sitting in on other pharmacogenomic sessions in other venues. We are working the best we can to try to keep ahead of this issue, and Dr. Tunis is very much attuned to everything that's going on here. He'll be here tomorrow in person. He might add some more to that.

But our research budget is fairly well defined already. We have a lot of devices that we're looking at that are in the billions of dollars over years -- ICDs, the long-volume reduction surgeries, the left-ventricular-assisted devices, a slew of oncolytic agents which will dwarf anything financially that you will come up with in the near future in pharmacogenomics. But this is very much on our horizon, and it's a topic at our medical technology council.

DR. LEONARD: Can I make a comment about CMS coming? Can they please come also to comment on reimbursement for genetic testing? Because the codes that are used currently for genetic testing are so low for reimbursement, they are nowhere near realistic of what it even costs to do the testing.

DR. McCABE: Do you wish to comment on that?

DR. SULLIVAN: I'm a CPA and an MBA, as well as an M.D., and I think I've heard in the prior sessions and this session that we don't have a lot out there. It frankly is something that we're looking at to see how we should reimburse and should we reimburse for the test that would determine whether someone is going to be susceptible to the drug, or how do we reimburse for the drug. I have something of a dichotomy. I was listening to Reed earlier, and it's somewhat humorous. I'm sitting in the morning approving -- well, I don't approve, Dr. Tunis does -- billions of dollars in cancer drugs, and then in the afternoon I go down to Medicaid and take 20,000, 30,000, 40,000 people off the drill rolls for fecal incontinence.

So I'm a little bit schizophrenic on this because where do you go when you have a drug that's working for 90 percent of the people, and then you have an expensive test that will determine whether some more people will be better benefitted, and at the same time people aren't getting the basic drug? So we are looking at reimbursement. At one of our recent meetings we had a discussion about reimbursement for pharmacogenomic agents, and I think some of the people in this room have visited us in our OCSQ offices recently. So it's very much on our radar. It's not at the top of our radar. We've got a few other things with Medicare reform and Medicaid.

DR. LEONARD: Right, but I'm not talking about pharmacogenetic testing. I'm talking about the CPT4 codes that are used for simply doing any kind of molecular-based test. I mean, you can't do a PCR for $5.71 or whatever the reimbursement is. I mean, it's not realistic. They were set so long ago with no data on what to set them at that unless this is fixed, we're not going to move forward with genetic testing. We may as well stop discussing genetic testing, let alone pharmacogenetics.

DR. SULLIVAN: Well, let me say there's a long line of people in front of you saying that they don't get reimbursed enough. I will be taking this back to Dr. Tunis to see how we can pay more money for pharmacogenetic testing as soon as we get a better handle on how much it should be reimbursed.

DR. LEONARD: Genetic, not pharmacogenetic. And there are only about eight codes.

DR. SULLIVAN: Genetic testing is what you're talking about. Okay. Excuse me.

DR. LEONARD: That's okay.

DR. McCABE: Reed?

DR. TUCKSON: As I try to follow all the balls that are in the air, I think I'm encouraged by what I start to see. First is that as a result of our last conversation, our last meeting, we clearly identified the areas that we've talked about today as being important, and we've learned a lot so far in this meeting. I think what we're hearing is that we've learned enough that we have interest to know more because we think this is important and we think there are some opportunities that the Secretary can use in his bailiwick to intervene.

I think that the work that we have to do next, Emily helped a lot by saying we have to be very clear in defining exactly what it is that we are interested in, and the use of words are important. So I think we have to have some mechanism either before we leave or in a subcommittee on the telephone, but starting to really clarify with more specificity what it is that we are interested in learning.

Secondly, I think it is important to bring with more specificity of questions the people from the pharma industry in to help us to really understand the answers to some of these very specific questions, whether the question is how do you view pharmacogenetics for the purpose of designing new drugs and improving the clinical trials process; and secondly, if I understand Emily's point, how do you use pharmacogenetics as a way of better targeting the use of drugs in their safety and so forth? There are two different issues as she presented it, and I think both of them are important.

I think we ought to specifically try to understand more about the safe harbor issue and

have somebody who really can explain that to us in another level of detail, because I think there's something there that's relevant here.

Third, I think we really do need to have somebody help us to understand better what would be the research infrastructure and the relationship between the public research dollar and the private sector research dollar that would start to answer these questions. If, in fact, as Debra has just taught me, there's a lot of this going on in the private sector, then what is the best way to leverage that so that, in fact, we get these answers, and what is the rational use of public resources given the private sector initiatives? I think that's a question that I think we're beginning to say we're interested in, and I think it's reasonable.

Finally, I think this idea of CMS coming forward to us is also important, because if I understand Hunt's point, what he's saying is let's get the federal government agency reporting to the Secretary which has to make cost decisions and coverage decisions. But where I want to go beyond what my good friend Dr. Sullivan has said is that I think the question we want to ask them is what do you, CMS, need from your sister agencies to be able to answer these questions? I think it's going to be important for us to know what they need. I'm not happy with this being thrown into the CMS research budget.

Basically, the government agencies are supposed to work together, and if we're advising the Secretary, I think what we ought to be doing is helping to provide at least some input for how to coordinate the rational use of scarce public resources to answer critical public questions, and I think that maybe what we ought to start doing is making the CMS person say what do you need from these other people.

As far as the other people who have to make payment decisions, such as plans and others who are also in this drama, I think that also makes sense, but getting them very specific questions about what information do they need if they're going to meet their real-world needs. So I think I'm encouraged that we're moving along a trail here.

DR. McCABE: Emily?

DR. WINN-DEEN: I actually thought that the prioritization comment that Reed made was maybe a place we could start to actually do something concrete. So we definitely would need to understand how and who would fund studies, but we also need to understand, out of all the things that are out there in the global world that could be done, what are the things that are most important to be done, and that's something that this committee I think could work on independent of where funding might come from in the future, and then have something very concrete with some specifics surrounding it regarding what are the criteria to get on the priority list.

Is it known frequency of adverse events, or is it that there's already something in a drug label that refers to a gene but we just haven't gotten a test out for it? What are the things that we could do to move things ahead in a real practical way so that we can make -- I'm very concerned that this committee just doesn't make these sort of broad, hand-wavy recommendations, but we need to make some very specific actionable recommendations. So I thought the priority list might be something we could work on, and I know our friend over here from CMS is anxious to say something back, so I'll stop here.

DR. McCABE: Yes, Dr. Sullivan, and then Cindy.

DR. SULLIVAN: What do we need? Sharing of information among all the agencies, and we're working on this, but there are legal hurdles to that, there are cultural differences. It reminds me of when I was in the military. We had the Army, Navy, and Air Force, and we're all doing the same tasks. We're wearing different uniforms with the same mission. I see a lot of positive developments.

I wanted to talk earlier about how FDA, AHRQ, CMS, CDC were all knowing that we need to work together, thanks to the Institute of Medicine report about federal leadership in many areas, and we're trying to do that. There are a lot of bureaucratic and legal hurdles to that, but that's what we

need. We need to share information so that we can apply it to the benefit of our beneficiaries.

DR. McCABE: Cindy, Brad, and Debra, and then I'm going to actually wrap this up. I'll give you my thoughts on it and then we'll move on to another topic that I think we need to discuss.

MS. BERRY: What would be helpful for me -- and I don't want to bring the rest of the committee down because I know there are so many here who are scientists and physicians and already have this knowledge. But what I'm struggling with is I don't have a good sense as a layperson what is out there already that we know has practical implications for the practice of medicine and improving health and health outcomes, versus what's the big unknown. I realize the big unknown and the work yet to be done is a larger bucket than what we currently have.

But when we were talking about CMS, it occurred to me that perhaps some of the research that's already out there that's proven, the tests that are out there, a lot of that could have practical applications in perhaps disease management, demonstration projects that HHS is already undertaking, and in other real and currently existing programs.

One of the mandates I've always felt this committee has is how can we improve access to genetics, genetic testing and these services to improve health outcomes. So in the first bucket, that's where I would want to focus the attention, to actually work on that. What we were talking about this afternoon I get the sense is more what is the promise of the future, what research has yet to be done, and what is the private sector doing? What can the government do to facilitate additional work in this area? That's what I don't have my arms around.

I don't have a good enough sense of what exactly we're looking at, and the time frame. Are we talking five years, ten years? I realize it will be an ongoing thing. We'll never reach a point where we'll say we've done all we can do, we know everything. That will never happen. But what time line are we talking about before we get to real applications in the health care system?

DR. McCABE: Brad, and then Debra.

MR. MARGUS: I get to answer that question?

(Laughter.)

DR. McCABE: Debra, do you want to answer the question? Go ahead.

DR. LEONARD: I was at the CLIAC meeting recently and Muin Khoury was talking about what the CDC is doing, and they have a very interesting project where they are identifying the 50 highest-impact genes on health care, I mean on actual outcomes. So I think the CDC is beginning to address what are the high-impact areas. I don't think it's pharmacogenetics necessarily, or pharmacogenomics. But as far as genetics in general, the CDC is making an effort to do that, and maybe they could talk about that.

DR. McCABE: Tim, do you want to comment on that?

DR. BAKER: I think Muin offered earlier to come and address a lot of these issues that we're trying to assimilate, the population knowledge and the efforts to fit this into the evidence-based approaches that are important in guiding the kind of decisions you've been talking about here. But we are looking at the project you referred to and characterizing at least the top 50, and we're finding through learning about technology that it's just as cheap to do five of them as it is to do 50. So we're looking at how many gene variants have public health significance and what does that really mean.

But we'd be happy to come and address the committee and describe some of those projects in some detail, but we're trying to take the public health approach and say when does this mean something. To borrow a phrase from our friend Elliott, what do we know and what do we not yet know?

DR. McCABE: Brad?

MR. MARGUS: So Reed, one thing I wanted to clarify was on Hunt's idea on the

CMS. It wasn't about maybe the CMS should -- some money should come out of the CMS' budget to do this. The whole point was that the CMS should have interest because it actually could reduce the amount of money that CMS spends. So the idea is if you had $100 million being reimbursed for a drug that only 80 percent of the people respond to, a very expensive drug, and you had a genetic test that could eliminate or reduce not all of them but a large number of the nonresponders, you'd pick up $20 million or $15 million right there. So if it costs a couple of million dollars to do this study, it's a no-brainer that you ought to do that study to find the markers that could cut your cost.

I would say that means it hasn't been done yet, Cindy, and we'd like to have it already done and saying there's an obstacle here, let's get that test out there right away. But at the same time, if the technology is getting to the point where you can do it, I think we can have a role to also say let's make sure that people are working on getting those answers so that they can be applied.

I think it would be great if the CMS -- I don't know if it's possible, if the CMS came back at another meeting and said here are the top -- I don't know if you can do this, but here are the top 50 drugs you reimburse for by the dollars each year that you reimburse, and of those, here are the response rates, and you look down that list and you see in many cases clinicians thought it's 90 percent or whatever, but in some cases it's only 50 percent. That's where pharmacogenomics could be applied.

Not only would we all be much more excited about it, but that would also give tremendous teeth to any recommendations we make about why pharmacogenetics needs to be pushed and why the FDA needs to work with you, and maybe even the NIH has to chip in too. But that would be a concrete thing, to see where there's really value in it.

DR. McCABE: That's a great lead-in to what I wanted to talk about next, and that is what I would like to do is ask for volunteers to join a task force, not a working group, not something that's going to take on a life of its own and last for the next year or so, but a task force to get together and try and identify and prioritize these issues and really identify among the issues what CDC is doing, what we're hearing that pharma is doing, what Debra mentioned about reimbursement, because it's all academic if we're not going to have any molecular genetic diagnostics labs because they've all had to shut their doors.

But of the topics that we've just talked about, coming up with prioritization and where this committee could really have an impact. So we'll be accepting volunteers, then, at the end of the session today. If anybody wants to volunteer publicly now, feel free. I certainly think that a few of the agencies have been involved in the discussions. I hope they will volunteer, like CDC, CMS, NIH. They have certainly been a big part of these discussions this afternoon.

DR. SULLIVAN: CMS volunteers.

DR. McCABE: But then the others I won't be so Draconian in naming names. But since Reed is always speaking up so much --

(Laughter.)

DR. TUCKSON: I volunteer.

(Laughter.)

DR. LEONARD: Could you clarify how this task force will do its work, as opposed to a work group?

DR. McCABE: First of all, I think of a task force as --

MR. MARGUS: False advertising.

(Laughter.)

DR. McCABE: I think of a task force as having a much shorter time horizon. We had work groups in the predecessor committee, and they seemed to go on and on. This is really to just help us organize and plan for our agenda for the future. So it's not coming up with a work product. It's just to

really help us gather from all of you in a group that's smaller than this committee so it can really help to set our agenda. So that's what the purpose is, really to set the agenda.

The other area that I want to be sure that we cover because it also, when we were talking about it, had a lot of interest, and that has to do with the oversight of advertisement and promotion.

Debra?

DR. LEONARD: You posed the very first question, and we went off on the pharmacogenetics tack -- not tangent, but relative to the question you had asked. You said does this committee want to focus on oversight or is CLIA, FDA and FTC doing okay with oversight? I think this is a really crucial question to me. If it's not important, we can just take a yes/no vote and then be done with it.

DR. McCABE: No, that's fine. But I do want to get to the DTC stuff also. I don't want that to be left on the shelf this afternoon.

So do you wish to weigh in on that question? You clearly have an opinion.

DR. LEONARD: I say this committee doesn't have to focus on oversight. But I think that CLIA, FDA and FTC -- I mean, CLIA at least, and FDA are regulating what they're regulating. I find that the fringe is the problem, and I don't know that we need more oversight of what's being done because I think it's being done well for those that are following CLIA and being CLIA-certified laboratories for the most part. So that's just my opinion.

DR. McCABE: Well, I think that I probably shared my bias in a Freudian way, probably by skipping over the oversight issue, having seen the predecessor committee get really bogged down in that, seeing that CLIA and the FDA are moving forward. And also I shared my bias at our last meeting that I think labeling is an important part of education, and I see it also from the presentations that labeling is getting a lot of attention as well. So I agree with you. I think that in terms of those processes, they're moving forward. I agree with you also that the problem, as always, is the negatives, those who aren't CLIA-approved, those who are not a part of the process and how does one include them.

DR. LEONARD: Right. I just wanted a definitive statement from the group.

DR. McCABE: Hunt?

DR. WILLARD: I would support your definitive statement, with one exception. I think before we leave it, this committee could provide a service to the Secretary and to those agencies by coming up with a crisp statement of to what extent -- and I've alluded to this several times today -- to what extent genetic and genomic testing is different and therefore deserves special attention from them, as opposed to just do your job. What aspects of it are the same as everything else they're doing, and which aspects really deserve to be flagged?

I think we're the group that can do that, because otherwise every single agency is examining that question from the ground up. We could advise the Secretary on that point, where it deserves special treatment and where it absolutely doesn't deserve special treatment.

DR. McCABE: Debra?

DR. LEONARD: And if you look, for example, at CF screening as an example, the issues that have been raised with CF screening since it's been implemented have been in the post-analytical phase. I don't think there's anything that CLIA is going to do to regulate a laboratory that's going to improve that post-analytical phase of interpreting the result properly to the patient. So that gets us to the topic, one of the prime topics that we had targeted and that we'll be discussing tomorrow, which is education and how you educate physicians to communicate results properly.

Laboratories know an awful lot about that, and so they can help physicians, but physicians sometimes don't ask and sometimes that information isn't communicated. Even when it is, then

on the next generation communication to the patient it's not communicated properly because the person in the middle, the physician, the other health care provider, doesn't understand really what the laboratory is telling them.

DR. McCABE: Steve, do you want to comment? Because one of the messages I got from the presentations was that your focus is on high-risk tests, not so much on genetic tests, except to the degree that they're high risk.

DR. GUTMAN: Yes. The internal discussion that was sparked by SACGT was one which stepped back and thought that while there are clearly unique features about genetic testing -- many genetic tests you might order only once, and many non-genetic tests you might order endlessly. But it was our general notion that the issue of ASRs and/or the issue of home brews was one which was better approached either generically or device by device on the basis of risk per se, not its specialness as a genetic test. So at least the deliberations that are going on now, long as they may be and as big a struggle as they may be, are trying to focus on the general principles of risk that the entire device program is based on.

DR. McCABE: Reed?

DR. TUCKSON: Yes, I would agree with you, Mr. Chairman. I think that we don't want to get overwhelmingly bogged down in revisiting all that work on the oversight of CLIA and so forth. I was particularly heartened to hear how much the predecessor committee to this one, their recommendations are alive and are part of the fabric of what's going forward. So I think that's terrific.

If I understand Hunt's point, which I think I like, I'm not sure whether you were saying we should do it or ask the Secretary to do it and report back to us, but at some level defining, then, based on all that we now know, what are the special areas of concern which merit attention, and then to be able to determine from the agencies how well are we doing now in being able to attend to assuring the public that those concerns are, in fact, being well addressed.

I think that's very specific. I think it doesn't put us into an awful lot of complexity. It's just saying where are the danger zones here based on where we are today in genetic testing, and then based on what we know, with all the oversight that is going on, what are the danger zones, and what do you consider to be -- do you know if you're in danger? I mean, what are the data points that you're looking at? I mean, that's the question that we didn't get answered this morning.

What are the data points that FDA, CDC, and somebody --

PARTICIPANT: CMS.

DR. TUCKSON: CMS. Thank you. What are the data points that those three organizations -- and by the way, again, what I keep getting nervous about, even though at some level we know it's not true, but CMS has their issues, FDA has their issues. At some point, what is the Secretary's office, whoever is like the superstar monitoring all this, what does that person who has a little checklist saying we are going to be in deep doo-doo if the following things are happening, what does that list look like? I just want to know what that list is, and then find out how we're doing. That's all I think Hunt is ultimately saying. If that is what he's saying, then I think that's all we want to do is get that report.

DR. McCABE: Emily?

DR. WINN-DEEN: So I guess my reason for getting into public policy and out of just the lab is that I think we need to think about how to take the promise of the Human Genome Project and make that promise a reality. We have to affect the health of our society. We didn't do that just -- it's cool that we've got the sequence, but if we don't do something with that, then we've really spent a lot of money, our NIH money, on something that isn't benefitting society.

So what I would like to see us do is really to look carefully at what is the current landscape, and I think that the reports that we had last session and this session have gone a good deal into

telling us where are we today, and then I think this committee could really help the Secretary by saying where do we want to be, where is the promise, and what are the gaps, what are the barriers. Is it that we need better reimbursement? Is it that we need more translational research? Is it that we need better, friendlier guidance from FDA? Which are all things that we've talked about. There may be some other things.

Then we can make specific recommendations about what the Secretary could do to move us from where we are today to where we want to be in the future. I think if this committee could get focused on -- I mean, first we have to have the information to assess where we are. I think we need some external experts to help us describe where we would like to be, and we can set a time horizon on that, five years from now, ten years from now. And then let's identify some very specific steps that could be taken with the right federal support.

The Genetic Non-Discrimination Act is one thing. Physician education. I mean, we have to prepare every aspect. We can't have the consumer being afraid of the testing, we can't have them being misinformed, we have to have educated health care providers who know how to do it, we have to have good validated tests, we have to have qualified laboratories to perform them. There are many, many things that all have to be in place to make this a reality, and I think it's up to this committee to try and identify what is that vision that we're striving for, and what are the steps we need to take to get there.

DR. McCABE: Hunt, you started this off.

DR. WINN-DEEN: Sorry, Hunt.

DR. WILLARD: Well, my fear in responding to Reed is that maybe there is no one in the Secretary's office who has that deep doo-doo list that you want to get your hands on, and in part we're the group who is going to both say someone needs that list and here's our best thinking on the items that ought to be on that list or should not be on that list. My fear is if we simply say oversight is being taken care of and move on, that we will have missed what I view as an obligation to try to clarify those issues and really define which things you shouldn't be afraid of, because genetic testing isn't uncovering any -- you know, this is the brave new world -- and where might it be the brave new world and the public's ill ease is perhaps well-founded and it requires more study.

DR. McCABE: Well, that's a nice segue to think about another thing that we raised at the very beginning today, and that was about taking the minutes from the first meeting and whether we turn that into a report. If we say we'll wait until we get the minutes of this meeting, I'm afraid that will delay it, because we'll wait until the next meeting to approve the minutes for this meeting.

But what are people's thoughts about turning at least the minutes of the first meeting into a report to the Secretary? Because we began to lay out some of the issues and certainly said we needed to hear about the oversight and the progress in oversight at this meeting. Any thoughts on this?

Debra?

DR. LEONARD: I think a report would be very useful to the Secretary as long as it was no longer than two pages. You've got a tone in there -- he's never going to read something like that, I don't think. I don't know him personally. So I would think that whatever report is generated, it has to be very brief and targeted.

DR. McCABE: There will be a one-page maximum executive summary.

So do I hear any objections to turning those minutes into a report that we could bring back to the next meeting, discuss at that meeting, and then take any suggestions from the next meeting and incorporate those but move them forward? So there would be some documentation and work product, and there will be additional prioritization that will come from the task force. But at least it will begin to have us thinking about priorities.

DR. LEONARD: I think that the executive summary is also over time. I mean, this committee is going to have a life. It's useful to be able to look back at what we've discussed and refresh and see what we've missed when we're moving ahead.

DR. McCABE: And also it's good to see the cycle, as Elliott Hillback pointed out from this morning's conversation. He's been talking about these issues since 1991 was it, Elliott? And they're continuing to be the same. So it's important for us to document so that we see the same topics coming up, and that helps us know where to focus as well.

So we will also take that as guidance from the committee, and Sarah and her staff will work on putting those minutes in the form of a report that we will bring back to the committee at the next meeting.

Hunt, did you get satisfaction on -- okay.

Now I do want to talk a little bit about advertising and promotion of genetic testing, because that was an area that people seemed quite interested in at the time we were discussing it. So where should we go from there?

Oh, by the way, we won't drop the oversight issue. We will continue to monitor it. We enjoy seeing Steve at these meetings, so we wouldn't want him to disappear and not come back to brief us. So we will continue to be updated on oversight, but I think it's my sense of the committee that that doesn't need to be a highest priority issue, that it will be more a monitoring task on our part at this point. Should we feel that it's gone astray, we will certainly discuss that, but I think quite the opposite from my view. I feel that I'm really pleased with how it's moving forward.

Hunt?

DR. WILLARD: My concern is that if we simply monitor it, we won't do what I tried to articulate, which is to actually as an action item come up with a statement of where is genetic and genomic testing different and where is it not in terms of an actual report or action item of this committee to allow the Secretary and all the various alphabet soups of agencies, to help focus our attention given our best recommendations.

DR. McCABE: Sarah was commenting what I was also thinking, and that is I think that's important to have in this first report. I'm not sure we'll come up with full agreement. We never came up with agreement on the SACGT. The discussion was some of the things that people thought were the same other people thought were different. But we can certainly come up and frame the issues and at least where we agree and where we are willing to disagree on these issues. That may be important as well.

So I think probably from the discussions that we had with SACGT, as well as we review the transcript from this meeting and your comments and the comments of others, Hunt, that we can begin to frame those issues, and then we can make that a point -- I'm sure that will be a point of discussion at the next meeting, to firm those up. Is that okay?

Back to the advertisement and promotion.

Yes, Chris?

DR. HOOK: This is an area that I have a lot of personal concern about, but as Brad very eloquently pointed out, direct-to-consumer marketing isn't necessarily a bad thing. It all depends upon how it's done and the nature of the test and so on. But that involves a number of complex requirements, such as informed consent, can informed consent be done simply by checking a box on a computer screen when all of us know, who have to obtain informed consent, it usually requires much more open-ended questions to ensure that the patient or the prospective individual truly understands what they've put their name on, and ensuring that the counseling mechanisms with the results are available and how can that be ensured.

I'm not sure that that's something that this committee can articulate, but I think that the industry would have a significant interest in making sure that there were mechanisms in place, and it might be -- I don't know if I'm imposing too much on Elliott or others from BIO to perhaps give us a model to shoot for of what would be doable and achievable by those who would want to market things directly and how they would be able to ensure that the concerns, the basic concerns are met.

DR. McCABE: I'm past president of the American College of Medical Genetics, and I know from our board meeting that the College is working on a statement. It should be published early next year, I'm not sure how early in 2004. But it might be one of the things we might do is to invite the American College of Medical Genetics to at least discuss, if they haven't published their statement yet, at least where they are and some of the background to that.

Yes, Reed?

DR. TUCKSON: Two things that I think we heard today -- and again, I just really think that the presentation of the FTC was just terrific, and I think his openness was commendable. I think what he's basically saying is send me, send our agency some areas of concern and prioritize those a bit. Send us some of the things that we as a committee and/or professional experts like the American College and others, that you feel represent important things, potential egregious sins that ought to be looked at. I think he's sort of asking for that. I'm overstating, of course. As a government agent, he's not allowed to come and ask us that, but whatever.

Anyway, I think he's really interested in this issue, and I think we ought to send him something. I think we ought to say, whether it's Francis' example on the nutriceuticals, maybe what we need is a couple of people again just in a little small group to determine what the priorities are. Should it be one that's based on nutriceuticals or one on face cream? I mean, clearly we had that good discussion, so maybe there ought to be some categorization of what makes it more important than others.

But they want to get started looking at this, and I think we ought to at least start them on that, and I think we also ought to solicit from the American College and from responsible manufacturers who have seen corporate competitors do scurrilous stuff that makes the good guys look bad. Maybe they can give us some examples.

The second thing I thought he was particularly good about is the potential of at least exploring as one of our future goals some kind of education of the public, which could be part of some of our other public education themes which we'll discuss in the coming days, something that sort of says how do you as a mature and responsible consumer wade through some of these advertisements in this area, and just give them some keys and tools and tips that would help them do a better job of using their native intelligence.

DR. McCABE: Yes, Barbara?

MS. HARRISON: I was sitting here and came across the article in Genetics and Medicine about direct-to-consumer marketing, and it kind of seems there are two different issues. One is what Dr. Tuckson was talking about as far as junk DNA, false DNA type of testing. But the other is legitimate testing that's done that's offered to consumers over the Internet without having to have a physician or a genetic counselor involved, and they describe in here a test that's done for $165 for hemochromatosis testing with no need to go through a physician or any other kind of health professional.

I don't know under whose purview that would be, and I don't know if we can put a recommendation toward that.

DR. McCABE: The issue about whether or not direct ordering of tests, which is really different than direct-to-consumer marketing, though I would argue that if you don't know that you can order a test directly yourself, then you're probably not going to do it. So if you're going to have a business plan,

you have to have some direct-to-consumer marketing as part of that. In point of fact, I think the College statement focuses more on direct access without a health professional being involved.

It turns out that's a states issue. It's not a federal issue. But that has to do with state rules about how medicine is practiced in their state, and different states have different rules about that. So that gets to be a little bit difficult for us who are advising the U.S. Secretary of Health and Human Services. But I think we could discuss that and have the College bring that and really focus on that.

Emily?

DR. WINN-DEEN: I guess what I'd like to see, and maybe this is in the ACMG statement, is some kind of guidance on -- there may be some things that actually a consumer could read about on the web, click a box, consent to, get their results, and there would really be no harm. I'm not sure what those are, but let's hypothesize that there is something. What we could do maybe is start to create a list of things that would never be on that list, things that aren't on that list today but might move there in the future, and things that might be okay to be there, in much the same way that we consider through FDA right now what things are allowed to be marketed over the counter to individuals for home testing.

You're allowed to home test for pregnancy. You're allowed to home test for glucose. You need a doctor's prescription to get the meter, but you can then do it yourself. You're allowed to home test for coagulation, again with a doctor's prescription. So how do we create some guidance document about what criteria would be used to put things in those different bins? It may be very similar to the criteria that we outlined in the low-risk, medium-risk and high-risk genetic testing, that there certainly are things that never, ever should be done without counseling involved, but we're going to face this issue in not just direct-to-consumer testing but in how much time and energy the limited number of genetic counselors can put into things as we get more and more things rolling out that are genetic-based tests and how to put our scarce resources on the right things and roll informed consent and education about testing out to a wider variety of health care providers.

So I think at some point we're going to have to start putting this list together. I'm not sure, maybe this isn't the right group to put the list together and maybe we should defer to ACMG, but I personally think we're going to have to do that.

DR. McCABE: I only mentioned ACMG because I have insight and knowledge from being at the board meeting. My guess is that it's not the only group that has discussed this. If there are other groups that have discussed this, I would ask them to notify us and we can include them as well.

DR. WINN-DEEN: But the other direct-to-consumer thing that I'll just bring up is so what if you don't market the test directly but in the drug store is available a buckle swab sample collection kit that you rub your cheek, you send it in? I mean, you could envision that some of these things could be done by a very reputable lab, not a home test for genetics, not a home CF test, but you could get the information and it could be done by accredited lab professionals, and what comes back to the consumer could be a report with a very nice explanation of what the results mean to you and how you should use that in your future health.

I think we need to explore whether that's going to be needed as part of making access available to a wider variety of people.

DR. McCABE: So one of the things we might do is try and identify groups who have been thinking about this and may have begun to consider these kinds of lists to present, and I saw some body language indicating from the audience that other groups are working on this as well. So please let us know if you're working with a group, whether it be a consumer group, a commercial group, whatever, so that we can include you in the next meeting.

Brad?

MR. MARGUS: Back in 2000 during the genomics bubble, I personally was shown at least 50 different business plans for businesses that would be typically web-based, because that was the rage, and genomics, which was the rage, and there was venture capital up the wazoo for those opportunities. They included everything from you go into a store and get a little test kit, anonymously put your cheek swab in, send it in, and it has a password. Three days later you get online and you can log in anonymously and see what the results are to whatever it is they're going to promise you, and then over the future more tests will be available as long as you have a credit card, and you don't have to take a sample again because (inaudible).

There were kiosks in malls that we would have where they'd take your sample and three days later you'll get your stuff. Sometimes, when we thought pre- and post-test counseling was important, you needed at least someone in a white coat, so it was under the Lenscrafter model in the mall, where you'd go in and there'd be a booth where you could privately talk to your counselor before and after.

Some of those were probably legit, and the idea was that the sequence of the genome was almost done and there was going to be such a landslide and waterfall of genetic information that the current infrastructure of physicians and counselors could never handle it, and it's all converging and you should take advantage of it. Maybe fortunately, the capital for all those ideas ran out, and so nothing has happened. The only thing that has happened is the content, the things you would test for that you could tell people anything useful or actionable hasn't come along as fast as people had hoped.

But I assure you, there were lots of innocuous, entertaining, good science genetic ideas that were out there. One was we can test you and your three siblings and tell you which sibling you're more like, things like that. Have you seen the market data? All you need is one-tenth of 1 percent of people to want to pay for that thing, and if you extrapolate over the U.S. population, at Christmas time it's a great gift for marketers to have in the catalog.

So the opportunities are out there, and I'm just hoping that some real content comes along so that the junk science isn't sold or given a bad name.

The one thing I wanted to say is if you do have this question, in the future there is going to be genetics delivered directly as well as through the traditional channels, so how can you insure some standards? Well, I imagine there must be a lot of models out there. So those of you who know that I have a strange background know that I used to be in the seafood business. I'm like Forrest Gump in shrimp.

But in that industry -- and unfortunately I think the USTC guy is gone. But in that industry it's a particularly slimy industry in more ways than one and people cheat a lot, and there's a lot of bad stuff out there. And yet the fine restaurants want to know where to buy good things from, and there are standards.

The USTC has Grade A, right? In other industries you have Good Housekeeping. So you could imagine, I think, the day coming where some agency or someone promotes a particular label like that, or a Seal of Approval, and if you're a website with a legitimate thing -- and who knows, maybe even Roche will have a website someday selling good stuff. But if you have a legitimate test with really good science behind it, you can get that Seal of Approval, and it's been advertised enough so that consumers trust it.

The big problem then comes with two things. One is the responsibility. What we heard today is there's kind of a gap that doesn't have to do with people being really, really sick, or if it doesn't have to do with a test that you sell or the reagents you sell, then nobody seems to be responsible for those things, so that's a big problem I have. The other problem is, of course, this thing about "good science." I can only imagine us putting 50 scientists in a room to decide whether a particular thing is good science or not. That's going to be a big challenge.

But I think if you can reach some standards on that thing, there are ways to convey to consumers what's real and what's bogus without actually killing the idea.

DR. McCABE: Other comments? I think we've gotten some guidance for the next meeting.

Debra?

DR. LEONARD: Just two points. One is I was just at a meeting called Lab Institute. It's by G2 Washington Reports, and there was a whole section on direct access testing and exactly what you're saying. In Seattle there's a company that goes around and collects your specimen and in three days you get your results and you can pick them up. In Nebraska there's direct access testing in a mall with the white coats. Actually, they make it more like a living room setting so the people are more comfortable walking in. In New York City they have one.

So these are people who are actually doing direct-to-consumer marketing of tests, but I didn't hear any genetic tests on there. But they were regulated by state regulations, like Ed was saying. So this is coming, and I don't know what's happened to all the genetic ones, but it's being done for other kinds of testing, and we may be able to learn what they're doing. I could get Sarah the names of people.

The other thing everybody keeps talking about, informed consent, if you're doing direct-to-consumer marketing of genetic tests, informed consent is something that we say is needed for genetic tests, but my question is will informed consent become less important with the genetic non-discrimination laws if those are passed, since a large part of genetic counseling is describing the risks and benefits, and the risks as well as the interpretation of the test? I think interpretations of tests could be provided. I mean, we do this with CF screening. It's a little piece of paper with ten lines on it that ACOG created that describes what you're doing when you're getting CF screening, and many tests could be done in that same way.

One of the things we need to think about is how important will informed consent be when every test you do in medical practice is a genetic test because genetics is part of everything medical, and can we continue to require informed consent for genetic testing, which gets to what Hunt keeps pounding on, is genetic testing really different than other kinds of medical testing? Informed consent is one of the things that sets it apart, but that's historical because genetic tests were relatively rare. Single-gene diseases are still.

So I think we need to think about informed consent, as to whether that's something that we'll continue to need in the future or can realistically do in the future.

DR. McCABE: I think, again, I would refer you back to Fred Ledley's commentary that was in Nature Biotechnology, which is in your packet. I don't know if it's age or what, but the concern about direct access, there will be direct access. The movement of autonomy, the movement away from a health professional controlling our access to medicine, that's well on its way, and this is really one of the things that Fred talks about in here is direct access to testing, personal control, generate data to guide consumer choice. It's the natural course of things.

So I think it's really important that we chart that course and that we recognize where the Class 4 rapids are in that course, because it's going to happen. It's part of the whole -- it started with the printing press, and now with the Internet, and people want more control and have more access to information. So we need to recognize that, but then also identify where the problems are there. So I think it's a good idea if you can get Sarah some of the names so that we can learn from other areas that will be very important.

Other comments? Are there other areas that I may not have picked up on that people feel are critical that we take up within the next meeting? Or we may have given Sarah enough for the next two meetings here. But I know one had to do with the breadth of genetics, how broad is our charter. Debra

has just said that everything is genetic, and many of us feel that there's certainly something to that.

DR. LEONARD: Will be.

DR. McCABE: Will be. Well, some of us think it already is, we just don't realize it yet. But I think the charter was pretty broad. I see the discussion which really has to do with the limits or even existence of genetic exceptionalism being discussed next time, taking that up. Even though our charter is broad, what do we choose to focus on within that charter? So I think we will discuss that at the next meeting.

Our 5:00 guest has arrived, but are there any other issues that people wish to make sure that Sarah highlights from today's discussion? We'll have more tomorrow.

(No response.)

DR. McCABE: I think the education, workforce, some of these issues were coming up, and they will be informed by tomorrow's discussion as well.

Okay. Let's move on, then, and I think we have had a very profitable day today and have learned a lot and are beginning to help focus the committee.

So now we're going to turn to an update on the status of federal legislation to prohibit genetic discrimination. We're delighted that Ms. Kristin Fitzgerald, who is with the House Committee on Education and Workforce, is here to brief us about prospects for passage of genetic anti-discrimination legislation by the House of Representatives. Ms. Fitzgerald has worked on Capitol Hill for almost 10 years. In June of 2001 she joined the staff of the House Committee on Education and the Workforce, chaired by Representative John A. Boehner of Ohio, and has primary jurisdiction over employer-sponsored pension and health benefits.

Before joining the Committee staff, Ms. Fitzgerald held leadership positions in government affairs and directed grassroots efforts for the Health Care Leadership Council, a coalition of the nation's leading health care companies and institutions. In addition to genetic non-discrimination, the focus of Ms. Fitzgerald's work during the 107th and 108th Congresses has been the Patient's Bill of Rights, the Mental Health Parity Act, the Pension Security Act, and the Small Business Health Fairness Act, among other issues.

Ms. Fitzgerald will give us a brief history of the House's actions on genetic discrimination and give us her perspectives about the Senate bill and how the House will proceed. I'd just like to point out for Ms. Fitzgerald what I mentioned earlier today, and that is that this has been a leading priority for this committee and our predecessor committee, the Secretary's Advisory Committee on Genetic Testing. So this is a very important issue for us, and thank you for coming this afternoon.

MS. FITZGERALD: Well, thanks for having me, and I would like to compliment you on your timing. When you first talked to me about speaking, I thought, oh, this is going to be really easy because I'm going to say, well, the House is likely to follow the lead of the Senate until the Senate acts.

Well, lo and behold, one week before the speech we have the Senate passing the legislation on genetic non-discrimination with a vote of 95 to zero. So it's really nice timing, and it's good timing I think for you all to focus a little bit on the House side.

Definitely the Senate's actions have vaulted this issue to the top of our list. I hadn't heard too much about the issue this year, but the day after the Senate passage, or even the day of the Senate passage I feel like my desk is -- every person that calls, that's what they're calling about and they want to know what we're thinking and what our views are and all those kinds of things. So it has definitely become an issue that I think we're going to be spending quite a bit of time on.

In terms of talking about the House perspective, I think it's easier to do that by talking a little bit about the background on both the House and Senate sides. This is not a new issue, as you all

know. There are lots of different state laws that focus on this area in all different aspects of it, the privacy aspect, the insurance aspect, the employment aspect, and Congress has also looked at it in the past a little bit with the HIPAA law, the Health Insurance Portability and Accountability Act that prevented discrimination on a number of different health status factors, but including genetic information.

That was probably the first time on the House side that legislation passed that addressed it in terms of the discrimination aspects of it. The Senate has been a little bit ahead of the House in looking at the issue. Both times that the Patient Bill of Rights passed, I think two years ago and maybe three years ago, or maybe it's two and four, I'm not exactly sure, it kind of all runs together, but they adopted amendments that would have, addressed this in the health insurance area.

I think the House had not spent as much time on it, although admittedly on both the House and Senate sides there was legislation sponsored by Representatives Daschle and Slaughter that would have prohibited genetic discrimination in employment and in health insurance, and those had quite a bit of support from rank and file members of Congress, both on the House and Senate side, but particularly on the House side.

I think the issue or the actions that really sparked the House's attention was the President's radio address in, I think, June of 2001 where he talked about supporting legislation that would go forward and that would protect genetic privacy and ensure against discrimination, and that really caught the House's attention, and shortly after that address there were three House hearings, two of which were at the Education and Workforce Committee and one at the House Energy and Commerce Committee.

But the hearings, I think, investigated the state of play, looked a little bit at the science, looked a little bit at the current laws that there were and how they did and didn't address the issue, looked at the current proposals, at that time the Slaughter bill and the Daschle bill, and how there may be impacts of those particular pieces of legislation, unintended consequences, those kinds of things. Then the Senate has gone on from that, and I know this isn't news to you all but they've spent an exhaustive amount of time working on this bill. I think they negotiated probably two years to come up with bipartisan legislation that had the support of all the Senate and the President to prevent discrimination.

So it's not surprising to me that the Senate acted because they've spent a ton of time on it and they voted on it in the past, and it is sort of a more mature issue on the Senate side being that they've considered it several times.

The House, we're a little bit behind on this, but I think we're starting to catch up. I think members of the House see this as a unique issue both on the employment side and on the health insurance side. Typically when I work on health care issues, there's often very strong feelings on both sides, a lot of opposition and then a lot of support. But people who are opposed in viewpoint on this particular issue, I think that everyone believes there shouldn't be discrimination on the basis of genetic information, and so there's agreement, and it's the same kind of thing on the employment side.

People do not believe that there should be discrimination on the basis of genetic information. That's different than when we've acted in the labor area before and in the health care area before. It's just there's a lot of folks that are in agreement about the goals, and I think that's a positive thing about the issue.

Another area where it's a little bit different than perhaps past actions is that when Congress has acted, particularly on the employment side, to ban discrimination, for example, on age or race or religion, there has been typically patterns that they're trying to rectify. If the Congress goes forward in this area, it seems as if we're a little bit on the protective side before there are huge discrimination cases, that kind of thing. Congress will be moving forward in an anticipatory way to protect people on the basis of their genetic information, and that's a little bit different than perhaps other types of labor laws that we've

looked at in the past.

I think another area that is unique about this that is a challenge for legislators is just the science, the fact that before we even have ink dry on any kind of bill, the science will have changed and will continue to evolve, and these statutes that we're looking at as models, they tend to be, particularly looking at the civil rights laws, ones that stand. I mean, we're not spending a whole lot of time every Congress going in and reauthorizing, for example, as we do in some areas. They are the laws of the land and far reaching. So it's a little bit more complicated looking at this issue, simply because we know we don't understand the science and that it will continue to evolve. So you just have to have legislation that's nuanced enough to anticipate that.

I think right now what the House is doing is evaluating the Senate legislation, and I think that, first of all, the House looks very positively on the effort that went into the Senate bill. I know that my counterparts on the HELP Committee, they have shared jurisdiction over a lot of our same issues, worked very hard and very diligently for a long time to rectify a lot of concerns that folks had about past legislative proposals, and I think some of the areas where they definitely made improvements that we had been concerned about are, for example, on the employment side, just following the patterns that we've set with regard to EEOC enforcement and damages and sort of conforming them to the way the other labor laws look in that area.

They looked at the issue of disparate impact, whether or not there would be disparate impact suits allowed. That was one that we had pondered a little bit in looking at the Slaughter legislation in the past. It seemed to us that were you to allow a disparate impact suit, that you were actually in effect creating an incentive for an employer to know genetic information to protect against such a suit. So I think it was very positive that they were able to look at some of those issues and come up with solutions that would prevent those kinds of things.

I think they also made improvements on the health care side. The Slaughter bill and the Daschle bill had really tight use restrictions that we were concerned about. For example, you could use the information that you had to pay a claim, but if you were subrogating a claim, that was not quite payment of claims, and different kinds of things. I think the HIPAA privacy regulation had spent a long amount of time working out what uses were allowable for health care information, not to disclose but in order to use the information for those kinds of things. I think it was important and good that they tried to conform to the HIPAA privacy reg where they could.

I think they've also gone a long way to try to look at the dual regulatory issues. I don't even know if you can say dual. It would be more like tri or quad regulatory issues that you come across when you're working with a lot of different agencies that are overseeing various people but with similar kinds of responsibilities, and where you have a little bit different kinds of restrictions here in privacy, a little bit different here in the bill. I mean, those are things where the regulators are really going to have to work together, and I think they've done a good job trying to anticipate that.

I think that the House is still, though, looking at the Senate legislation and trying to investigate all of the various details about it. For example, we're looking a little bit at how exactly you cross over when you have a new piece of legislation that has a health title and an employment title. We haven't done that in the past. You can make crossovers with the Americans with Disabilities Act and, for example, the Mental Health Parity law that Congress did, or even the HIPAA law. But they weren't adopted in this model where we set forth and said this is one title and this is how we're going to deal with an employer when they're an employer and this is how we're going to deal with a health insurance plan. So that's something that we're looking at, just how exactly those kind of work together.

I think that we also are still looking at how the bill does interact with both the HIPAA

privacy reg as well as the HIPAA protections, the way the Congress protects and the way the law protects folks who have health status factors, how this will impact group premiums, for example, because it does make a change there, those kinds of things. We're taking a look at that. I think we're looking a little bit at how genetic information, how genetic tests, all those kinds of things, how they're defined and how that will impact someone's current medical information, as opposed to what might be some kind of predictive information and just kind of what the interplay will be with the various titles of the bill in terms of those definitions.

I think another aspect of the House that is a little bit more complicated than the Senate is the issue of jurisdiction. Over on the Senate side, the HELP Committee has jurisdiction of the bill and they've done a great job working out their version of it. On the House side, we have three committees that have jurisdiction over the bill, the Ways and Means Committee, the Commerce Committee, and our committee. We have jurisdiction over the health title and the labor title. The other committees focus on the health titles.

But any time you have more cooks in the kitchen, it takes longer to develop the recipe. So I think that will be a factor also in the House, that all the committees have to take a look at the bill, all the committees have to ask their questions, all the committees have to evaluate the consequences of various parts of the law. Those other committees particularly are working as we speak on Medicare, and I think that's going to be a factor, at least in terms of the prospects for the year.

So in terms of looking at the outlook for the legislation in the House, I'd say that particularly given that we're supposed to be done by November 7th, and I continue to say that because I hope we are -- I don't know if we will be but that's the target adjournment -- that leaves us two legislative weeks with about two legislative days, because I think they're in about one or two days each week. So that means that this is not an issue for this year. Certainly staff will be spending a great deal of time and are already spending a great deal of time looking at the bill and looking at the issues surrounding the bill and evaluating it and hearing the statements from various parties who are interested in it from a variety of different perspectives, and I think that's what we'll spend the majority of our time doing this year.

And then I think during the following year folks are still making decisions about how this will proceed. Certainly it's something that I think will go in a regular order process, meaning that we'll spend the time to do the hearings and the kinds of things that are necessary to inform the Congressional members about the issue and that kind of thing. I think that will determine how the House proceeds and what the perspectives will be for the coming year on the issue.

So I think that's kind of my view for the House perspective, but I'm happy to answer anybody's questions about the bill or thoughts about it.

DR. McCABE: Well, thank you very much for taking time out of your very busy schedule. Now we hear how busy it is than we even appreciated before this. We also know that the spotlight is on the House with the unanimous passage in the Senate, but we really do appreciate you coming.

We're now going to have a roundtable discussion, and Cindy Berry is going to lead that discussion.

MS. BERRY: Welcome, Kristin. Good to see you. Thank you for being here.

I'll kick it off with one question. I have a few others but I want to pass the mike around, so to speak, because I know people are very interested in this issue on the committee.

We are hearing and have read about in the media some angst, I guess, among some folks in the business community about this legislation primarily. At least I'm hearing that this isn't really necessary because it's kind of a remedy in search of a problem and the problem doesn't exist. In this

committee we have heard a lot of testimony and were presented with a lot of information indicating that the problem isn't necessarily evident, that people have a certain fear factor and therefore don't seek the appropriate genetic services that they may need out of a fear of discrimination. It's not that the discrimination has necessarily occurred, but it is serving as a barrier to important services.

Is that the only opposition that you're hearing? Is there a major objection or several objections that are being raised to legislating in this area beyond that, beyond the issue of, well, it's not really a problem?

MS. FITZGERALD: Well, I think anytime Congress moves forward on legislation, they want to be sure of the problem that they are solving or of the consequences of the actions that they're taking legislatively. So I would say that there are some who are looking at the track record or lack of track record compared to the other -- I know there have been some cases of genetic discrimination, but compared to the track record of the other employment discrimination laws that we also might have looked at. There are some that are expressing concerns about that.

I think that employers and all parties who will be impacted are taking a look at the legislation and evaluating it and trying to ensure that they understand it and trying to ensure that they understand the impact. I think that discrimination legislation is always well meaning, and I think that Congress may not have anticipated some of the suits that have come out of various discrimination laws that we have in the past. So I think in this particular case, it's all the more difficult to anticipate just understanding the science.

So I think, rightfully so, we want to be sure that we are crafting this correctly so that it would address the kinds of things that need to be addressed and not sweep in other kinds of consequences. So I think that in terms of an evaluatory process, I think all the Congressional members are going to go through that, and I think they'll hear from the employers and they'll hear from others. But for our own sake I think we have to better understand the law and the state of the law and the way the new law would interact within itself even, to see how we can make sure that we know what we're going to get out of it the best that we can.

MS. BERRY: Sure. Well, as just a quick follow-up to that, you identified several issues that you think the various committees, particularly your committee, are going to examine to that end.

MS. FITZGERALD: That's not by any stretch an exhaustive list. I just gave a few examples. There are certainly a lot of things that we're looking at, and I think the other committees as well.

MS. BERRY: Is there, though, any glaring problem or one area in the Senate bill that's creating serious difficulty or angst among members in the House that you're aware of? Is there some real major concern that we should be aware of, or is it just a series of all these very important items which, once you examine them, you have the sense that we can work through them?

MS. FITZGERALD: Yes, I think some of the stuff I had mentioned in terms of the EEOC enforcement and the amount of damages, I think had those things stayed in the bill, you are absolutely right, you'd have a bull's eye on there where folks would be saying we cannot move forward because of this. I don't think that's the case here. I think that it's more folks are looking at all the impacts of the legislation and all the various parts of it. I don't think that there's one particular thing where folks are saying we cannot surmount this particular provision or something.

MS. BERRY: Ed?

DR. McCABE: Ed McCabe. I'm curious, and you may not know the answer to this, but given that the employers made their feelings known on the Senate side and yet the vote was unanimous, I'm wondering, assuming that the employers did make their opinions heard, then why there were no votes against the Senate bill.

MS. FITZGERALD: I couldn't speculate as to the Senate processes, but the House is different than the Senate. I mean, I think that there is, like I said, a lot of support for making sure that people aren't discriminated against on the basis of genetics. But I think our process will be different, and that's why we're the House and they're the Senate.

DR. McCABE: Can I have a follow-up, then? The other thing that I heard you make an analogy to other civil rights legislation, and I've heard that as well. So this is felt to fall within that genre of legislation, that it is civil rights legislation?

MS. FITZGERALD: Well, I think that parts of it are. There are two titles to the bill, as you know. I know that you are very familiar with the bill. But I think that the health insurance title would be similar to the HIPAA non-discrimination. I mean, it amends HIPAA. Then the legislation on the employment side is modeled after the Civil Rights Act. I mean, they've used the language directly from it. So I think it's most similar to that.

MS. BERRY: Hunt?

DR. WILLARD: Hunt Willard. I'm not going to try to understand the nuances of how things work in Congress. I'm having enough trouble today.

(Laughter.)

DR. WILLARD: But I do know enough to ask the question of whether this has -- and, of course, we wouldn't dream of quoting you on this, so feel free to just tell us --

DR. McCABE: This is being Webcast. The camera there is --

MS. FITZGERALD: Thanks for telling me. Now you tell me.

(Laughter.)

DR. WILLARD: -- whether this in fact has the support of the House leadership so that there's any sense that someone is trying to drive this to the Floor, or whether this will languish for a while. I guess the comparison question for that is whether there's any sense that the electorate is paying attention so that that will force this because someone will finally say, look, the Senate is 100 percent behind this. What's the matter with you guys in the House? Who is holding it up? And, by the way, we vote next fall.

MS. FITZGERALD: I wouldn't necessarily say this is an electorate-driven issue. I think that there are certain issues that are like that. The Patient Bill of Rights comes to mind, just because I'm thinking about health legislation. This isn't necessarily one where a member is going to go back to his town hall meeting and get barraged. There are certain issues like that. I'm just thinking of lots of different things. This is more complicated. So it's not quite in that same level there.

In terms of the leadership, I think that the leadership is wanting the committees to go through their process, go through the regular process, have hearings, investigate, hear the concerns of folks who are concerned and hear the support from folks who support. I think that they think that's a helpful process to get the members educated as to where we are. Like I said, the Senate had acted on this in the past, so they were a little bit more cognizant, whereas the House hasn't passed legislation like this recently or ever since HIPAA, and I think it will take a little bit of time just to spend the evaluatory time we need to look at the issue.

So I think it will progress based on the committee process, the way that much of the legislative process goes through.

MS. BERRY: Kristin, I don't know if you have a sense of this or you can handicap it, but do you think that it's possible or likely that a bill would pass the House before the end of the next Congressional session sometime next year?

MS. FITZGERALD: You know, I'm so bad at handicapping. I was giving a speech earlier and I said I handicapped one particular issue all year last year, that it was for sure going to happen,

and it didn't happen. So it's so difficult to predict, and I think that part of that is that the process will be serious and that the members will really be studying the issue. So I think that will determine the outcome. To the extent that they feel there's a compelling force that we must move forward that year, then it will. If it's something where there's a sense that they need additional time, then they'll take additional time.

So I think that's kind of what we'll see out of the committee process. Like I mentioned, it's not just one committee's process. Remember, it's three. So each of those committees will have to work their will.

MS. BERRY: Any other questions from anyone on the panel?

(No response.)

MS. BERRY: I guess not. Hearing none --

DR. McCABE: Well, thank you very much for coming and speaking to us. This is an incredibly important issue for us. It was the first letter that the Secretary's Advisory Committee on Genetic Testing sent to Secretary Shalala and to Secretary Thompson, and the first correspondence we had with Secretary Thompson with this committee. So it has been a priority for this and our predecessor committee, so we really appreciate it. We may ask you to return at some time in the future to update us assuming that it doesn't pass in the next two weeks.

(Laughter.)

DR. McCABE: As you have predicted, though, with your other experience with handicapping, maybe you'll have this one in error also.

(Laughter.)

MS. FITZGERALD: That's true. That could happen. You're right.

DR. McCABE: But we really appreciate you working on this, and we appreciate the House taking it seriously too. This is something that we think everybody must agree upon and really know it's the right thing to do. So we understand that process and we endorse it. Thank you very much.

If there are no other issues, then we will adjourn until tomorrow. I'll remind you that the instructions for dinner are in your packet. For those of you who are joining the group for dinner tonight, we will meet in the lobby at 6:45. Our reservation is at 7:00, and we have to take cabs, so please be there at 6:45. If you're not there at 6:45, bring your flyer and get your cab on your own and we'll see you at the dinner.

Thank you very much. I look forward to tomorrow.

(Whereupon, at 5:22 p.m., the meeting was recessed, to reconvene at 8:30 a.m. on Thursday, October 23, 2003.)