SECRETARY'S ADVISORY COMMITTEE ON GENETIC TESTING

Eleventh Meeting

Friday,
November 16, 2001

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

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C O N T E N T S

P R O C E E D I N G S (8:11 a.m.)

DR. McCABE: We're going to begin this morning with Dr. Judy Lewis for an update on the progress of the Access Work Group. Before you begin, Dr. Lewis, I want to offer our congratulations for the service award you received from the International Society of Nurses in Genetics or ISONG. ISONG presented Judy with the Society's 2001 Founder's Award, an award honoring a genetics nurse who has made outstanding and significant contributions to genetics nursing. Congratulations. Well deserved.

DR. LEWIS: Thank you. I'd like to give people an update on the work of the Access Work Group over the last three months. Our work group is composed of the people listed above, and we'd like to note the fact that we have two new ad hoc members of the Access Work Group, Michele Schoonmaker and Marc Williams. I would also like to acknowledge the work of Suzanne Goodwin, who's the lead staff person on this project and who's been incredibly helpful to us.

Just to review, the goal of the work group is to address access issues, including reimbursement and health disparities, as they relate to genetic testing and genetic testing services. Our current projects are developing a white paper on billing and reimbursement of patient education and counseling services and developing guideline principles for coverage of and reimbursement for genetic services by health care payers. We're also working to address issues regarding health disparities as they relate to access to genetic testing services, including the inclusion of broad populations in test development and the availability of culturally-appropriate genetic services. We're also working to gather information on scientific developments and understanding the

relevance and significance of human genetic variation to health status, health promotion and disease prevention. Let me update you on each of those tasks.

As far as the first task is concerned, our white paper on billing and reimbursement, the goal of this is to outline existing reimbursement and billing mechanisms and policies for genetic education and counseling. We're assessing the limitations of these mechanisms, examining the barriers limiting the availability of adequate billing methods and considering potential impact of current billing mechanisms in reimbursement rates on access to genetics services. We're doing a small survey of nine medical institutions and laboratories under development to assess how the broad range of providers bill and how they're reimbursed for their services. We hope to have this white paper ready to submit to SACGT for review at our February meeting.

One of the difficulties we've encountered in developing this white paper is that there are few data in published literature available on billing and reimbursement for genetic education and counseling services that are provided by non-physicians to demonstrate how the current system is affecting reimbursement of providers and ultimately patient access to genetic testing and education and counseling services. In other words, evidence of the magnitude of the problem is lacking. To this end, we're considering a small survey of nine medical institutions and laboratories to assess the mechanisms by which the broad range of providers bill for their services and the extent of reimbursement. The Paperwork Reduction Act allows us to survey up to nine organizations without going through the extensive OMB clearance process. That's why that's the end. Although data gathered will not provide evidence of the magnitude of the problem, we believe it will provide qualitative information that will help guide the further development of this paper. The work group will be discussing and refining a draft of the survey

instrument in an upcoming conference call. Did we ever identify whether or not we could get volunteers beyond the nine? Would that be legitimate?

MS. CARR: We're still checking that.

DR. LEWIS: We're still checking that, and if we can survey nine people and legitimately get other people to choose to volunteer, we'll let you know about the availability of the survey.

DR. McCABE: And again, you need to check on whether this is acceptable or not, but have others in the queue in case any of those nine don't come through.

MS. CARR: That isn't.

DR. McCABE: That isn't acceptable. Okay. Muin has another suggestion.

DR. KHOURY: You know, I think for sake of generalizability and accuracy of the data, you might want to consider that one academic institution undertakes this perhaps with some support from the Feds because, I mean, this is very preliminary.

MS. CARR: Will you contact CDC for us?

DR. KHOURY: I don't know what my budget looks like right now, but I think this is so important, that I think we should be able to find some money between all of us.

DR. McCABE: Perhaps we could start with nine as a pilot and then look to other sources.

DR. LEWIS: But I hear Muin saying that we need some professional help with the data analysis, and we'll certainly look into that.

DR. LLOYD-PURYEAR: You can get a lot of base data from us. The networks used to do this yearly. The regional genetics networks looked at genetic services, how they billed, what was available, and so as of five years ago, I mean, I have that data.

MS. CARR: As of five years ago?

DR. LLOYD-PURYEAR: Yes.

MS. CARR: But it's five years old?

DR. LLOYD-PURYEAR: It's five years old, but that's baseline data. I mean, that would help look at changes, and if you do this through a grant, you don't have to worry about it.

DR. McCABE: That's what Muin was saying. Why don't we move ahead, and let Judy continue, and then we'll come back to the discussion?

DR. LEWIS: Our second task is looking at the guiding principles for coverage, and under this task, we're going to be addressing a broad array of issues related to genetic testing that health care payers will need to address now and in the future; such as, the scope of coverage for

genetic tests and services, oversight of genetic tests and testing facilities, development of policy decisions regarding coverage, member access to genetic health care providers, genetics education of health care payers, and member outreach. We're hoping this guiding principles document will serve as a model to health insurance providers as they address these issues. The challenges to developing these governing principles include the requirement for FDA review of all genetics tests has not yet been implemented, the fact that clinical validity for tests may vary for different populations, the issue of public fear about genetic discrimination is affecting the use of genetic tests and of policies, and societal consensus about the value of genetic testing in the absence of therapeutic and preventive options.

We're currently grappling with these issues about whether we are ready to make recommendations regarding coverage principles. First, if we recommend coverage of tests in the absence of an operative regulatory review program at FDA, how will the public be assured of safety and efficacy of the tests? Would we be inconsistent with the recommendations we made about oversight of genetic tests? Even with an independent assessment of tests, the analytic validity, clinical validity, and clinical utility will be limited for many tests, and there will be need to be careful in promoting their clinical use. Comprehensive federal protections prohibiting misuse of genetic tests by insurers and employers are not in place, which discourages individuals from being tested and health care payers from promoting their use. Finally, society as a whole has not yet decided the value of genetic testing and incidence where there's no medical benefit. Because of the sensitivity and complexity of these issues, we're taking a stepwise approach to addressing the issues, and we plan to confer with outside experts before review by the full committee to ensure that we're provided a thoughtful, appropriate and timely document. We hope to have a draft for the Committee to review some time next year. I'd be interested in

hearing your thoughts and your suggestions on these issues as well as any other suggestions you may have on how the work group may address them.

In terms of our third task, looking at population data and health disparities, we're planning, in conjunction with the Data Work group, to convene a session at an upcoming meeting on how population data are collected, how they're organized, and how they're reported, in order to provide clarification on health disparities issues as they relate to genetic testing.

In terms of our fourth task, which is looking at health disparities, we're planning to reach out to public interest and advocacy groups to gather perspectives on specific issues that we should be addressing related to health care disparities, and I really would be interested in any, you know, given the time that we have left, in any comments that people have. Thank you.

DR. McCABE: Thank you very much. Any other comments for Judy?

DR. KANG: Just on Task 2. I think Judy did put up a very good list as to what are the issues facing the Access Working Group. I'd actually add a couple of others. You know, I think that the problem is we've got finite health dollars and that your genetic services are actually competing with all sorts of other services. For example, just take Medicare, in the context of Medicare, a drug benefit, and the issue that you are wrestling with is also the marginal kind of benefit or contribution to the health of the population versus kind of the money. So I think that just that particular task is going to be very daunting, and I think maybe the best we might be able to do is to identify the barriers and then kind of work on them one by one, quite frankly.

The other issue, of course, on the disparity is not everyone's insured in this country. So we're well aware of that.

DR. LANIER: In Task 4, you have it listed as health disparities. Do you really mean health care disparities? Because I think there's a difference between health disparities and health care disparities, because health care disparity is something that I think is much more easily addressable than changes in health itself and especially related to genetics. I'd just be clear on that point.

DR. BURKE: I just want to note that the point Judy made about there not really being a clear societal consensus about the value of information in the absence of treatment is a fundamental issue around genetic testing and actually addresses all other -- I mean, sort of relates to all other issues because it has to do with issues of how you present opportunities for tests, how payers make decisions about use of tests, you know, what the purpose of the test is, if it isn't for improving health care outcome. It is a fundamental issue, and it's fundamental in it leads us in a variety of directions. One is to discover how best to support autonomy, which is an important principle in our health care system, but also what kind of boundaries are reasonable to put around what health care payers should pay for. It's just a fundamental issue.

DR. LEWIS: I certainly agree, and one of the things that we've spent some time talking about is, is health just physical or are there also biopsychosocial -- you know, in other words, does knowing something and having your mental health affected, is that as important as having a physiological intervention? So I think you're absolutely right.

DR. KANG: If I could just expand on what Wylie said, I mean, if you look at most insurance policies, at least on the commercial side, the medical necessity language does not place a value on information, and they're basically arguing that it's not covered. The other interesting thing that we get into is if in fact society really does value the information, it's important to have, there is this double bind where I value the information so much, but I want it to be private, and I'd just as soon kind of pay for it on my own. I want my insurance private, and we get into this real issue, you know, of the carriers have it and their underwriters and the whole business. So I'm not saying that this is going to be mission impossible, but this is going to be an incredibly difficult issue to sort through.

DR. CHARACHE: I think the point Dr. Kang just raised is very key, the question of the definition of medical necessity. We know that in some populations where there's federal funding, and I don't know about the private sector, this becomes a major barrier because there's no reimbursement unless it leads to a therapeutic intervention, and this seems to me to be key to this whole question of access and reimbursement, and these tests are costly.

MR. HILLBACK: It's a very interesting line. I mean, given what our role as a Committee is supposed to be, is this enough of an impediment to the growth of this technology, the growth of genetic testing, that we ought to be making recommendations about some other type of education? We talked all day yesterday about educating practitioners, but are we into the area of educating, you know, talking through the Secretary somehow, educating the public, educating the insurance companies in some different way? Is this a major effort that we ought to be giving more than just a couple minutes' chat to this morning? Maybe that's included, Judy, in what you're doing, but it didn't jump right off the page as much until Jeff sort of expanded on it.

DR. LEWIS: And I think part of our goal was just to let you know where we're at today, and given all of the other committees that, you know, staff have limited time and resources, and we have been working, but we've been working more in the background, and we're going to be kicking into gear now, and so I think you can expect to hear more from us, and I do agree that, you know, maybe educating policymakers needs to be a big piece of this as well as the public. So I think, and we've got people from the insurance industry. So we've been trying to educate them and give them a sense of some of the scope, and they've been educating us, and I think it's very informative. So I agree with you, Elliott, and, you know, we didn't have time at this meeting for a lot of talk, but I'm hoping at the next meeting, that we'll have more time and be more available to focus.

DR. BURKE: The point I would make, Elliott, is that you can't call something an educational issue until you're clear what it is that you want to educate about, and what I think is difficult about this particular problem is there isn't agreement. I think it's probably fair to say there is not agreement. There's not any simple agreement, and it's going to be very hard to come to agreement. There are two difficult issues. One is, when genetic information provides only information or when the treatment involved is speculative in terms of benefit. There are going to be differences of opinion about some tests being more valuable than others maybe because they have greater predictive value or maybe because of the nature of the risk. In other words, there's a lot of range for discussion there, and I think the other issue that's already been alluded to is we might all agree as a society that certain information has tremendous personal value, and it's a good thing for people to have access to that test if they choose to, and yet we may not feel that that is something that it's reasonable for a health care payer to be obligated to pay for, given

finite resources and a focus in health care funding on improvement of health care outcomes, and again, I think there is tremendous room for differences of opinion on that issue, where you would draw the line.

DR. KANG: The only thing I would suggest is I'll agree it's not an education because we haven't figured out what it is. One of the things, I think, that might be helpful is if we actually think about this in the context of making recommendations to Congress for Federal legislation. The reason why you can do -- because then you can begin to get insurers engaged in an honest conversation. There's actually no insurer that's willing to take a lead, an enlightened lead on this issue because if they do, they'll be at a competitive disadvantage. But even if there's federal legislation, and it's mandated that everyone does it, they still just say fine, let's have that discussion, mandate it for everyone, everyone will do it, and I just pass the costs on in terms of premiums to the employers or what have you. So part of the agenda that you're dealing with here is that there is no enlightened insurer that wants to take the lead here, and I think you can have a more honest discussion, quite frankly, if you do it in the context of recommendations for congressional legislation.

DR. McCABE: Yes. I just need to remind everyone that our recommendations are to the Administration regarding what their priorities should be, but then that can move forward.

DR. WHITTEMORE: Okay. I'll be brief. I just wanted to comment back on what Elliott said, and I think there is room for education. I was recently at a meeting with about 20 medical directors from managed care organizations. It was organized by the American Academy of Dermatology, and when we sort of got talking about genetic testing, they view it as very black

and white and don't really understand the issues in terms of if you test positive for a genetic test but do not show clinical symptoms, how that might down the line change your follow-up and screening, reproductive decision making, and they were very interested in being educated and hearing about those kinds of things, rather than thinking about it as a medical necessity, but rather as just another tool to improve health care.

DR. KOENIG: I just want to turn away from the insurance back to the disparity issues and follow up on David's comment, too, about the issue of what are we talking about? Are we talking about differences in access to care or are we talking about fundamental differences across populations in which genetic research is going to make -- and genetic research presumably is going to make a contribution to sorting out some of these really complex factors, and so I just want to get also on the record the fact that I think one of our responsibilities may be to keep thinking about those issues. For example, we had the haplotype report in our briefing book to review for this meeting. I think we're not going to discuss it specifically, but I think we do at some point need to decide how to act on that. NIH has a lot of initiatives about it at the moment, but are some of these issues that move beyond just NIH, and might we want to get involved?

DR. KHOURY: Yes, I think everything I wanted to say has been said, but I just want to underscore the fundamental concept that health disparities and health care disparities are both probably the most important public health issues that this nation faces, not only in genetics but in general, and I think this Committee can go a long way in making recommendations for HHS and the various agencies around the table and ultimately to Congress for fixing this. This is really the weakest link in genetics right now because we can talk all we want about IRB, about the need

to collect data, about FDA regulation, but really closing the loop here is probably where the rubber meets the road, and I would applaud the efforts of the Committee, and if there is anything we can do to help, I mean, I'll start thinking more about these issues.

DR. LEWIS: Muin, we might take you up on that when we get to data analysis.

MR. HILLBACK: Yes, just I think, listening to the comments, after my comment, I probably chose the wrong word, listening to you folks. Instead of education, maybe we ought to raise the level, the noise level, of the dialogue, rather than think of it as the education. We don't know what the answer is yet, but we know we have a problem, and we ought to be raising it on this committee to a higher level of dialogue to see what comes out of it.

DR. LEWIS: Stay tuned.

MR. HILLBACK: That's a better way to say it. Thanks for the education.

DR. McCABE: Thank you very much, Judy. We're going to move on to our session on genetic testing for rare diseases. In August, Ms. Davidson and Dr. Watson, the co-chairs of the Rare Disease Work Group, briefed the committee that they would begin work on an outline for a white paper on the development, translation, availability and accessibility of genetic tests for rare diseases. In order to gather information for the paper and understand the current oversight and relevant issues at stake in this field, the work group has organized the session this morning, inviting seven speakers to share various insights with us today on the field of rare disease testing. I'll now turn the gavel over to Mary and Mike to lead our discussion and introduce the

various members of the panel.

MS. DAVIDSON: Good morning. Thank you, everybody, for turning out early this morning to talk about rare diseases. This is something that's very close to the heart of many of us, certainly the National Organization of Rare Diseases, the Genetic Alliance, the March of Dimes, many other consumer advocacy groups, as well as the American College of Medical Genetics and other professional organizations.

Just a quick overview of the rare disease landscape, which I'm sure is fairly familiar to all of us, but I just want to capture it for this session. An estimated 20 million individuals live with one of thousands of rare genetic diseases in the U.S. alone, and we all know that genetic testing is already an important element of the diagnosis and treatment of these patients and their families, and rare diseases is also a very important element in the development of genetic testing in general. With advancing technologies, genetic tests will become even more critical to the quality health care management of those with rare conditions.

In July 2000, we, the Secretary's Advisory Committee on Genetic Testing, recommended that FDA evaluate the validity and usefulness of all new genetic tests on the basis of analytical validity, clinical validity and the documentation of clinical utility. The intent of these recommendations is to ensure that patients at the point of service receive genetic tests and services of the highest possible level of quality. We recognized at the time the particular importance and challenge of these recommendations for rare genetic disease tests, and it was for that reason that this group, the Rare Disease Working Group, was established, and it's composed of Secretary's Advisory Committee members as well as a robust list of ad hoc

experts in rare disease, many of whom we will hear from this morning as they come in.

Our initial charge was to outline criteria to identify rare disease genetic tests that would receive more or less scrutiny. This was according to a proposed classification methodology that was dropped and was then followed by an adaptation of a revised approach to test classification. The charges that we're currently working on are to propose a way to incorporate the interests of rare disease advocacy groups, many of whom are centrally involved in funding and directing genetic test research and development in the test review process. We're also charged with developing technical assistance models for small and academic laboratories, and this is in collaboration with CDC, professional groups, and relevant private sector organizations, and this is specifically to address gaps in CLIA certification. Our third charge is to explore access and cost issues that are specifically relevant to rare disease mutation testing, and with this, we have some crossover with the Access Working Group, and our fourth mandate is to gather information from rare disease groups and test providers to assess the impact of the oversight process that we are recommending on access to rare disease mutation testing as well as to quality.

A brief summary of our progress. In last February 2001, we had a working group meeting that was held in conjunction with the SACGT meeting at that time. We heard presentations about the CLIA certification of rare disease testing laboratories and the development of technical assistance models to meet CLIA certification models. Specifically, Judy Yost talked about CLIA certification requirements, and Dr. Jennifer Puck of NHGRI talked about investigators, in particular -- her own experience with CLIA, that was positive experience, with the CLIA certification process. During the fall, we have been developing a draft outline for a white paper

on rare genetic disease testing. This paper will focus on the development and translation, availability and access, and oversight of genetic testing for rare diseases. I want to refer you to Tab 7, where you can see the draft outline of this proposed white paper.

To give us the input that we need for the white paper, we've organized, together with Susanne Haga, who I want to take a second to really thank for all of her efforts in all of this, we've put together today's session. Our intent, and you'll be hearing from seven panelists representing stakeholder interests and experiences ranging from consumer advocacy to commercial, academic and government agencies, and our intent is to gather information from these individuals and the organizations they represent about the research, development, oversight and marketing of rare genetic disease tests. Following the presentation, we're going to ask all presenters to join us in a roundtable discussion, specifically trying to draw from the major themes of their presentations and link them to the SACGT recommendations on rare genetic disease tests.

I want to remind all of us that we are particularly interested in the compelling need to strive for the highest degree of quality but also always striving to optimize access and quality. There's a balance here, but from the consumer advocacy perspective, we don't want to lose this tremendous window of opportunity to set a high bar on quality for genetic tests for rare diseases. Remembering that rare diseases affect more than 20 million individuals and their families, and this is not a small number by any measurement, and when we look at genetic tests for rare diseases, and the variety of uses of those genetic tests, both on an individual family and population screening, diagnostic or prenatal basis, we're talking about tests for rare conditions with potential impact on enormous numbers of people.

So going forward, I want to take a second to introduce my co-chair, who probably needs no introduction to anyone, Mike Watson, and I don't know, Mike, whether you have something you want to add.

DR. WATSON: Actually, not much to add. I think you covered it pretty well. I think one of our interests here was to look at the various pieces of this, at manufacturers, why they haven't developed products to a large extent in rare disease testing, to begin to think about some of the clinical and analytical validity issues, where the analytical validation can be very complex in many rare conditions when you have a range of mutations within a single gene, and each of those mutations may individually have very different clinical validity attached to it, that it may not just sit at the level of the individual gene but clearly may extend to the individual mutations which may be multiple within a gene. So I think the genetics paradigm is going to be an interesting one to try to work our way through, thinking about rare diseases, rare ways of causing mutation in genes and always trying to ensure that we can get these tests out there.

I think it's important that as we begin to move into a period where we may very much change the way we regulated the individual laboratory testing sector through FDA, that we actually really begin to look much more carefully at how we ensure access for some of these rare conditions and the rare genetic changes that can lead to some of these conditions, both common and rare conditions actually. That's about all I have to add. I think Mary covered it well. We can go on to the speakers.

MS. DAVIDSON: All right, and what I'd like to ask is that the speakers that are here now, if you can come up and join us around the table. Maybe there's something about rare diseases that requires particular flexibility. I think we've got a couple of speakers right at the beginning who

are not here yet this morning. So David, would you like to come up? I know that you're later on in the session, but thank you. You may come earlier.

I want to refer you to the bios on presenters, and I'm going to do just a very short introduction of each person. Each presentation is going to be followed by a five-minute opportunity just for points of clarification on that specific presentation. I ask that you hold larger, broader issues until the roundtable discussion toward the end of the morning.

Our first speaker, and you know, very logically, we're starting with a consumer's perspective, and so I'm going to introduce someone who I think needs no introduction to this group, Dr. Vicky Whittemore, and Vicky is now the Senior Scientific Advisor and Director of the Center Without Walls for the Tuberous Sclerosis Alliance. Many of you know that the Genetic Alliance was very fortunate to work with Vicky this past year, and now she's back working together with the Tuberous Sclerosis Alliance. The Center Without Walls is a research consortium that involves 30 clinical and basic science researchers from 22 different institutions worldwide, and these researchers, who have been funded largely through Tuberous Sclerosis Alliance funding, have been instrumental in identifying the two genes for the tuberous sclerosis complex and for the development of diagnostic genetic tests for tuberous sclerosis, and this is a rare autosomal dominant genetic condition. And with that, Vicky?

DR. WHITTEMORE: Good morning, and I'd like to thank you for the opportunity to be here and speak with you today. Due to family issues and travel and computer challenges, I don't have written comments for you here today, but I will be happy to provide those to you, but I think my message or messages are fairly simple, but what I want to do today is to start by giving

you some background as to what my perspective is, tell you what I believe are the issues that individuals with genetic conditions, specifically rare genetic conditions, and their families are facing, and the issues that we have encountered in both gene identification, translation of that into a genetic test, and then, finally, translating from the research phase to a commercial test for tuberous sclerosis.

My introduction to genetics, other than through very basic genetics in college and graduate school, was in 1985, when my nephew Clint was diagnosed with tuberous sclerosis when he was three months old and started having infantile spasms. I was four months pregnant at the time. There was no obviously genetic test at that time because we had not yet identified the gene, at that time, we thought it was one gene, for tuberous sclerosis, but there was some clinical testing that was available, and so at the time, my sister and her husband went through the genetic testing or the clinical testing and neither one of them showed any signs of tuberous sclerosis. So we felt fairly certain at that point that Clint was a new mutation or a spontaneous mutation, the first case in our family.

Had there been genetic testing at that point, would I have had genetic testing? Yes, I definitely would have. Tuberous sclerosis is a multisystem disease that's characterized both by tumor development and especially during fetal growth in the heart. So it is important to know at the time of birth if the child has tuberous sclerosis and has heart tumors, because that is the time when it will be crucial, because those tumors actually regress with age, unlike the other tumors that can develop in the brain and the kidneys, which generally don't develop until the adolescent or adult years. The other reason I would have been interested in knowing was that early onset of seizures is very important, and, as you can tell from my comments, I would not have chosen

elective abortion at that point, but that is everyone's private decision. For me, it would have been a decision of having the genetic testing, so that I knew what to prepare for, and what we have found over the years are that the families want access.

The issues that are important to the families is that they want access to the test, they want a test that is available to them, and they want to know the facts about the tests. In other words, truth in advertising. Currently, and I'll go back a little bit as I talk about the development of the test and raise some issues that I think are important as we move forward with potentially regulation of rare genetic tests.

Right now, the tuberous sclerosis test, as it exists, can identify approximately 80 percent of the mutations in individuals that we know have tuberous sclerosis. So if someone has the clinical diagnosis of tuberous sclerosis, we're able to find the mutation in one of the two genes for those individuals. The other 20 percent, we believe 10 percent of them are probably low-level mosaicism. In other words, only a small percentage of their blood cells actually contain the mutation. So that, it's very difficult to identify the mutation when only a certain percentage, and we're able to detect down to 4 percent mosaicism, but nevertheless, it is very difficult to detect those mutations. The other 10 percent, we don't know. We're hoping there's not a third gene, but it's possible that there is. In talking with the families, it's not crucial to them that we can identify 100 percent of the mutations. What's important is that they know what the level is of detection and potentially what a negative finding may mean for them. The important thing is that the families understand what the uses of this test are.

As we have been developing this test -- the first gene was identified in 1993, the second in '97 -- what has happened over the course of those years, since the two genes have been identified, is

that the major effort has been primarily underwritten by the Tuberous Sclerosis Alliance, and what I mean by that is that in order to identify the two genes, there was a large consortium worldwide of research labs that worked together to identify the two genes. That then was narrowed in the United States to two labs that continue to do the mutation analysis.

First, on strictly a research basis -- so they were not returning clinical results to the families --we soon found that once the families realized that the test, so-called test, or that the genes were identified, they wanted access to it. So what we were able to do in both of those institutions, at the University of Texas-Houston, with Hope Northrup, and at Brigham and Women's Hospital and Harvard, with David Kwiatkowski, is to partner with CLIA-approved labs, and the samples come in through the CLIA lab. The DNA is prepared. Some is reserved there. A sample is sent to the research lab where the mutation is identified. That finding goes back to the CLIA lab which then confirms the finding with the reserved DNA that they have from that sample, and then the information is given back to the physician who then relays the information to the family.

What we have found in the course of this is that the families who want access are very variable, like the disease is. Primarily, it's young couples who have one or more children, one of those children has tuberous sclerosis, and what they're interested in is knowing both the mutation, so that they can have the other siblings tested, as well as knowing if either of the parent has tuberous sclerosis, so that they can use that information for future reproductive decision making. The other large group of individuals who are requesting testing are individuals, adults, who themselves have tuberous sclerosis and who are very interested in having children and either using the information then for prenatal testing or there's growing interest in pre-implantation genetic diagnosis in this population, something that we have not yet attempted but is very

interesting and important, I think, for this population of individuals.

So the issues that we have faced in the development of the test that I think are important to think about as we move forward is, first of all, we were able to have the research labs partner with the CLIA labs but only after we understood why the research labs did not want or could not become CLIA approved themselves. At the University of Texas-Houston, Hope Northrup is a pediatrician and a medical geneticist. We didn't understand why she did not want to -- initially, we thought she was just putting up roadblocks to not have her research lab CLIA-approved. It turns out it's an institutional policy that research labs cannot become CLIA-approved, and they therefore had to partner with another lab, and she's doing that very successfully with Baylor University. At the other lab, Dr. Kwiatkowski, he's running a research lab. He did not want to become CLIA-approved and felt his relationship with the CLIA lab was working very well and therefore saw no reason to go through the process of becoming CLIA-approved and has not, and again that relationship has worked quite well.

Right now, the test, if I send a sample in to one of the CLIA-approved labs, the test would cost approximately $250 per sample, per individual, and that is simply the cost of the processing within the CLIA lab. The actual cost of the test is closer to around $2,000, which is now being completely underwritten by the Tuberous Sclerosis Alliance. So right now, there's excellent access to the test, but because of the underwriting, and we're not faced with individuals who cannot afford it. However, that will be certainly a different issue as it becomes developed into a commercial test.

At this point then, where we're at with the test is that we have been working, the Tuberous

Sclerosis Alliance and the researchers have been working with Athena Diagnostics to translate this test to a commercially-available test and that relationship has been excellent. They have been the individuals who have negotiated with universities and really carried out that whole aspect of translating the test to a commercial test. What has been difficult are the tech transfer offices and especially at one of the institutions, that when the Athena wanted access to some of the cell lines from the patients to verify the testing that they are developing, the tech transfer office insisted on charging an exorbitant amount per cell line, and so we actually have decided to unfortunately avoid working with that university, go around them by recollecting samples which we haven't done yet, and we're working exclusively with the other institution, and so I think that there are issues there in terms of how these things need to be worked through regarding the whole process of translating a test into a commercial test.

The other issues that we've faced, as we've moved through this, and clearly we have not had individuals yet who have requested that their medical insurance cover the test, but we have run into a situation where a woman, a grandmother, wanted to be tested because she had clinical symptoms, and her grandson had tuberous sclerosis, and Medicaid put up all sorts of barriers for collection of the sample. So I think that those are huge issues.

The other issue is professional education. In many cases, it's a neurologist who is collecting the sample, who then is giving that information back to the family, and does not clearly understand the implications of mosaicism, low-level mosaicism, gonadal mosaicism, and the implications for the family and for future reproductive decision making.

So in closing, I'll just say that genetic testing for rare disorders is very important to the families.

The families want access and want the test to be available. They want to understand what that test will tell them and will not tell them, and they do not want barriers that will make it difficult for them to have access, and, you know, as we have seen, also, and the last point I'll make, is that clearly continued information gathering is going to be critical for rare diseases, such that as the test moves forward and more and more mutations are identified, that information is fed back to continue improvement of the quality of the test.

Thank you. Questions? Comments? Yes?

DR. KHOURY: Thank you. Maybe you mentioned this, but what is the case hypothesized clinical utility for genetic testing tuberous sclerosis, this condition? You mentioned a bit about early diagnosis and finding out about tumors early on. Can you elaborate on this? And the other thing is, what's the status of genotype-phenotype correlation type analysis? Do we know enough to do this?

DR. WHITTEMORE: I'll start with your last question regarding genotype-phenotype. We know, there have been, I believe, close to 400 mutations identified. There are a couple of hot spots on the genes, but there are no clear common mutations. So each individual and their family pretty much have their own private mutation. We don't know much about genotype-phenotype. We have some indications that individuals with the TSC2 gene will be more severely affected but that is not clear, and so continued data collection there will be important and critical.

The clinical utility or reason to have the genetic test, especially, I guess, for someone who is asymptomatic, and I guess this would fall for parents, it clearly is for reproductive decision

making. Also, we have found it's very important to detect specifically the kidney tumors early, and so increased vigilance in looking for the kidney tumors would be indicated if you tested positive for the gene, say, at an early age. Those kinds of tests usually, even something as simple as a kidney ultrasound, are not done in siblings but would be indicated if you had a positive genetic test.

DR. KHOURY: And would that lead to better health outcome?

DR. WHITTEMORE: Yes, that would definitely do better at health outcomes because the approved treatment now is to go in and do embolization when the tumors are small, rather than waiting until the tumors are very large, symptomatic, and could potentially cause you to lose an entire kidney.

DR. WATSON: I'm curious about the difference between a $250 -- I guess that's what the labs get reimbursed -- rather than charge versus an actual cost of 2,500. Is that because in the billing system, you don't have a way of dealing with the difference between individual specific mutation detection and the fact that many of these mutations are either rare or private within a family, so you have to scan the entire gene, and systems don't exist to deal with -- because I think that's going to be a common problem in rare diseases, is just the enormous individual variability where things just won't be mutations with signs on them that say I'm disease-causing, and it's going to be a very different kind of analytical method that we've expected this to be?

DR. WHITTEMORE: Yes. In the actual process of doing the genetic tests, they have to scan both genes to try to identify the mutation, which is, both of these genes are huge. One is 23

exons, the other is 40. So the actual cost is that, is $2,500. That's not an inflated cost. In terms of that fund being collected by the lab up front, that would be possible now. Initially when we started talking to the CLIA labs, they were not willing to do that because we did not know enough about the test, and they felt it was still in the research phases. So they were only willing to bill for the processing of the sample within the CLIA lab, at least the two labs that we were working with.

DR. KANG: It's a question. I'm not sure I particularly understood the relationship with the CLIA labs. After the research lab runs a test, it goes back to -- and the CLIA lab is rerunning the test, or what's the nature of that confirmation you were talking about? I didn't quite get that.

DR. WHITTEMORE: What the research lab does is identify the mutation on TSC1 or TSC2, so then the CLIA lab actually goes back in and confirms that that is a disease-causing mutation.

DR. WATSON: I think what you're getting at is the fact that the CLIA lab confirms something that's found but doesn't necessarily confirm a negative test. And those are substantially different kinds of problems.

DR. WHITTEMORE: That's right.

MS. DAVIDSON: Thank you, Vicky, and I'm sure there will be some other questions, and we can bring them up at the close of the morning.

Our next speaker is Dr. Marlene Haffner. Dr. Haffner has served the FDA as Director of the

Office of Orphan Products Development since 1987. She's certainly known to everyone in the rare disease community. She's responsible for the leadership and management of the FDA Orphan Products Development Program and is a sought-after speaker on anything to do with rare disease treatment and research, including international orphan product legislation. She's committed to the development of products to treat people who suffer from uncommon disorders, and our specific intent in having her speak this morning is to understand how orphan product legislation might relate to some of the issues that we're looking at with respect to rare disease genetic tests.

DR. HAFFNER: And the Lord said, "Let's have a slide show." It's a pleasure to be here with you today. I know that a number of people that are here have heard about the Office of Orphan Products Development, those sorts of things that we do and the sorts of things that we do not do. Our thrust is finding ways to develop products to treat people with rare diseases.

A rare disease is defined in the 1984 Amendments to the Orphan Drug Act as a disease affecting fewer than 200,000 people in the U.S. So everything that you all are talking about or virtually everything that you all are talking about falls within that definition or the other part of it is or a drug or a product that will not be profitable seven years following FDA approval.

Prevalence of the disease is determined at the time that a sponsor applies for orphan status, called orphan designation, and while not an issue for you all but an issue for, let's say, AIDS patients or other diseases that then have better case finding, is that if the population grows, those products that are orphan products prior to the threshold being met remain as orphans, and as I said, our mission is to find ways to obtain treatments for patients with rare diseases. Those

treatments should be as safe, must be as safe and as effective as products for non-prevalent conditions.

How do we go about doing that? In 1982, Congress passed the Orphan Drug Act which was signed by President Reagan in 1983. There are a number of incentives in that law and in subsequent laws that have been passed. Seven years exclusive marketing upon FDA approval. In other words, a patent-like protection, personal property protection. You might ask why the heck do you need that with a disease that has a frequency of 200 in the U.S., but shareholders in companies and companies themselves like to know that there is a way to protect their product. Protocol assistance, assistance of our office, and the Center for Drugs and the Center for Biologics, in evaluating protocol as to how one should proceed. The way the law is written, this is formal protocol assistance. You send in a question. They send back an answer. In actuality, it's done much better by face-to-face meetings, and formal protocol assistance almost does not exist. Tax credits for clinical research expenses. Fifty percent of the clinical research dollar can be written off as a 20-year carry-forward period and a one-year fall-back period. Grant support for investigation of rare disease treatments. The entire Act has been very successful, but this has been a particularly successful part of the Act because many of the products have never been given to man. No company is willing to invest. An academic researcher has a great idea. The Center for Drugs and the Center for Biologics says it's safe enough to give to people, and our grant support is that bridge then that shows that it preliminarily does or does not work, and from that data, we can interest firms in taking over some products.

Waiver of the filing fee is $309,000 this year, not an inconsequential sum of money, and then the assistance of our office. We do not do drug reviews. We do not do biologic reviews. But we

remain very, very knowledgeable in those areas, and we're your ombudsperson or the firm's ombudsperson in getting a product through the system.

The process. A sponsor submits an application to OPD, which is not the out-patient department but the Office of Orphan Products Development. It drove me nuts for a long time. I've gotten used to it now. And that application is a product for a specific disease. Our staff reviews it, verifying the population and particularly the rationale for the use of that product, and then assuming all systems are go, the product is designated as an orphan and that's when some of the incentives, like tax credits, can kick in. Our staff receives and reviews the designation. We see all kinds of just fascinating cutting-edge stuff. I mean, it's just wonderful the ideas that people come up with that hopefully are going to work. We administer the grants program. We work with something called the Humanitarian Device Exemption Program which I'll mention a little bit more later, and we are information people, health education people. We love to go out and talk about our program and get more ideas and hopefully provide some insight to folks.

Just to show you a little bit as to how we work vis a vis how the centers and FDA work, on the left is our office assessing the designation. We interact with interested parties, and our result is orphan designation. The review divisions, and we go back and forth, provide scientific advice to the individuals developing the product. They review the formal marketing application, and their result is marketing approval, and in between, as you can see, there is lots of crossover and good communication.

Marketing exclusivity is indeed the most sought-after incentive. That incentive says that FDA cannot, will not and may not approve the same disease for the same indication, except during the

exclusivity period, except with the consent of the sponsor which rarely does occur or if, for some reason or other, the sponsor could not provide a sufficient amount of the product.

We work with sponsors, review divisions, and we work with the sponsors in meeting FDA requirements, and quite frankly, we also work with FDA in saying, you know, that's a great idea but, you know, this company can't do it, and it won't change the safety and efficacy of that product. Those fights generally go on behind closed doors. You won't see them. When you come to a meeting, it will be all sweetness and light, and people will say our office didn't say a word. We're not going to in public, but we've done a lot of discussions before and afterwards, and that's labeled protocol assistance, but that's what we do even without the formal protocol assistance.

I mentioned the tax credits for the costs of clinical research has become increasingly valuable since those clinical research credits have become permanent. For a long time, Congress would let them lapse. They've now become a permanent part of the Tax Code, and it's administered by the IRS and not by us.

The application fee, as mentioned, for 2001 is$ 309,000. Almost 310. I don't know what it will be for 2002, but it isn't going to go down. That's not an inconsequential amount of money, especially since you figure that a number of the firms that get involved in rare diseases are start-up firms hoping to grow.

Humanitarian use devices. For a long time, there was a lot of discussion about, well, shouldn't we have orphan devices, and no one knew how to figure out what in God's name they were, and

even what kinds of incentives would have been useful to spur their development, and then in 1990, Congress passed the Safe Medical Devices Act and included therein was something called the Humanitarian Device Exemption, and what that says is that if the use of this product is going to be fewer than 4,000 in a year, you may provide it to patients without the usual efficacy requirements, so long as it has IRB approval, being given in an established institution, and the individual utilizing it meets certain requirements. The sponsors come to us, our office, with the request for the exemption, and then the application itself goes to the Office of Device Evaluation in the Center for Devices and Radiological Health. We have to bless it first. We have 60 days to do that. We've never missed a deadline, and to date -- oh, 45 days -- we still haven't missed a deadline. Sometimes they bring them in to me, and they say, it's 4:00, you've got till 4:30. We manage. But that's what our office does in reviewing the particular product, and again it's fascinating cutting-edge technology.

Since 1996, we have received 74 applications. We have either turned down 14 or sent 14 back for additional information, and the Center for Devices has approved 23 of those. That doesn't mean the other 37 will not get approved. It just means that they're not at that stage of development at this time. After 17 years, we have 224 orphan products that have been approved. These treat more than in the aggregate 11 million United States residents, not inconsequential.

We do not support research in our grants program. We support only clinical trials, trials of man, and these can be in addition to drugs and biologics, medical foods and medical devices. Basically, once again, we're trying to get product to people, product that will be helpful to people. Prevalence has to be documented, has to be done in the usual way that studies are done. INDs, IDEs have to be utilized, except in the case of medical foods, where that is not a requirement.

We support mainly Phase I and Phase II trials, up to $300,000, in a three-year period of time. Those are direct costs. You add indirect to that. We're talking about well over a million dollars. That's not a lot of money in NIH standards, but again it's been very successful.

Sodium phenylbutyrate, urea cycle disorders, certainly a genetic disease, one you all are probably interested in, tobramycin for cystic fibrosis. The others that you see there are not genetic diseases.

Biotech firms and biotech industry has done a lot of growing up around the Orphan Drug Act, and we've seen a burgeoning number of those firms, and this is us.

This is where we live, the Parklawn Building. I suspect just about everybody in this room has been there more than once, and that's our website, which I am told is very useful, and an 800 number and our direct line. Are there any questions?

DR. WATSON: I have actually probably two related questions. Now that the DNA laboratory-based test, I guess, is essentially considered a product, have you begun to think through the sort of regulatory or device exemption types of issues that would arise for a laboratory test as opposed to a kit?

DR. HAFFNER: Well, in vitro testing is regulated both by Biologics and Devices. We haven't quite figured out yet where they would fall vis a vis the Orphan Drug Act because if they're a biologic preparation, then they get the full benefits of the Orphan Drug Act, because the chances of using these in more than 200,000 patients is, let's say, unlikely. On the other hand, if they are

a device, while they might fall under the Humanitarian Device Exemption, since one waives the efficacy requirements, one may want to think about that.

DR. WATSON: And one related question that you sort of touched on was those --. I assume it's just a historical fact that we ended up with the numbers we ended up with, which is, if it's 200,000 in a population, that's about 1 in 16,000 in the U.S.

DR. HAFFNER: No. It's 1 in 1,350, but anyway.

DR. WATSON: Well, it's 1 in teens thousands, and then if it's 4,000 per year, if it was newborns, we'd be talking about 1 in 100,000 newborns roughly, I presume?

DR. HAFFNER: Yes.

DR. WATSON: Is there a reason why we ended up with such disparate numbers for --

DR. HAFFNER: You've got to talk to Congress about that. The 200,000 is --

DR. WATSON: These are legislated numbers?

DR. HAFFNER: Yes, they're legislated. They're in the law. But the 200,000 figure was used as a surrogate for profitability. The original law said, you know, not profitable. Nobody knew how to figure that out, and so 200,000 figure was arrived at because 100,000 was too small, because some of the very important people in the orphan disease arena had families with

Tourette's, Huntington's disease and so forth, and the prevalence of those diseases is somewhat over 100,000. So 200,000 was arrived at. Actually, one can be profitable at 25,000, if you charge enough for your product. I have no idea where the number 4,000 came from. It appeared one day. That actually was head honcho'd through with devices, and then only afterwards, I said, hey, hey, you guys, we can administer this for you, but where it came from, I don't know. But devices are indeed very different in their use than are drugs.

DR. CHARACHE: Yes, I was on the same trail as Mike. It's the definition. I see two issues here. One is the definition of rare. The tests that we're thinking of are certainly well under 4,000 per year per test for most laboratories, and the other issue is your definition of safe and effective and the importance of that. Thank you.

MS. BEARDSLEY: One point of clarification. I don't know if this is a question for you or for Joanne, but when you count numbers, when you're getting to 4,000, are you counting the number of tests or are you counting the number of people with the condition?

DR. HAFFNER: We're counting the number of tests. We've had some discussions about that. I don't know whether Joanne's going to touch on that or not. The law is not exactly clear, and we figured that the intent of the law was to make things available to the people that needed it.

MS. DAVIDSON: Okay. I think this is a good transition then to our next presenter, and these questions are terrific, and I just want to remind everyone that we've got lots of time set aside for a full discussion of the issues at the end of this morning.

Our next presenter is Dr. Joanne Less, and she is the Director of both the Investigational Devices Exemption Program and the Humanitarian Device Exemption Program at the Office of Device Evaluation at the Center for Devices and Radiological Health of the Food and Drug Administration, quite a mouthful. She comes to the agency, joined the agency in 1992 as Scientific Reviewer, and she has a background in biomedical engineering, and I think we can continue our questions after her presentation.

DR. LESS: Thank you. Thank you very much for the invitation to come speak today. This program, the Humanitarian Device Exemption Program, is a relatively small program within our center. We have three basic mechanisms to get new devices to market. Some of you are probably familiar with the premarket approval program. We do about 40 to 50 PMAs each year. We do 4 to 5,000 510(k)s in which a company is claiming equivalence to another product that's on the market. In contrast, we only do about four or five HDEs every year. So I'm happy to come here today to try to push the program a little bit and increase its visibility and awareness. I just came from Baltimore last week, where we were talking about it with industry to try to drum up some interest in the program because we're not exactly sure whether part of the problem of not getting a lot of these applications are some of the restrictions that you'll see are imposed by the statute or the money, the reimbursement issue, or exactly what it is.
In order to get a Class III medical device on the market, a company needs to show that there's a reasonable assurance of safety, reasonable assurance of effectiveness. In 1990, with the Safe Medical Devices Act, Congress said because there's a small patient population out there which they defined as 4,000 in the United States, they decided to exempt those products from demonstrating effectiveness, and the idea was to encourage the discovery and use of devices intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect

fewer than 4,000 individuals in the U.S. That number was originally 8,000, if you look at the draft legislation. We don't know where the 8,000 came from, and similarly, we don't know why it was cut to 4,000. So that is an issue that we can certainly use some discussion on and maybe the 4,000 is too restrictive, but we don't know exactly where either of those numbers came from.

What Congress was trying to do, we think, was say that because these are small patient populations, a company couldn't go out and do a full-blown clinical trial to demonstrate reasonable assurance of effectiveness. So they exempted the companies from demonstrating effectiveness. That's why it's called the Humanitarian Device Exemption Program. But that doesn't mean that the companies get a free ride by any means.

There are several statutory conditions, the first one being that the device would not otherwise be available. So the company, when they submit their application, needs to show us that somehow they wouldn't bother pursuing marketing approval otherwise. So it's just not economically feasible. There's not enough patients. They couldn't make a profit, and so they wouldn't bother pursuing the device. They also need to show that there's no comparable device, meaning that there's nothing else out there to meet that patient's needs because it wouldn't make sense to approve a device where the effectiveness has been exempted, if there are other devices out there that could treat that medical condition. The device will not expose patients to an unreasonable risk of illness or injury. That is the definition of safety for humanitarian device. Instead of showing the reasonable assurance of safety, companies need to demonstrate that the device wouldn't expose patients to this unreasonable risk and instead of demonstrating effectiveness, the company needs to show that the device would provide a probable benefit to the patients, and the probable benefit outweighs the risk. So the criteria for approval is more like

that to start a clinical study, rather than marketing approval. Some of the other statutory conditions include that the device has to be used with IRB approval. Congress added that in, the patient protection measure. When we were writing the regulation, we tried to impose that the companies also need to get informed consent from the patients, so that patients would know it's a humanitarian device, and the Commissioner's Office told us we weren't allowed to do that, that if it wasn't in the statute, we couldn't require informed consent, but we have asked companies to provide patient labeling so that the patients do know it's a humanitarian device and exactly what that means, that effectiveness wasn't demonstrated for the device, but that FDA has reviewed it and made a decision that we think that probable benefits outweigh the risks of using the device. And last, probably one of the bigger statutory conditions is that the company can't make a profit off of the device. It's similar to the IDE restriction, where the company can only charge the amount so they can recoup their research, development, manufacturing and distribution costs. We put in the regulation that if a company made incidental profits, we wouldn't oppose that. However, the idea that Congress was trying to put in the statute was that since they didn't demonstrate effectiveness, there's a lower threshold for safety. They didn't think it was reasonable the company should make a profit. This has become an issue with some of the companies deciding it's really not worth pursuing an HDE if you can't make a profit, you have to get IRB approval, maybe it's not worth it to pursue it, and maybe it's better to just try to struggle along with your clinical trial and submit it PMA.

As Dr. Haffner was mentioning, we got the statutory provision in 1990 with the Safe Medical Devices Act. It took us a couple of years to come out with the proposed rule, and when we looked at all of the statutory conditions, the IRB approval, not making a profit, the low-risk threshold for safety and effectiveness, we thought this looks more like a clinical study. So we

amended our IDE regulation. The comments came back from industry saying that we totally missed the boat and that this was supposed to be marketing approval, not a clinical study. So we looked at comments. We agreed, we said that they were exactly right, and we modified the regulation in 1996 to say that it is basically a form of a PMA, premarket approval application. So the content of it and the form of it looks like a PMA, except there's less information in the application.

With the Food and Drug Modernization Act of 1997, Congress changed the review time from 180 days, which is what we get for a PMA and we had for an HDE, to 75 days. So the message was clear to us that it should be more like an IDE in terms of the review times and the threshold, and they weren't really expecting us to be taking these to our advisory committee panels, unless we absolutely needed to. So we now have a 75-day clock on these applications. They also removed the reapproval. In the original statute, companies had to come back every 18 months and get reapproved for their HDE. They no longer have to do that. Once they're approved, they're approved. They submit annual reports to us, like they do for any other marketing application under PMA.

The HDE application actually consists of two parts. First, they go to the Office of Orphan Product Development, and they get their HUD designation. They submit some information to them, authoritative references, description of patient population, documentation to support the 4,000 in the U.S. We did change -- the statute says 4,000 patients in the U.S. We added per year when we wrote the regulation because we thought if it was strictly 4,000 in the U.S., it would be too restrictive. So we went to 4,000 per year, and as Dr. Haffner was saying, they review those in 45 days and either approve them, disapprove them or ask for more information.

Once the company gets their HUD designation, then they can submit their HDE application to us in the Office of Device Evaluation. So the idea was that they would go to Orphan Products first, make sure that they meet that criteria, so that they wouldn't prepare a whole HDE. We wouldn't bother reviewing it if Orphan Products was going to turn around and say you don't qualify, you don't meet the 4,000. In a couple of cases, we have reviewed them simultaneously when we've known ahead of time that they are going to meet that criteria. We have allowed them to consider them simultaneously.

When they come in to us with the HDE, the first part is supposed to be their letter from Office of Orphan Products showing that they got their HUD designation. The second part is an explanation of why the device would not otherwise be available. We're not looking for a whole thesis there, but we do want something from the company trying to explain why they would not otherwise have pursued marketing of the device. They also need to tell us why they don't think there are any other comparable devices, and that is one of the key issues that we look for. We use our panels to help us with that decision. We look at the literature. We search our own databases to see whether there's something that's approved for that indication that they're claiming, and we have had cases where there have been other devices that have been cleared or have been approved for marketing, but they failed, practitioners don't use it because of the adverse event rate associated with the device. So they've still been able to make the case that there's no comparable device, even if there had been something cleared a few years ago or in the past for that indication. They also need to include their HUD labeling or humanitarian use device designation which again is to tell the patient that it is a humanitarian device, and there's an actual statement that says that FDA has not determined the effectiveness for this indication.

Last, they're supposed to give us some sort of demonstration that they're not making a profit, and it's a little bit more than what we asked for in the IDE, but we basically review it the same way. We're not members of IRS. So we don't know how to review all of that in a lot of depth, but we do look to see how they are itemizing their costs. If they charge less than $250, they get an automatic waiver, so they can just say we're only charging 250, and we don't need to review the costs for that device.

The main part of the application is the second part, which is more like a premarket approval application, and this is where they tell us everything about the device, the description of it, how it's made, the principles of operation, the material for their use of the device, give us all of the preclinical testing, the biocompatibility, animal testing, bench testing, and this ends up being the bulk of many of the HDE applications that we have, and I'll discuss an example with you.

A lot of the HDEs that we have rely more on the bench testing than animal testing preclinical than on a clinical simply because there aren't enough patients to do a clinical study. So the clinical, according to the regulation, instead of saying clinical data, it's clinical experience, and in that, we're looking for literature from outside the U.S. Some companies have done small clinical trials with 20 or 30 patients. We get information from those trials, anecdotal information, whatever the company has access to or whatever's in the literature. We get full-blown manufacturing information just like the PMA. We go out, and we do do a GMP, good manufacturing practices, inspection before we approve the device. So if we have already reviewed the HDE and the company is not in compliance with GMPs, we don't approve the application. We wait until they do get the design controls and manufacturing process under control before we would issue the approval order.

And the last thing we look at is the labeling. We get physician labeling, and we also get patient labeling, again so that the patient knows what it is. In lieu of the informed consent, we have a patient brochure that goes out with the device, so the patient knows what we reviewed, what the indication was, what some of the possible risks are, what the alternatives are to this device, so that they can weigh and make the decision for themselves whether or not they want that device to be used on them.

The statutory threshold for marketing approval is different than anything else that we have. As I mentioned earlier, for a PMA, a company needs to show reasonable assurance of safety and effectiveness. For an HDE, the company needs to show that the device does not expose patients to an unreasonable risk of illness or injury, probable benefit outweighs the risk of using the device, but this last part is the part that's rather unique. Taking into account the probable risks and benefits of alternative therapies. Our first HDE was a fetal bladder stent that was submitted by the Cook Group in Indiana, and Cook was actually backing the legislation. So they came in with the very first HDE. They had a fetal bladder stent that had been used in Europe for the last 15 years or so. They had 700 patients worth of information in Europe and not necessarily clinical data. They had been trying to do a clinical study in the U.S., and they had 15 patients enrolled in that study. When they came in with their PMA, we took it to our advisory committee. The panel said they're not ready to be approved. There's not enough data to show effectiveness. Well, right after that, the HDE provision went into effect, and so we reviewed it under the HDE, and basically, it's a very simple device. It's a little double pigtail. It's used for urinary tract decompression and fetal obstructive uropathy, and the alternatives are repeated needle aspirations or open fetal surgery as opposed to this device, where, if you look at the

material, if you look at tensile strength, elongation testing of the biocompatibility, they insert the stent with ultrasound. There's really no risk of the device, except migration or that it might become clogged, and then you put in another one. So it was easy in that sense to look at this device, to say, you know, we have literature, we have information from Europe, we have literature showing the device had been used in this indication as well as in the lung to drain fluid, and so it became a relatively easy decision to make, knowing that if you didn't treat that indication, 90 to 100 percent of the fetuses would die. If you treated it with this device, you dropped that mortality rate down to 50 percent, and there was virtually no risk of using the device.

So it's a different type of decision that we're making. We're looking at the risks and the benefits. We're also looking at the alternatives and how risky they might be in comparison to this device.

Over the last five years, we've had 41 HDEs submitted to us. These have ranged from devices, such as heart valves and hips, and I'll give you some more examples in a minute. Twenty-three of them have been approved. Ten of them have been withdrawn.

Some of the main problems that we see with the applications is that they come in from companies that have never dealt with FDA before, and so when the application comes in, and in a number of cases, they've been grossly deficient. We had one HDE that came in that was 12 pages long and that included a clinical protocol. So we had to go back to them and say this isn't a clinical study. We don't need your protocol, but we need to know what your device is, how you're making them and all of that. So we didn't file it, and they have never come back. But a lot of the applications are coming from very small companies. We've had a couple of them

submitted from companies, such as Cook and Medtronic, where they've done well, and they've gone through in 75 days. The smaller companies, we've had to non-file them, go out with major deficiency letters. We found over the years that even if you ask minor questions, like asking them to change the labeling or add more information to labeling, it takes weeks or a month or so for the company to come back, and so the review times have stretched out in some cases much beyond the 75 days that we try to adhere to in the statute.

We've approved 23. These included two fetal bladder stents. We interpreted the statute to mean that you could have more than one HDE for a specific indication. So we actually had two fetal bladder stents. We have a heart valve, where a company took porcine, treated it with glutaraldehyde to reduce the calcification rate in pediatrics, in recognition that it's harder to get those small valves from cadavers. There aren't very many around. The polyester valves don't work as well in pediatric patients. Medtronic submitted a gastric stimulator. Again, they had been doing a clinical trial for a long time. It's a pacemaker for the stomach for patients with intractable chronic nausea and vomiting due to gastroparesis, and they had been doing that trial for a long time, were having a lot of trouble enrolling patients and decided to stop the trial. When they decided to stop it, we started hearing from all the patient advocacy groups. We heard from the Clintons, and we eventually called Medtronic and said please continue your trial and work with us on an HDE because they were getting pressure, we were getting pressure, and so we worked with them to get that HDE through. We have an artificial skin disease for mitten deformity, when patients' fingers start to fuse together from REDB, and we have a hip prosthesis with antibiotic bone cement. It's bone cement with ankotobramycin for patients with myelitis. So it gives them some mobility during that intervening period where the infection's trying to be treated, and the last one, the only in vitro one that we have, in vitro diagnostic, is a

clotting time test kit for patients that are undergoing bypass surgery and are allergic to Heparin. This is a test kit to monitor the ecarin levels.

One of the issues that we've been struggling with and that we've been hearing from industry on is whether or not the 4,000 is the right limit, both for therapeutic and for diagnostic. We do look at the 4,000 as the number of patients in the U.S. per year, but at the same time, we're looking at how many devices are shipped, and we've said in the regulation, that if a company shipped more than 4,000, and they were slightly over, we wouldn't necessarily take any action. If, however, a company went out and shipped twice as many as that, that might be a reason to say there's a market for the device, and they don't need to be under this provision. We've said that most of the diagnostic devices probably wouldn't meet this criteria because if they had to screen 20 to 30,000 to find the 4,000, then there was a market for that device, and so for rare diseases, that could be obviously a consideration since you'll be screening many more to find that 4,000.

We've heard from companies that the postmarket requirements, the IRB approval, is burdensome to them. The IRBs complain and say they don't really know what they are supposed to be looking at. They're used to looking at protocols and research, and since this isn't research, they're not exactly sure what they're supposed to review. So we've been trying to work with them to give them some idea of what it is that they are supposed to be looking at, but at the same time, there aren't requirements for adverse event reporting to the IRBs. So they're sort of stuck in the middle, being told to review something without knowing exactly what it is that they're charged with reviewing.

And then, there is the cost containment issue, and since the companies can't make a profit, and

we don't have a formal agreement with CMS, like we do for investigational devices, we don't know for sure that HDEs are being reimbursed.

So there's a number of issues that we've heard from industry. We don't get a lot of complaints from industry, but at the same time, we don't get a lot of applications. So we're trying to increase the awareness of the program, hopefully see if we can get some more HDEs submitted. Thank you.

DR. McCABE: Thank you. We have time for one or two questions.

DR. CHARACHE: Two questions. One is, how do you get the patient labeling to the patient? Is that done by the laboratory or is that done by each individual physician, and if it's done by the physicians, how are they distributed? The second question has to do with the HDE process. If a device has been approved through HDE and then the market goes up to 80,000 a year, would that be re-reviewed?

DR. LESS: In answer to your first question, most of these devices are not used in the laboratory, and they are used either by surgeons or physicians. We review the patient labeling that the company submits to us. We make modifications to it and then agree to the labeling before the approval order goes out. Then the company is responsible for giving that to the physicians and to the IRBs, and since these devices have to be used in institutions where there's an IRB with IRB review, that labeling would go to the physician, and then they would distribute it to the patient. I'm sorry. Your second question?

DR. McCABE: The issue about if the market increases.

DR. LESS: If the market suddenly increased, and the company came in in their annual report and said we're now shipping 10,000 or 8,000 devices a year, we would have to look to see and say you don't really meet that criteria. Do you want to consider withdrawing approval of the application? What we have seen in the last few years is that for some of these devices, like the occluders for atrial septic defect and ventricle septic defects, that they have moved towards marketing approval through the PMA process, that once they have the HDEs, they've collected data under that HDE, even though it has marketing approval, and then are submitting PMAs.

DR. McCABE: I think we should probably move on. Mike, do you have a brief question?

DR. WATSON: I'm trying to reconcile the numbers here because I did bad math before with the four million newborns. But nevertheless, it's really an intended use kind of problem, which I don't think exists for any of these products. Under biologics, that seven years lasts regardless of if your marketplace increases, but under devices, you lose it if your marketplace increases. So if somebody found a test for a rare biochemical disorder at a laboratory level, since that's now a product, and got the exemption and then that became useful in newborn screening, that could potentially, if it was under biologics, be protected for seven years versus as soon as the market expands under devices, if it expanded to newborn screening, they'd lose the exemption.

DR. LESS: We did say in the regulation that we wouldn't necessarily withdraw it, that we would look at the criteria to see whether they met it, but we would take into account the public health need. So probably what we would do is work with the company to try to get them

approved for a PMA, to get more information from them, get the PMA approved, and so in that way, they would lose the exemption, but they wouldn't have to get IRB approval anymore. They could make a profit. They wouldn't be subject to the 4,000.

DR. WATSON: That, or the intended use, would be a different test. If we define intended use as the test, then the use of newborn screening would be a completely different intended use and therefore a fully different test.

DR. LESS: Right.

DR. McCABE: Thank you. I think we do need to move on, and we'll have to hold other questions till the roundtable.

MS. DAVIDSON: Our next presenter is Henrietta Hyatt-Knorr. Henrietta is the Director of the Office of Rare Diseases at NIH and a long-time friend of everyone in the rare disease community. She served on the National Commission on Orphan Diseases from '86 to '89 and also has served as a Deputy Executive Director of the National Bioethics Advisory Commission from '97 to '98.

MS. HYATT-KNORR: I'm sorry to say, I'm the old-fashioned type. I still use overheads. So you have to excuse me for a second. Everything that I'm going to say today, I really want to frame with in this aspect of the NIH mission, that we require new knowledge to help prevent, detect, diagnose and treat disease and disability from the rare genetic disorder to the common cold. Of course, we focus entirely on aspects of rare diseases. In my comments, I'm going to

try very hard not to duplicate what Dr. Haffner, for example, has said already because I'm sure you're very familiar.

When we work with issues of rare diseases, we use the definition of the prevalence of fewer than 200 persons in the U.S. There are over 6,000 rare diseases that are identified, and currently on our website, we have a list of, I think, 6,100 and something, which we just recently completed, and now we're pretty certain that these do not include any symptoms. These are really distinct rare diseases. We think that there are about 20 to 25 million Americans affected by rare disease, and I think the estimate by the task force in 1999 was as many as 90 to 95 percent have a genetic or inherited component of this.

The mission of our office is considerably different from what you've just heard from FDA. We provide information to the public, to researchers, to physicians and anybody else who's interested on rare diseases. We at times link investigators with subjects and patients, and we identify emerging opportunities in rare diseases research, and when such situations exist or when there is a lack or lag in the development of treatments of rare diseases, we co-fund with the institutes at NIH scientific workshops on rare disease issues, and by the same means, we stimulate research. I have to say, however, that at this time, we do not directly support any research on rare diseases. That is done at the institutes and centers at NIH.

The office was established in 1993, and I wasn't part of that at the time, but I think it was a one-person effort and it was really my boss, Steve Groft, who's currently on detail and will be back later on next year.

Our mission is to respond to reporting requirements of the Orphan Drug Act, to update the Office of the Director at NIH on matters relating to rare diseases and orphan products, and for this purpose, in particular, we are located in the Office of the Director at NIH, to act as a liaison between federal, non-federal and international organizations, and for example, the recently-updated List of Rare Diseases was a direct cooperative effort with the Engelhorn Foundation in Luxembourg, and to prepare the NIH Director's Annual Report on Rare Diseases, research sponsored by NIH. Now, this is not to imply that this is necessarily all we do, but I think those are just the highlights and something that we do year after year.

Our current activities are in large part to work on implementing the recommendations of the National Commission on Orphan Diseases, which was in the 1980s, and I was delighted to be part of the staff at that time, and the NIH Special Emphasis Panel on the Coordination of Rare Diseases Research.

I have to say here, this is a very tall order, and we are a very small office with a huge mission. Currently, we only have two full-time professionals and three other staff. We can have as many as five, but we have a budget of a little bit over $2 million. So you realize that that automatically limits considerably what we can do, but we never lose heart.

I guess I should add that we also have a substantial scientific workshop and symposium program. About half of our budget goes to this effort, and we work with the institutes and centers at NIH and voluntary support organizations to put together scientific workshops, again when there is either a scientific opportunity or when research is lagging behind or lacking. Usually we do not support scientific workshops each year on a particular issue. So we try to

have at least a year or two in between so that we see some progress in this respect, and then we very often have supported field workshops.

We have an ORD website, and this is our address. This is not a website that necessarily has a lot of new information that we generate. More so, it's really links to other sites and also an email address through which we get most of the requests for information. We also maintain the Medical Genetics and Rare Disorders Subfile of the Combined Health Information Database, which, you know, is usually more known as CHID, and this is a very, very useful subfile, and we have seen the use of the subfile increase considerably. We hope that in the next few months, we will have a new update because many of the information, particularly about voluntary support organizations, can be outdated rather quickly. We also, as I told you before, maintain and improve this listing of rare disease names. Now, so far, this is just a listing and has never really been meant to be more than that. However, in the near future, we hope to link to certain databases, particularly clinicaltrials.gov, PubMed and OMIM. We think that would be really very useful because it's very difficult for the average, I think, person who requests information from our office, when they go to our website, and then they leave the website, and they have to use different search mechanisms at each of these particular databases, and not everybody who contacts us is necessarily terribly computer literate, and I think we're very sensitive to that, and we're working with the National Library of Medicine and a contractor to develop this, and I think it will be a great improvement. I mean, I'm an end user of computers myself, and when I first started working for this office and looked at the website, I thought this was really one area that in particular needed some improvement.

We also have, together with the Genome Institute, awarded a contract on an information center.

Until the end of this year, I should say, we have and will provide information on rare diseases from our office directly, and we have one person who is working on this, and I have to say I have trained this person, but one person can only do so much, and we're actually certain that this information center is going to be a huge improvement to people who request information. Usually, at least from my experience, and I see everything that comes into our office in this respect, people have just been diagnosed or family member or friend has been diagnosed with a rare disease, and they're really upset. They may not even have heard the name correctly, let alone know the spelling, and they really want to know what is this all about and what does it mean, and with rare diseases, in particular, very often there isn't that much useful information available or it is written in such a way that it may be very difficult to understand for the "average" person, and even for the not so average person, if you will, when you're really upset, it makes it much more difficult, and we hope to also develop new materials that are easily understood and are really truly up to date. So this is going to be a great challenge. We have awarded the contract. We think that the information center is going to be at least partially operational before the end of this calendar year, and we're looking forward to it tremendously and really not as a worksaver for us but as a really greatly-improved service to the public. Our future activities, I think, are largely dependent on whether the Rare Diseases Act, which has been proposed by Senator Kennedy and others, is indeed going to be implemented. What this Act would do for us, and please do not misunderstand this in any way as a loving effort on my part, but what this Act would do for our office, it would, first of all, provide statutory authorization for our office. It would not make us a center. It would not make us an institute, but at least it would be some guarantee that this office would be there year after year. It would also hopefully authorize funding for the office and thereby stimulate research and aid in research on diagnoses. What the current proposal would actually do is double our annual budget for the

office as such and give us $20 million for Centers of Excellence on research in the area of rare diseases and conceivably would include genetic testing as part of the whole diagnosis issue. My understanding is that currently, this Act is in conference, and, you know, we'll see where it goes.

As I said before, we do not really fund directly any research on rare diseases. So our assistance, I guess, to this group or any other group who is focusing on genetic testing and screening as well, what we can largely do is really provide some assistance and some coordination. For example, if, for a particular genetic test, there is a good reason to have a scientific workshop to move this forward in some way, we would work with one of the institutes or conceivably a voluntary support group or federation to put together a scientific workshop, and we would certainly partially or totally fund it.

I think on this particular overhead, it's not something that I need to discuss with you since I'm sure you're very familiar with the issues. But I think what it does show is that genetic testing and rare diseases is just ever so different from genetic testing for more common diseases and just as you are concerned about any possible shift away from rare diseases to more common diseases, we're equally concerned about that because we think the availability of genetic testing is tremendously important to genetically-based rare diseases.

Here's a list of the obstacles, of course, and again I think you're pretty aware of those. Single diseases are very often known by different names. Very often, very low prevalence, and thereby low demand, even if the whole family is tested, and many of these diseases and conditions are still extremely low, and, of course, the issue of case abandonment, which I think was discussed at considerable length at the earlier task force, I think in 1999.

Now, what we broadly define as possible incentives, and I think this echoes what Marlene Haffner said, is the Orphan Drug Act of 1983, the Humanitarian Device Exemption of the Safe Medical Devices Act, as discussed before, and in some perhaps more indirect way possible passing of the Rare Diseases Act because it would certainly enable us in particular to respond to the recommendations of the Task Force on Genetic Testing. I read through it again just to remind myself, and, of course, every single recommendation that affected us said if there is funding, and as long as we don't have the funding, of course, it makes it next to impossible for us to do something in a very effective manner.

You have handouts, and you can peruse them, and, of course, we're always available to discuss this with any of you individually.

We certainly share your concerns about the implication impact of profit incentives on commercial production of genetic tests for rare diseases, and we are particularly and adamantly concerned about the continued availability or the availability to begin with of safe and effective tests for rare diseases, once the research institutions have ceased to offer them.

I think, I hope this is fast enough for you, I think that really concludes my remarks, and I'd be very delighted to answer any questions you may have.

DR. McCABE: Thank you very much. We have time for a couple of questions.

MS. HYATT-KNORR: Either I told you everything you wanted to know or it may not directly

relate to the purpose that you're currently discussing. I want to add, though, that we're very interested in the discussions of the Rare Diseases Subgroup, and we hope to follow that and participate in that.

DR. McCABE: I would ask a question about the integration between the agencies, between yourselves at NIH and FDA, that we've heard about, other possible activities in the Federal Government and how they interface with each other.

MS. HYATT-KNORR: I think our interaction with the institutes and centers and offices at NIH is pretty well established in the very least to the production of an annual report on rare diseases that we do every year, and we did, in addition, a report on rare diseases in children that was congressionally mandated. So by that process, we always have a very good understanding of what's going on at the various institutes. Our regular director, if you will, Steve Groft came from FDA, and I think at one point actually worked with Marlene Haffner. So there are also a lot of informal links, and he's a pharmacist by training. So I think there, the interaction is very good. When it comes to other agencies, it really depends on the issue. Sometimes, I think there's very good cooperation and close cooperation, and sometimes, there's very little, and I think that's really where the informal relationships come in, particularly with some of the federations and alliances in the rare diseases community, particularly the Genetic Alliance and the National Organization for Rare Disorders. If we don't know already, they will be sure to tell us.

DR. WATSON: Just one quick question. I've been trying to figure out how the money changes, and I know you don't want to lobby.

MS. HYATT-KNORR: No, it's not that I don't want to. I can't.

DR. WATSON: But my question is actually, as a freestanding part of the Director's Office now, I presume that when you do rare disease stuff with NCI or other institutes, they subsidize those costs to some extent?

MS. HYATT-KNORR: Well, when we co-fund workshops, it is almost always a joint effort between an institute or a center and us and very often voluntary support organization or foundation as well.

DR. WATSON: I mean, you commented that you didn't have the funds to do many of the things that the Task Force had suggested be done.

MS. HYATT-KNORR: Yes.

DR. WATSON: By becoming a freestanding office, do you end up with more or less money?

MS. HYATT-KNORR: Instead of having 2.3 million, which I think we had hoped for, we would have 4 million just for the office itself and another 20 million for Centers of Excellence in research on rare diseases. I think that's substantially bigger, and actually that Act also would provide more money for FDA as well. So I think it would make a substantial difference just simply by the sheer number. Does that answer your question?

DR. WATSON: I suppose.

MS. CARR: I just want to clarify, because you would still need to get that through appropriations. Those would be what you would be authorized, but you would still need to work through the appropriations?

MS. HYATT-KNORR: Well, we don't know yet. It's currently in conference. So we don't really know.

MS. CARR: I'm saying if that were enacted, you would not be guaranteed those funds?

MS. HYATT-KNORR: That's correct. That's correct. Unless it was specifically appropriated.

DR. HAFFNER: Yes, I just wanted to concur with what Henrietta just said. Those are authorization bills and have nothing to do with the appropriation. We've seen lots of authorization bills.

DR. McCABE: Thank you. I think we need to move on. So Mary, if you will?

MS. DAVIDSON: Yes. Our next presenter is Dr. Glenn Miller, and Dr. Miller is the Associate Scientific Director of Genetics Applications or Genzyme. His laboratory is responsible for the technology development and assessment as well as assay development for Genzyme Genetics. A major focus of his laboratory is the performance of clinical trials surrounding the development of appropriate protocols for testing of complex disorders to be offered on a commercial basis in

the future.

DR. MILLER: Thank you. Good morning. I've been asked to talk about some of the issues in test development and especially for those of rare disease but really there isn't much difference when it comes to test development whether it's rare or not. It's still many of the same issues.

This slide is really there just to kind of set the stage that we do a lot of this kind of testing and test development, and it's for a wide variety of disease incidences, but when you talk about the three areas that we normally look at with test development, they all surround various areas of quality information, assay process quality. When it comes to information quality, the thing that we're really looking at early on is clinical utility, and there are a few decision points when it comes to clinical utility that we're looking at. Is there a peer-reviewed body of evidence indicating that the information we're going to be deriving from the test will actually be useful? Are we able to technically perform the test? Is this something that we can physically do in the lab? Do we have to acquire the technology, and what that hurdle will be, and what the impact of that information will be when we try to offer that information to clinicians and/or their patients and their families?

When it comes to the assay quality, we've spoken briefly this morning about the analytical validity and the clinical validity, but really when it comes to trying to validate a test, there are three main issues when you're trying to select what kind of test you're going to be validating, and it breaks down into the kind of gene you're looking at. There's the first type that's the easiest kind, where you have a limited set of known mutations that are clinically relevant, and then you just go about designing an assay that has fairly high clinical relevance and is fairly

straightforward to put together. The second set is perhaps a bit more difficult, where you have a very large set of known mutations, and you have to decide how your assay is going to assay for those mutations and whether or not you have to pick a subset of those mutations that really hit the largest fraction of the people you're trying to serve. Cystic fibrosis is perhaps one of those types of things where the variety of mutations that are done out of the 900+ that are known. The last is one that I think we're talking about quite closely today, those genes that have a wide variety of novel mutations or mutations that don't really have a lot in the way of population frequency information, and there, gene-scanning assays are often the way to go, and I'll talk a bit about that more later.

If you're talking about how we go about validating the tests once we've looked at a technology, we're really looking at various sets of technical specifications and assay specifications. The numbers that we commonly use when we're looking to validate an assay, develop an assay, is that the failure rate has to be less than about 1 percent and that's that the assay you know just doesn't work, and you have to repeat that assay, but the error rate, which is something completely different, an error rate in our hands is something that it looks for all the world like the assay worked but it's the wrong answer. That has to be as near to zero as we can possibly make it.

Now, there's two validations that we normally go through. One is a technical validation, which is really the early stage of selecting a technology, doing the proof of concept experiments, and then writing that first SOP that we're going to use to transfer it to the clinical laboratory. The second step of that is a clinical validation which is writing a clinical SOP that incorporates all of the things that we need to do in the clinical laboratory and is done on a production level.

One of the challenges, particularly with rare diseases, is finding enough clinical samples with informed consent to be able to develop your assay and validate your assay. You really have to look at a variety of mutation types to make sure that the sequence contexts you're working with are able to provide you with the information you need. That can be particularly difficult if the clinical samples are limiting. In some respects, you can use synthetic positives for that but that may provide you information on specificity but may not in fact be appropriate for sensitivity of your assay. So again, you have to be very careful in how you go about designing that assay and where you can make claims and where you can't.

The other issue that we deal with is, especially with rare diseases, is how has the mutation been characterized? Has it been seen in more than one study? Are you confident in the sequence, the DNA sequence information that you have? Has it only been seen in one paper and hasn't been backed up very well? Is there evidence for a mutational effect for what everyone else is calling a mutation? Is there sufficient sequence context available so that even if you're confident of the mutation itself, are you confident about the sequence around that mutation, that there aren't polymorphisms, and if there are polymorphisms, what are the frequency of those polymorphisms? That's particularly important if you are using a technology where the presence of a polymorphism near a mutation may affect your answer.

The last step that we really look at in this, and this is going through a fair amount of information in a relatively short period of time, is the process quality and that takes on a variety of areas from technical development through the transfer of that technology and then the QC issues. It's a very milestone-driven process. It involves initially the selection of the appropriate technology. There really isn't one-size-fits-all technology out there. We do the initial proof of concept

experiments and then validate that technology. As part of this and in a home-brew environment, this is as opposed to a device environment, this is something that's relatively new. There's a tremendous effort in-house and around the industry to do design history now and design control, and the real effort there is to be able to document what you've done and why.

Well, of course, the problem that I think we're really focusing on today is the fact that there's a lot of genes we're looking at. We heard earlier this morning about the numbers of rare diseases that are out there and the number of genes that cause those rare diseases, and there really isn't that much in the way of great technology to look at those genes. The biggest problem is that the genes that we're looking at don't have the one or two mutations that account for the vast majority of the population. There are, by and large, a large number of even private mutations. So there's consequently a very strong need for gene-scanning technology and that is not something that's currently available that is at the same time sensitive, reproducible, cost-effective and user-friendly. The one thing to keep in mind is that with the Human Genome Project, there's a lot of technologies that are being tossed on to the market for a single nucleotide polymorphism detection. Those types of technologies may be very good for research. They are not immediately transferrable to the clinical setting. They often have error rates that are much higher than you would ever tolerate in the clinical situation. So it's not that all of that money that's being tossed at the Human Genome Project is necessarily yielding immediately with clinical assays.

One of the problems with gene scanning is it does have a fairly high false-negative rate. This is particularly when you look at assays other than sequencing, and even sequencing may have a high false-negative rate when you really look at large genes. Sequencing, as I said, is good, but

it's not perfect. It really should be redundant over the entire gene. One-pass sequencing doesn't get you there when it comes to finding all the mutations and variations that you need. The technology is not perfect and that applies both to the chemistry as well as the software that's involved in finding those mutations. The resulting bottom line is that sequencing is still a very laborious time-consuming process, and most of that time consumption is in the analysis of what you get out at the end of that. Known mutations. The good news is that given the appropriate technology, if you're looking for known mutations, most of the technologies that are used in the clinical setting are actually quite accurate.

Well, once you've selected your technology and begin doing the proof of concept experiments, you have to answer a couple of questions. One is the assay throughput. Once you've decided that your failure rate -- not your error rate, but your failure rate -- is acceptable, does this assay actually meet the needs for providing timely information to the clinicians? What's the scope of the mutation detection you're trying to achieve? What are the known mutations that you're looking at, if any? Is there a clinically-relevant number or do you have to really go looking for every mutation in the gene?

Well, in this case then, you're starting with a set of technologies that you're doing a very small-scale technical validation on, and you have to design your reagents, and it's really starting from zero, even if you're using the same technology base that you've done before. You're looking at designing the reagents, setting up the parameters of QC and going through a series of things that result in an SOP that you can then transfer this assay to a clinical lab. You then move from there to the clinical lab introduction, which gets you the initial batch of QC reagents and drives down through the various QC procedures to a final completed clinical SOP. At the end of that,

you're left with the clinical laboratory launch which just starts the process of having to file the regulatory approvals and the various state approvals to get a test done. In particular states, you have to make sure that all of your CLIA and CAP regulations for the lab are appropriate for this as well as providing the information systems. You have to make sure that the samples you're getting in the door can be tracked all the way through from the time they arrive at your door to the time the report goes back out your door, and as far as we're concerned, you also have to provide some of the educational materials that are needed.

Now, all of this, of course, takes time and money to finish. It's not a short process, and it certainly can't be shortcut just because it's a rare disease. If anything, you have to develop the test to the same high standards you would use to develop any other test. You are operating in a fairly strict regulatory environment. You face additional challenges often with rare diseases in obtaining the proper controls and test samples, and for most of these, you are required to develop these in a home-brew environment which really means you can't rely on the nice prefab kits in a box. You have to develop a lot of the reagents yourself to meet your own internal standards as well as external regulations.

The bottom line that I'm hoping to convey here is in this process is for either common disease or rare disease, a difficult time-consuming and costly process, and the part that we try to keep at the front of our minds at all points is that the sample that comes in the door is attached to a patient, and it's very important. That particular piece of information is very important to the patient and their families. I'll stop there and take questions. Thank you.

DR. McCABE: Thank you. Any questions for Dr. Miller?

DR. WATSON: I'm just curious. I guess you've never gone for an HDE or humanitarian device exemption application for some of the rare disease testing?

DR. MILLER: We haven't. I'm not sure that all of -- to be honest, a lot of those regulations, I'm just hearing about this morning, but we haven't been a device. Most of the tests we're looking at are not really thought of as devices. They're home-brew environments.

DR. CHARACHE: I'm hearing the difference here between laboratories developing assays and the kit manufacturer developing assays. You've developed a strategy that ensures your accuracy in what you produce. It sounds as though FDA, what we heard from Drs. Haffner and Less, is using an approach which makes the kit manufacturing review realistic when you don't have a large patient base to draw from. So your challenges would be primarily at this point the CLIA regulatory control with the discussion now in place about the home-brew review with FDA. Is that a correct formulation?

DR. MILLER: Yes, it really is. There's a lot of the things that we have to do that the regulations are changing as we speak. You know that better than I do.

DR. BURKE: I just want to make a brief comment about the term "clinical utility" and the fact that clarity about that term relates to the very issue that we were talking about as a problematic issue earlier that we need to discuss. As I read the DOE/NIH Task Force definition of clinical utility, it's pretty precise, and it basically says that there is clinical utility when the test used leads to the potential for an outcome benefit, and the implication is the health outcome benefit, but it's clear that there is a notion of value to genetic tests well above and beyond that fairly strict

definition, and I think we just heard that thinking about the value of a genetic test includes thinking about whether people want the information, rather than thinking about what kind of health care outcome benefit might lead from the use of the test. I'm not saying this as a judgment one way or another. I do think it would be preferable to be very precise about our use of the word "clinical utility" because I think it's useful to be precise about that concept. If we find that we can't be precise about that term because the term "utility" seems broader, then we probably just need to think about another way to distinguish clinical validity, the ability of the test to have some predictive value, value applied to the information, and, as I say, a separate concept, the possibility that the genetic test will lead to a health outcome benefit.

DR. McCABE: Good. Thank you very much. We're going to take a break. We will return at 10:35.

(Recess.)

DR. McCABE: Mary, do you want to introduce our next guest, please?

MS. DAVIDSON: If we can get started again. I want to introduce Dr. David Wenger. Dr. Wenger is the Director of the Lysosomal Diseases Testing Laboratory at Jefferson Medical College in Philadelphia, and since 1974, the diagnostic component of this research laboratory has tested more than 29,000 individuals in an attempt to arrive at a diagnosis in the adults and children suspected of having one of the lysosomal storage diseases. They do carrier testing on family members and prenatal diagnosis is available for at-risk couples, and I think with that, Dr. Wenger.

DR. WENGER: Well, thank you for inviting me. I feel a little bit like a brown shoe at a formal party here talking about protein-based testing and using slides. But maybe I can give you some perspective about -- I guess when I was asked to talk, the discussion was research labs taking on clinical testing, and I can tell you just from my experience and maybe some of the problems that we have run into and how we handled things and maybe some ideas for your Committee.

This is the lysosomal storage disorders. It's a group of about 30, a little more than 30 genetic diseases. The ones that I put a little star here are ones that we diagnose in my lab, about 21 different genetic diseases that we can test for. As I told you, we are a protein function-based diagnostic lab, not so much a molecular lab, but I think there's some things to be learned from the lysosomal storage diseases. These have set the trend in many ways in being some of the earliest testing has been done in children and screening, carrier testing for the Tay-Sachs Program, and one of the first group of diseases that have some real therapy that have to consider -- obviously we have to consider early diagnosis. So I think there are some lessons to be learned from this group of diseases. There are a group of about 30 genetic diseases. Some of them are extremely rare, some are less rare, all of them, I guess, would be certainly considered rare.

There's a problem here that you'll see. We have a lot of children that die in infancy and are quite young and very severe. We do have a group of older patients, and there's a lot of clinical variability that would either preclude or make their diagnosis or suspected diagnosis very difficult, and this is also an interesting factor that comes in as we talk about therapy, which I won't talk about, but how do you look at effectiveness if there's a lot of variability even with

patients with the same genotype?

They occur in about 1 in 5,000 to 8,000 births, thereabouts. So that would make 500 to 800 patients born per year. In most of these diseases, the genes have been cloned. There's a great number of mutations that have been found in almost all patients which really precludes DNA-based testing. We really do not do it in my lab, and I'll explain some of that later. Obviously the carrier testing program for Tay-Sachs disease has been a remarkable accomplishment in disease prevention through identification of carriers, and I want to make a real point, that we need earlier diagnosis because there's real treatment, not just symptomatic treatment, for these patients are getting enzyme replacement therapy and bone marrow transplants early in their disease. They're doing remarkably well.

So the laboratory that I started at the University of Colorado Health Sciences Center, I was working on some rare genetic diseases, Tay-Sachs disease -- I mean, not so much Tay-Sachs but on Krabbe disease and Niemann-Pick disease, and we were asked to help with the diagnosis by local physicians of suspected patients. I was not a clinical lab. I was asked to help. We had the substrate. We worked out the assays that we could use in tissues, but we worked them out for easy accessible tissues, and we got a couple of samples that year. In the next couple of years, we expanded the number of tests, realizing that there was a lot of variability in the clinical picture, and we were receiving clinical history, and we couldn't do the tests. So we expanded the number of tests that we could run, and we started to get more and more samples from around the country. We initially for the first five years or four or five years, we never charged for testing. We considered it part of our research, and then we started to charge for our services, and in 1986, I moved to Jefferson, where we continued to see a large increase in more

and more requests for samples. Again, most of them are protein-based, but we're always increasing our methods and changing our methods or using DNA, if it will provide information. We get about 2,600 samples from 2,600 individuals a year. So we've screened about 30,000 patients, have come to me, a call from a physician, a genetic counselor, trying to make a diagnosis in their undiagnosed patient. That doesn't count carrier testing. These are patients. We've diagnosed over 2,400 patients. We sort of look at our hit rate, which is interesting, because that tells you about how many of these were successful. Some of you will look at that and say that's a nice high number. Some of you look at it and say it's rather low. I think it's a rather good number that we make a definitive diagnosis, not a presumptive diagnosis but a definitive diagnosis of about 8 percent of these patients. We do thousands of prenatal tests.

We require clinical information, and this is one of the issues that you'll get into if you just have a sample with a lab slip that just says run this test for this one disease. We don't do that. We will not do it. We will only do it when we have clinical information, so we can take part in the decision making, and if we don't make a diagnosis, and it's not a test that we can run, then we suggest other testing. We suggest other labs that could try to fill in for that test that we do not run.

Here's the names of the diseases that we've diagnosed and the number of patients. Some of these are relatively, you know, very, very rare, only a couple of cases. In fact, we found the first case in the world of that, but this is not actually their incidence because some of these diseases, let's say Krabbe diseases, our research interest, and you need natural substrate. You can't buy it. So we do most of those for the United States.

This is the reason for getting samples. Patient screens. This used to be a much higher number, maybe it was at least 85 to 90 percent. Now we're getting many more requests for carrier testing, more requests for prenatal testing, and this is the two areas that have really jumped recently. There's a realization that early bone marrow transplantation will help these children. We're getting many, many more samples for potential either cord blood or family members for hematopoietic stem cells for transplantation, and we're getting samples obviously to follow up on those patients that have gotten samples. So who we get samples from has changed dramatically.

We run them as a panel of enzymes. In other words, we're not looking for mutations. When physicians ask do you do this by DNA analysis, it is not a good question because we do not know what to look for, what gene to look for. We are running them by protein-based assays. So this is about 85 to 90 percent of the total. We do some metabolic studies and culture cells for some of the more esoteric diseases where there is no direct enzyme-based deficiency. Occasionally, we look for analyses to confirm the diagnosis, let's say, of metachromatic leukodystrophy, looking for sulfatide excretion because there is a pseudodeficiency allele that confuses the diagnosis, and we do some DNA-based tests when we have a defined population, either in the Jewish population in Israel or Niemann-Pick among the Hispanics of Colorado, New Mexico. We've developed a test and that's a PCR-based molecular test because we know exactly what to look for. In fact, we were just doing an Eskimo from Alaska. They have a high incidence of metachromatic leukodystrophy and have one common mutation, and we do that by DNA analysis.

Now, why do we see an increased number of samples being sent to our lab? We're seeing our

numbers go up year after year after year. I think people do appreciate our help with diagnoses of these relatively rare diseases in that they only send us clinical history. They let us pick the tests that can be run. We charge a flat rate for no matter whether I do five tests or 12 tests or 15 tests. I just charge one rate because I feel we should have free reign, basically, without running up a bill, of doing any testing I feel is indicated by the clinical picture.

We have a rapid turnaround time. Yesterday was diagnostic day. If I was there at work today, the reports would go out today. Every week, they turn around. Thursday, we do the tests. Friday, the reports go out. There has been the closing of other laboratories who are getting too few samples, and I think you'll run into this problem as you end up getting into other molecular testing. How many labs should be doing it, and whether they're going to see enough samples to really be confident when they finally do see an affected patient. We are seeing a physician awareness, and genetic counselors, who I would rather have a call from a genetic counselor than a physician truthfully, when they're discussing a patient and the reporting of the results that we're going to give them, and I think there is more of an awareness that now for some of these diseases, there is effective therapy, and they really have to get these patients diagnosed accurately and as quickly as possible to avail them of these new therapies that are coming and this legal -- obviously, there's always concern about missing a diagnosis, and since the clinical pictures are so varied, you can really -- we get a lot of nondescript, you know, mental retardation, developmental delay.

Now, I guess an issue that will come up when you develop a new test, as research labs are developing maybe one disease, they develop a test, how are people going to find out that it's now available? Well, for our lab, it was mostly word of mouth. We've never advertised. People just

keep calling me and say can we use your lab? We are listed in GeneTests. We have a website, and I think that some of this has come through my service on boards where we have family-oriented boards, foundations, where I provide information and research updates to them, and they sort of set us up as the lab that should be doing the testing for their families.

We do see some problems, and maybe my problems are rather mundane. I know I think maybe David Ledbetter will talk and other people will talk about the accuracy of testing. I see more problems with receiving samples and with the exchange of information, rather than doing the test. That's a bigger problem. Obviously there's a lack of awareness about some testing that is available. We don't get a good clinical history, and we have to wait until we do get some reason, other than run one test for one disease, and it wasn't even indicated when I get the clinical picture. They should not even have requested the one test that they did request. That's covered more here, but there's inappropriate tests. Yesterday, we diagnosed galactosialidosis. I'll send back the report. They won't know what this disease is. We need to try to get the qualified health care person at the other end to understand these diagnoses, read about it and provide information to the family.

Some diagnostic labs will just do the one test that's indicated, and they will not end up making any suggestion, and from personal experience, when I see a test in a patient we diagnosed recently, 14 years of age, it was sent to another lab eight years ago for one test. They did it. It was not the diagnosis, and the patient sat undiagnosed for the next eight years until it came to us. We did our screen, and it was obvious what she had, and even by the picture, the photograph they sent me, I knew what she had because she looked so classic for one disease, and again we have some silly things, like getting the right return address can drive us up the wall.

Now, again I'm more concerned a bit about the intangibles about who does testing, and it's not a money concern. It's really if research labs, and I know there will be other opinions about this, are doing these kinds of testing for rare diseases, it really has a lot to do with the intangible of having an interested person, the skilled people, that will perform these tests as opposed to, you know, worrying about whether my refrigerator is four degrees. I'd like to see that we really -- you can't measure this, but I'm very interested. I love it and so do the people who work with me, and it works. We need to have people to handle the inquiries into that lab about the state of the sample and the results, so that someone can call and get someone on the phone that can say this is what we did, and this is what that test means, and this is what it means for the family, and we need to have a system for providing results. Obviously getting results out is what a lot of research labs don't really understand, is you need to do the tests in a reliable way that gets the results out as quickly as possible.

Now, there's comments regarding research labs doing testing. I mean, my opinion is they are the best place because I think scientifically the best place, but I think this big "if" is whether they're interested in doing it. I don't have a big problem with accuracy. I have concerns about handling increased numbers of samples and returning results in an expeditious manner.

We need contact persons in the lab that are very knowledgeable, and obviously this is going to come up, and it came up already, if the test that you're doing is DNA-based, not activity-based or protein-based, obviously there's limitations to what that finding of mutation will mean. If a new mutation is identified, it may not be disease-causing and proving it could be difficult. This bottom one, the chance for complacency when you start getting large number of samples, this

may sound trite, but I think that a lab that's used to dealing with immediate families, and you had a high chance of finding patients and carriers, now they're going to be used as a screening lab, and they'll be getting many more samples of which you'll have a very low hit rate. The question will be, will that lead to some type of complacency and maybe not less accuracy but sort of you're not on your toes.

CLIA certification. Now, again I certainly think you can comply with the general regulations, but I have some problem with this input between the sending person and the laboratory about getting the right sample, interpreting the results, reporting the results and getting them back to the family in an accurate way. I don't know whether this is right, but I think the standards could be lowered, if they do only one disease, and they're just going to be doing that. Again, it's not the accuracy that I think I have a problem with, it's their handling of the samples and getting the results back. They obviously have to run their own control. We have to run our own controls. I can't run a disease control for each of these diseases when I see one every one year or one every two years. I can't put in a known case of every disease each time, and I think I'm very interested in fostering interactions between the person requesting the test, whether it's a physician or a genetic counselor, the laboratory, to be sure that all this information is supplied, and if it isn't the diagnosis, that somehow a mechanism is put in place to suggest other labs or other tests that might be indicated by the clinical picture.

So again, I think that I'm in favor of a few qualified labs doing testing for these diseases, but I think that I'll be interested to see how you reach your conclusions in your Committee because I know my lab has been a great source of pleasure to me. I've put a lot of heart in it, and I know it works extremely well as a research lab doing diagnostics.

DR. McCABE: Thank you. We have time for several questions, a couple of questions, for Dr. Wenger.

DR. KHOURY: A question about the availability of interventions. I mean, we come back to clinical utility. You said bone marrow transplants work.

DR. WENGER: Yes.

DR. KHOURY: Could you elaborate on this?

DR. WENGER: Well, again, I don't know whether we want to discuss treatment, but I think that there is no question in the diseases, the leukodystrophies, which is my main research interest, is that when children are diagnosed, either presymptomatically because they did not intervene in a pregnancy, and it was a factor or they didn't monitor a pregnancy, that these children do remarkably well with a bone marrow transplant, remarkably well. The same with other kids with the juvenile forms of these diseases, the lesser forms. Obviously enzyme replacement therapy for Gaucher, for Fabry, for Hunter's, MPS1, these will all require early diagnosis. If we're going to get these children when they're so far symptomatically involved, I think they have missed their opportunity for effective therapy.

DR. LEDBETTER: David, you said you started as a research lab with an interest in this, but given your current volume and the number of tests, why do you not consider yourself a clinical lab?

DR. WENGER: Well, I guess what's in a name? I consider myself a --

DR. LEDBETTER: The ones that worry about accuracy and sample mix is those that remain small and those who aren't as attentive to which personnel and which training and motivation and attitude of the personnel and continue to use graduate students, postdoctoral fellows or technicians with limited experience doing clinical diagnoses, carrier testing and prenatal diagnoses, and you've clearly graduated beyond that and operate now like a clinical lab.

DR. WENGER: Yes. I guess you could call me a clinical lab, but I agree, there's no other way I can say it, except that having well-trained interested personnel lowers your risk for mistakes. I mean, I've been sent the wrong sample a number of times. For prenatal tests, I've been sent wrong cultures. You cannot get human error out of this. The accuracy of the testing also depends on the reagents that I buy. If I buy a substrate that's supposed to have one sugar in a certain linkage, and it's contaminated with another, the best thing we do when we change lots is put in a known patient and confirm that it makes the diagnosis. But I agree with you. I don't consider myself a clinical lab. I still like to consider myself in my side-by-side labs of having a major research, NIH-funded research lab next to a diagnostic lab, that I am really a -- maybe I'll hyphenate it.

DR. CHARACHE: I was just going to comment that I don't think clinical lab is a dirty word. And I think that the ideal lab, regardless of what it is, is both. That's our charge. Our clinical microlab does research.

MS. BOLDT: I do think semantics are somewhat important, though, because when you have GeneTests, and if you have sometimes 27 different labs that someone's looking at, and as a genetic counselor, you may know what's a reputable lab or what's being done in certain labs, but to another physician or someone that's not a geneticist professional, they may not know. So if they see research versus clinical, they may never even call a research lab because of those issues.

DR. WENGER: Well, the issue of how people find a lab is another issue that's going to be difficult for you to tackle.

DR. LEDBETTER: But just to clarify on GeneTests, you are listed as a CLIA-certified lab?

DR. WENGER: Which I am, yes.

MS. BOLDT: Right. You're right. But not everyone knows to look at that as an important consideration.

DR. LEDBETTER: Looking at GeneTests, it should be fairly obvious now.

DR. McCABE: We need to move on. We'll come back to these issues during the discussion period.

MS. DAVIDSON: Our final presenter is Dr. David Ledbetter. Dr. Ledbetter is a clinical cytogeneticist and has actively directed clinical genetic testing and prenatal diagnosis laboratories

for more than 20 years. He has been a leader in the field of technology development and translational research for genetic diseases, particularly in chromosomal and mental retardation disorders. He's currently the Professor and Chair of the Department of Human Genetics at the University of Chicago.

DR. LEDBETTER: Thank you for the opportunity to talk today, and I think you'll see that Dave Wenger and I are coming to similar conclusions from different sides. I identify myself primarily as a clinical laboratory geneticist and running a clinical lab. I have a research lab, which gives me great satisfaction and pleasure, but the purpose of my research lab is to develop new genetic tests and then to do translational research, transferring that from my research lab to my clinical lab as rapidly as possible.

I thought I was going to present some novel paradigms this morning, but I was gratified to see Vicky Whittemore's presentation and to see that the TS Alliance and TS groups have created a research lab-CLIA lab partnership which I would like to generalize that paradigm. I could just say that they've done it right. Every other disease-specific group should copy them and do the same thing, and we'd solve this problem, and I can just sit down.

DR. McCABE: Thank you, David.

DR. LEDBETTER: But I won't. Because I'd like to emphasize a few points. In today's presentation, Patti Mills, some of you have met my genetic counselor who's worked with me on this project, and Soma Das is our molecular lab director.

So let's define the problem, limited access for rare disease testing, in part because it's still expensive testing with relatively low test volume. So that just means it's a cost-effective and financial issue. Researchers who are involved in this feel a moral obligation to provide beneficial clinical information back to their families, but they're not qualified to do that, and most would prefer not to, after they've extracted sufficient research value out of genotype/phenotype information over the first 50, 100, 200 mutation examples. I'd like to point out, although the technology is not perfect, the technology is good, and all of my comments are limited to molecular diagnostics primarily by DNA sequencing and associated and not in the biochemical and other functional type of assays.

Technologies are good, and there's no shortage of CLIA labs available to do this. There are plenty of CLIA labs. In fact, academic CLIA labs are struggling for survival, struggling for survival in an academic setting and trying to figure out how to develop a sufficient workload and revenue to stay in business. So this is also just a logistical and financial problem.

Now, rare disease genetic testing has been addressed before by the Holtzman Committee, the NIH/DOE Genetic Task Force, and they were sympathetic to the problem that a lot of rare disease testing is going on in research labs and worried that if research labs didn't do it, nobody would do it, and they suggested the possibility that the Genetic Subcommittee of CLIAC develop regulatory language under proposed genetic specialty that is less stringent but does not sacrifice quality. I'm not sure how one would accomplish those apparently contradictory goals. I think testing in research labs is a bigger, more important problem than has been appreciated, and although I'm sympathetic to maintaining testing, I think there's more positive proactive steps to solve this problem.

A recent survey of GeneTests shows there are 866 diseases where testing is offered. Only 511 are in CLIA lab settings. That means 41 percent of genetic diseases we're testing is available and performed in research labs only. Now, this is not 40 percent of tests because the CLIA labs represent the high-volume tests, and these represent low-volume tests. So it's a much smaller percentage of all genetic tests being done, but of the diseases, 41 percent are only available in a research lab.

Now, what are the problems with research labs? Dave Wenger's lab excepted, I think there are significant problems and that is the personnel are not trained as clinical laboratory technicians or medical technologists in terms of quality control sample handling, and the most frequent errors in any lab, clinical or research, is sample mix-up, and it's a big problem in all clinical lab settings, and there's significant efforts to try to drive down the sample mix-up error rate in all clinical lab settings, and part of this Committee is to raise standards for genetic testing and not to lower standards in order to solve this problem.

There's no good data on the frequency of errors or sample mix-ups in genetics research labs, although if you informally poll anybody involved in genetic linkage study, they will all cite the same 1-to-2-percent rate of sample mix-up identified in acquiring families and doing genetic linkage analysis. That means the potential sample mix-up for genetic testing on those samples acquired in the research protocol is 1-to-2-percent. So technically, they know how to perform the molecular tests. They're very smart, experienced, capable people, but they may give you Mrs. Jones' result instead of Mrs. Smith's result, and the rate of that is potentially 1 to 2 percent. This is not consistent with human subjects protection issues, and it's remarkable to me that this has not been a more major consideration, but the information coming out of research labs -- let's not worry about the formalities of CLIA regulations and Federal law. As a human subjects

protection issue, I see this as a major problem that we may be giving the wrong person's results, accurate technically results, but to the wrong person coming out of a research lab. My reading of the Federal Code related to human subjects protection is that it's our job to minimize these risks using procedures already being performed in a diagnostic setting. By partnering a clinical lab with good quality control and the research lab, you can solve this problem. From the Belmont Report, which forms a lot of the ethical principles for our attitudes about human subjects protection and Federal Code, I'll just remind you in genetics, the potential implications are beyond the individual patient or subject but extend to the family, and this could lead to wrong information about future family planning decisions if you give the wrong test result to the wrong person.

So here's the potential solutions, and I'll editorialize my opinion about these. So there are considerations of giving CLIA exemptions or lowering the standards for research labs, and I hope that I've made my position clear. I think this is a dangerous and inappropriate consideration from a human subjects protection point of view. You could encourage research labs to become CLIA-certified. If they do it in the way Dave Wenger's lab has done it, then they become real clinical labs. If they only do one test, and they still use the research personnel who rotate every year, they are not clinical labs, and it's not the intent of CLIA to have them pass the minimal paper standards but not behave in real clinical lab quality control standards. They can partner with CLIA labs, as you heard this morning, and I'll comment further, and this would be quite consistent with human subjects protection, and I think this is a straightforward solution, and ideally, we would establish a national laboratory network for rare disease genetic testing with a number of qualified labs available.

Our experience for this starts in 1996, when I moved to Chicago and wanted to have a strong diagnostic laboratory as a core facility for our research and for my own translational research. Our business plan was to not set up any genetic test offered by Genzyme. There was no purpose to duplicate. We couldn't do it any better or any cheaper than Genzyme or Baylor or the other good national genetics testing labs. We had to fill a different niche. Rare disease testing is an important and huge niche. Why not fill that niche? So that's what we did, firstly, by translating our own research into clinical genetic testing. As some of you know, we work on Prader-Willi and Angelman syndrome. We've developed a simple PCR methylation assay which we now do five to 10 samples per week, referred from around the United States. We also work in brain malformation disorders. There are two genes identified. We offer comprehensive mutation analysis by direct sequencing of the coding region of these two genes. We provide this diagnostic service on a worldwide basis. After we did this with our own research projects, we've sought collaborations with other investigators. The first example, X-linked myotubular myopathy. The MT1 gene was cloned in 1996. Phase I, Gail Herman at Ohio State had collected families, done linkage analysis, when the gene was cloned, identified mutations by sequencing the entire gene. When she had found a mutation, she didn't want to do the full family carrier analysis and prenatal diagnosis. She referred the families to send new samples to us. We would confirm the mutation and one exon by direct sequencing, based on her results, and then we would offer carrier testing and prenatal diagnosis to other family members. In the Phase II, she wanted to stop scanning for mutations, so we took over complete sequencing and mutation analysis. Now when people call the expert investigator, she refers them to us, and the national support group refers them to us. When we have questions about the mutation and the interpretation as it relates to phenotype, Gail Herman is our expert consultant. So we have the scientific expertise for this rare disease as well as CLIA quality control.

Just in terms of volumes, we do about 300 per year, Prader-Willi and Angelman syndrome studies a hundred per year, lissencephaly 2, and now 50 a year in TM1. We've recently added Minke's disease in collaboration with Jane Gitcher at UCSF, and Hallervorden-Spatz or sequencing of the PKAN-2 gene with Susan Hayflick from Seattle. This estimate is a minimum estimate just based on developing primers, flanking each exon of a gene for sequencing and a small number of confirmation studies of known mutations from the research lab. The real cost of doing a full evaluation as described by Glenn would be significantly more than this.

DR. McCABE: David, could you speed up a little bit, please, so we have time for discussion?

DR. LEDBETTER: So the general paradigm that I'm describing is CLIA molecular labs or pathology labs exist at most medical schools or hospitals. Many clinical research centers at academic medical centers have CLIA labs. We make the mistake now of having the CRC isolate the DNA in a CLIA environment. They give the whole sample to the research lab for linkage and mutation. Just give them half, keep half in a CLIA-protected environment. Then if anything clinically useful is identified, you're able to confirm it in a CLIA lab and to report the laboratory result.

IRBs have an important role, and I think they should more closely monitor research protocols. At the University of Chicago, 60 percent of IRB protocols include drawing blood for DNA isolation, for genetic analysis, 60 percent of our CRC protocols as well. I think funding agencies should provide some guidance to research labs that this model is appropriate, and the costs are an appropriate research cost that can appear in their budget requests.

In my view, since this is a significant risk to human subjects, the fact that it adds costs to add quality control by including a CLIA clinical lab as a partner to the research is an inappropriate counter-argument to this. Yes, it will add some costs. In other human subjects protection areas, it's my understanding that the fact that it's inconvenient or costs more is not an appropriate excuse to not do it right. Many researchers feel such a strong obligation, they're willing to ignore or break Federal law to provide this clinically-useful information. However, I think funding agencies have not done enough yet, and I hope this changes. The human research protection issues, I think, have been overlooked and translational research, in my opinion, has not been adequately supported. This includes the ELSI arm of both the DOE and NIH, where safety and efficacy of genetic tests is listed as one of the primary missions related to it but funding for translational genetic testing research has not been a high priority.

The Rare Diseases Act, I think I can lobby for this, will give statutory authorization and hopefully increased funding for rare disease research. There's a proposal for a network of regional centers of excellence, and this includes diagnostics research.

So the solution I'm proposing is a national laboratory network for rare disease genetic testing, and during the American Society of Genetics meeting, we decided to just start it without any particular funding yet. We have a website that's in your handout and that is online now. This is our home page. Our mission is to fill this need for high-quality clinical genetic testing for all rare diseases. We have a description about this network. There are two member labs so far, University of Chicago and GeneDx, which is here in the Rockville area, and Sherri Bale is here in the audience today, and an invitation for other labs to join and be part of this network. We

have links set up to SACGT, NORD, the Alliance, CDC, CLIA '88, and we're happy to add other interested parties' groups. Description of how family support groups and others might help in stimulating new genetic testing, and finally an invitation to be acknowledged in future presentations. Thank you.

DR. McCABE: Thank you. We have time for perhaps one question before we move into the roundtable. Any questions for Dr. Ledbetter? If not, I think we should have all of our guests join us at the table here for a discussion of the morning's presentations.

MS. DAVIDSON: First of all, I just want to thank everyone. I think I'm not the only one that sat here really for the first time getting a sense of the lifespan of a genetic test and how in different parts of the community, how tests really develop. I heard the term "the rubber hits the road" any number of times, but I think it was most informative and certainly the numbers of questions and discussion indicated that, and so, quickly, I just want to move on and turn it over to my co-chair, who may also want to add his perspective, before we open this up to Committee input.

DR. WATSON: I thank everybody for their talks. They actually came very close to where we wanted to end up without having to really tell you where we wanted to end up. I think we got a very broad perspective of the issues, and I'm happy to go straight on to questions, if anybody has one. I can ask the first.

One of the issues that struck me, and I think both David Ledbetter and David Wenger and probably Glenn may have perspectives on it, and that is the issue of it's one of the tasks the Task

Force on Genetic Testing had tremendous difficulty dealing with, and that was whether there should be qualifications for the people who request tests of laboratories. I think David certainly commented on reaching a point where he essentially decides what tests you're going to get because nobody could ask for the right test, and my laboratory certainly ended up in sort of mid-grounds there, where we let people ask for tests. We initiated all billing because they were wrong most of the time, and we changed what they asked for, and we talked to them and explained why they wished they should have -- they had asked for something different, which became our request for the test. It's a difficult problem for laboratories to be deciding what tests should be done for patients.

DR. WENGER: I just agreed to that statement, but I don't see how you can regulate who -- when I think about who requests testing to me, it runs the gamut from the small-town pediatrician to the well-trained child neurologist to the genetics and genetic counselors, but the idea that more than 60 percent of the samples come in with only clinical information and no suggestion of a diagnosis or of what tests they want run, and I think that just comes from trust, knowing that we're going to run whatever we're going to run anyway. They may ask for a test. I might not run it because it's just clearly they've got the disease and the enzyme mixed up. They've asked for the wrong test. I mean, it doesn't take any smarts to realize that. So I don't think you can regulate who sends me samples. We just would love to get good samples with a good clinical history and let us do the rest.

DR. LEDBETTER: So having been at Baylor when the molecular diagnostic lab started there, since I left, we follow what I refer to as the "Pat Ward model," and Pat Ward was the genetic counselor who was primarily associated with that lab and was the contact person to the outside

world and served an important role in educating the users of the lab what was appropriate, what was not appropriate, and when I was at NIH and now at the University of Chicago, the first thing I did was identified a genetic counselor who was experienced and knowledgeable who was that liaison, who would review the clinical information, the request for testing, and then get on the phone and educate the sender who had asked for something inappropriate or we had incomplete information. So it's a lot of time and effort to do that, but it's a valuable educational service back to the community.

DR. BURKE: On this issue of ordering the wrong test, I actually find your comments incredibly informative on this. I do think we want to avoid the issue of genetic exceptionalism. I think we're seeing a trend in medicine generally of recognizing that a partnership or collegial kind of relationship between the lab and the ordering physician, between the pharmacy and the ordering physician, between radiology and the ordering physician is very productive. Obviously physicians have extraordinary numbers of different kinds of diagnostic and screening tests that they need to consider or medications that they need to select. The opportunities and options are changing all the time. So I think what we're recognizing is not an issue particular to genetics, and it is a very important issue for genetics and for clinical practice generally, that we need to figure out the right dialogue and the right support mechanisms, sort of building on some models that I think you've suggested to us, to help health care providers to order what's going to help their patients most.

DR. ZULLO: Primarily, this is for Dr. Ledbetter, but I'm still thinking through your human subjects protection comments, and I'm not sure I have an answer yet. But one question I do have. I actually have a two-part question. My first question is, do we know the percentage of

sample mix-ups in CLIA labs? Is it significantly lower? Because the number you're giving in research labs is an estimate. So do we have a number in CLIA labs?

DR. LEDBETTER: Yes, that's also a difficult number to come by and perhaps Dr. Charache can comment on this. There is a literature on error rates that includes sample mix-up, and I think from that sample mix-up is the most common error or source of error in the clinical labs, and depending on how you define error and in what kind of lab testing, it may be as much as .5 percent, which is 1 in 200, which is only twice as good as research labs, down to about 1 in 25,000, which is clearly orders of magnitude better. So we don't have exactly the right number in terms of comparison. In genetics, certainly there's no data, and molecular genetics, errors due to sample mix-up, CLIA molecular genetics versus research genetics labs, and it would be nice to have that, but all of the anecdotal experience of clinical labs and research labs, my personal estimate would be the sample mix-up rate is 10 to 100 times greater, conservatively, in a research lab setting, and it's easy to imagine that when the research labs are depending on postdocs, graduate students or technicians with less than one-year training in a research lab and not in a clinical lab.

DR. McCABE: Pat, do you wish to clarify that?

DR. CHARACHE: Yes. It is very difficult to get the number, but one of the things that CLIA does is look at this very intensively. How do the samples come in? Where are they placed? What is the likelihood of steps that would cause mix-up? What we see when we review research labs, where they haven't had guidance -- once they've had instruction, they'll do it, but where they haven't had guidance or don't know about this, there are steps that lead to

misdiagnoses. We, for example, in one lab, I won't tell you which institution, saw the slides that were laid out for eight different patients, and no patient identifiers were on any of the slides that were about to be read. This was a research lab doing patient care. We've seen samples come in and have everything taken out of the box and put in trays without having first seen which member of the kindred was in which location, and then someone trying to remember who put -- you know, whether Ann was in this place and Joseph in another. So it's amazing what happens, particularly when there are medical students, graduate students, and whomever working in this research lab. It's a matter of education, and this is one of the orientations of the CLIA, which is to educate.

DR. McCABE: The real problem with the estimate, unless you do a very careful study, is that it's probably an underestimate because you pick up where the mix-ups are identified, and you don't pick up where the mix-ups were not identified. So that's why it's probably an underestimate.

DR. ZULLO: Can I do the second part of my question?

DR. McCABE: Yes, sure.

DR. ZULLO: And this isn't necessarily to David. This is not my OHRP hat. This is just trying to think through all of this. If genetic tests specifically for rare disorders were only allowed to be done in CLIA-certified labs, and there seems to be kind of a professional courtesy not to overlap because it doesn't serve a purpose, is there going to be a problem for patients that it becomes an access problem if it's done by one company? I'm just asking due to my naivete.

DR. LEDBETTER: I think for any clinical lab test, you need some opportunity for a second opinion or a confirmation, but I think the community of labs, academic and private, would agree to some system of allowing confirmation of a test result done primarily in one lab. I think practically, it makes the most sense for rare diseases, for one lab to be the primary provider, but in a system where there's some, you know, proficiency testing and coordination with maybe a higher level of standards and an ability for another lab in the networks, say, to do a confirmation or second opinion-type study.

DR. McCABE: Dr. Whittemore, do you want to make a comment?

DR. WHITTEMORE: Sure. My only concern there is in terms of the volume of the test and the turnaround time. So for example, if there was only one lab offering a test, and their normal turnaround time was six weeks, is that going to be sufficient. I think for turnaround time, it's potentially an issue, but I don't see for the most part that having one lab doing it is a problem, and in fact probably is a benefit because you gain more experience with that one test and with what the findings mean.

DR. McCABE: The only issue I would raise, as just a hypothetical, but what is that one laboratory now goes out of business, the individual retires? What is the legacy in terms of training and, you know, the other issues that go along, comparison? I'll take direct follow-ups to this.

MR. HILLBACK: It's direct to this. I was very happy that David said his strategy wasn't to do

the tests we were doing, but I don't think everyone plays by those rules exactly. I think that the odds of very many tests only being done in one lab over time is going to be fairly minimal. There will be certain ones that are, but I think then it goes back to you have to do enough tests to have some competency, and I don't think it's a big problem.

DR. LLOYD-PURYEAR: I was going to ask about the impact on newborn screening.

DR. McCABE: That's a different issue. So anybody else want to follow up on this before we move on?

DR. CHARACHE: I would just come back to the issue of the one-test lab. I agree. I don't think there's going to be that many diseases in which there's only one test lab, and they're going to be so rare, that I don't think we can do much about it. But the key issue there is the same one that came up in the patenting, and that is, the ability to do proficiency testing to have quality control and be sure you continue over time to have the right answer.

DR. KOENIG: I want to turn the topic and specifically address this question to the people from the governmental agencies considering issues in rare diseases and see if you might be able to offer us some guidance about something we talked about yesterday, which is the issue of informed consent, and it's clearly a complicated issue to make a distinction between when a test is clearly a clinical test and when it's a research test, and it seems to me that in rare diseases, that boundary is always going to be much more complicated than problematic. But you actually indicated some things which we weren't aware of, this process of with the humanitarian device exemption, for example. I was a little unclear about the issue of whether informed consent was

required, what it really means when you said that IRB oversight was what happens because if it's really a clinical test, that didn't seem to make sense to me. So what, from your experience with all of this and with the whole panel, is there any guidance you can give us as we're trying to think through what kind of recommendations to make about informed consent across this, you know, process of tests moving from research to clinical care?

DR. LESS: The informed consent and IRB issues for HDE is lightly different. The IRBs are charged mostly with reviewing research under 45 CFR 46 and our FDA Regulations 56 and 50, but for an HDE, they're asked to look at the use of the device at their institution, and over the years, they've asked us, you know, what does that mean? There's no protocol. What are we supposed to be reviewing? What we've basically been telling them is to look to see whether or not the physician asking to use that device is the appropriate physician. Is he trained to use it? Has he been compliant in the past as far as doing research and using the device or is he sort of maybe a cowboy that doesn't have the experience or shouldn't be using it or they've had problems with him reporting adverse events in the past? So it's hard for them. They don't know exactly what it is they're supposed to be looking at. They don't even know what an HDE is. So we've been working with Public Responsibility in Medicine and Research and the Arena Group in Boston to try to train the IRBs on what an HDE is.

DR. KOENIG: Can I just follow up, though. Were IRBs ever charged with this? I mean, I'm just curious about why anyone thought that they were the appropriate group to do this.

DR. LESS: They didn't have a choice. It was added into the statute. Congress told them that they had to review these, and so we built it into the regulation.

DR. KOENIG: But you also said that FDA, someone said or one of the presenters said that you weren't allowed to require informed consent, but you did come up with some sorts of patient brochures that were given out. So can you describe that process?

DR. LESS: Right. The statute required IRB review. It did not require informed consent, and so that's why the Commissioner's Office said we couldn't require informed consent, but we've tried to get around that by using patient labeling to tell the patient what their condition is, what the alternatives might be, what this HDE is, what kinds of information we reviewed when we approved it, to tell them that effectiveness wasn't determined by FDA but we think there's a probable benefit to using the device, so that when they look at it, it's sort of like an informed consent document. It doesn't say that it's research, but it does tell them what the options are and what we reviewed in making that approval decision.

DR. McCABE: Anybody else have a follow-up on this point before we move on? Yes?

DR. KANG: My folks may kill me on this, but it strikes me on this informed consent issue, there have been voluntary efforts amongst the laboratory community to kind of increase the amount of dialogue that's been going between the physician and the patient and making sure that -- it strikes me that one of the recommendations that this is an important issue for this Committee could be you could enforce kind of adequate informed consent through CLIA. The lab could not process, you know, a sample unless there was documentation of adequate informed consent. The area of genetic testing might be a really interesting place to consider that. So I'd just offer that for this Committee's consideration. I know that there have been voluntary efforts on a whole variety of other testing issues in terms of what are standard forms and et cetera, for both

the interpretation and reporting-out of results but also the intake of samples and what goes in.

DR. McCABE: Well, we've certainly recommended informed consent for all genetic tests. That's part of our formal recommendations to the Secretary.

DR. CHARACHE: I was going to say that the Genetics Working Group of CLIA and approved by CLIAC was for informed consent without specifying which tests would require it.

DR. MILLER: I had a comment about the previous things. It was actually just to echo what Dave was saying as far as even in a relatively high throughput situation, much less a rare disease, when it comes to getting the right information, we usually go back and do a lot of calling back to the physician and getting the clinical information as well as having a counselor talk to the physician to see what the appropriate test is. So that's an even much higher throughput than we're talking about here.

DR. KANG: If I could comment on this, because I got lost in the conversation, you know, actually, it strikes me in genetic testing that this issue of getting the adequate clinical information and actually sometimes tracking the physicians, sometimes actually based on that, there's a professional issue of deciding what tests ought to be run. This Committee could make a strong recommendation to reimbursers, to the extent that reimbursement rates ought to be calculated to actually include, let's call it, the professional services of the laboratory. I know that in many ways, the way our calculation works in the Medicare Program, we kind of just look at the throughput kind of the actual technical component of the laboratory and don't reimburse what I would call the cognitive components.

PARTICIPANT: The genetic counseling?

DR. KANG: Well, that's a separate issue, the genetic, but it is interesting. That's a separate benefit issue, but it's interesting to the extent that we are paying for labs. The question is whether this professional component of the laboratory is a legitimate component to cover it in the lab.

DR. McCABE: I think that that certainly would be an interesting opportunity. I'd also point out, though, there was quite a bit of discussion yesterday about person power and the fact that there's inadequate person power to deal with the genetic revolution. Quite honestly, the reason for that is the whole reimbursement schedule and the way it's organized in this country and people track according to where the money is. So it's a general issue. Certainly this would be one area where a concrete recommendation could be that could impact on this area, but it's a more general problem throughout.

MR. HILLBACK: Back to the informed consent for a second, over the years, with the various different tests, we've required informed consent, but we've tried to track it two ways. One is a box check that says the physician says I have done the informed consent, and that happens a lot. In some cases, we've requested a copy of something more than that and that has turned in generally to be a disaster to try and follow up to get, and quite often, we have samples sitting there where we can't get that. Samples go out of date. It's been a real mess. So we do try to get informed consent done on everything we do, but two different approaches, and the full procedure turns out to be very difficult in today's environment.

DR. McCABE: Vicky, did you still have a new issue to raise?

DR. WHITTEMORE: Well, it sort of takes this discussion a step further, I think, and in talking to some of the families with tuberous sclerosis, but I think more with some of the other patient advocacy groups, there's a desire among some of them to actually bypass a professional completely and have patient-initiated testing. In other words, I would send my sample directly to the lab either for privacy purposes, I don't want my insurance to know, I'm going to pay for it anyway, coded testing, and so I think there are some groups actually, I know the Alpha 1 Group has talked about putting in place a coded testing system, where it would completely bypass the professional. So I just wanted to raise that in this discussion because that's also something being considered.

DR. McCABE: Yes, we've discussed that here before, because this appears to be an issue from our read on it, and the other members of the Committee can correct me if I get it wrong, but that this is a state health department issue in terms of who can order tests. So that's a state-by-state issue. Very interesting issue that we learned of within the last year or so is that Canada does not require a health professional to order a test, so that in fact, some individuals, we've been told, may be using Canadian laboratories in order to get anonymous testing and not going through a professional who may feel obligated to put it into the chart.

DR. KOENIG: Just a direct follow-up that the one disadvantage of requiring the lab to actually look at a consent form with a signature is that it often becomes the one way in which the patient's confidentiality is violated, and I just visited a lab last week, and they had originally

started out with that procedure of requiring a consent form and then specifically for that reason abandoned that procedure and went with a check box kind of method.

DR. KHOURY: I'd like to switch gears a little bit and talk about the public health issues. This has been an incredible panel. I wish we had this panel earlier in the life of SACGT because we would have all learned a few things that we didn't know, at least I didn't know, until this morning. I'd like to step back and take sort of a global picture of what we're trying to do. This panel has an incredible opportunity to influence SACGT and in turn SACGT will influence us, the agencies, in terms of advice to the HHS Secretary, and until recently, I have not paid much attention to rare genetic diseases. I've been so preoccupied with common genetic diseases, and I think I've had the wonderful opportunity last week of being part of a workshop that CDC and other agencies have sponsored on what should be the public health approach for primary immune deficiency disorders, and this is a group of rare single gene disorders that range from the bubble boy, severe combined immune deficiency, all the way to more common things, like selected IgA deficiency, and they are individually very rare. You have a hundred of these conditions, and for about two days, we had a group of experts and public health people sit together and go over the data, go over what should be the public health strategies, and as I was listening to all of you this morning, it looked to me that there are some common threads that I took from last week's meeting, which is still fresh in my mind, and I'd like to challenge you to challenge us to tell us what to do because you all live in different boxes. I mean, you have different expertise, different concerns, different issues to deal with, and I guess as a public health professional, I look at the big picture and see what the needs are, and I want to focus a little bit particularly on some of the problems we face in implementing genetic testing for rare diseases.

The first issue, we don't have an idea about prevalence and incidence, and people throw around different numbers, and I mean, we've seen this morning how rare disease and numbers are thrown around, and I mean, I heard from the earlier speaker that lysosomal storage diseases might be as common as 1 in 5,000, did you say, or 1 in 7,000 collectively?

DR. WENGER: As a group.

DR. McCABE: That's an incidence. That's an incidence, not a prevalence.

DR. KHOURY: Out of 7,000 births, you have one. I don't know where you get your numbers from, but I know of no statistics that actually have shown that data. I mean, do you want to comment on that? I mean, this is very valuable information for me because that would stimulate a lot of discussion. So just give me where that number comes from.

DR. WENGER: The number, I believe, comes from the number of diagnoses per year that are made and assuming not taking everyone being a newborn, and let's say my laboratory diagnoses 150 cases per year, and you spread out to other labs do some, and obviously a number are missed. So it's not very far off.

DR. KHOURY: So it's an estimate.

DR. WENGER: It is an estimate. All these numbers are estimates.

DR. KHOURY: So stepping back here and looking at this picture and seeing how we can move

the rare disease agenda forward. I mean, we need the basic information, starting with prevalence and incidence, natural history of these conditions, genotype/phenotype correlation, all the lab issues that you've talked about, and I was particularly struck by the two speakers that essentially said oh, yes, we can do a lot for these kids, tuberous sclerosis early diagnosis, with lysosomal diseases. We heard that last week with the panel of experts that talk, oh, yes, we can do newborn screening for SCID, and we can do bone marrow transplant and save their lives, and, as a public health person, I mean, I step back and say this is important because although individually these diseases are rare, if there is a collective will to put that stuff together, implement genetic testing at the same time we're collecting data to improve our knowledge base, which, I mean, lots of gaps and holes in that, that requires some national attention. I think you guys can influence this Committee to tell us what to do.

I'd like to echo the issue that Dr. Ledbetter said about the lack of translational research or translational resources emanating in the Federal government into putting sort of the next phase after the Human Genome Project. I mean, you've made that point. I'd like to echo it as well. The idea of national networks and public/private collaboration, be it lab-oriented network which you've taken the bull by the horn and created your own network, or ones that the Federal government can help put together, convene, fund, et cetera, and a few years back, when the NIH Task Force Report asked the Office of Rare Diseases to essentially do a lot of stuff in this area, they asked CDC to help out with these efforts, and we've never had that discussion because resources never arrived either to your office or to us or to other Federal agencies. So this is an incredible opportunity to be driven by concerns of people, to be driven both by all the parameters of genetic testing from analytic validity all the way to clinical utility and the ethical issues that we have dealt with, but I do see lots of gaps, and I think what we need to do is put

together some kind of either one or more consortia that can push that agenda forward, funding and otherwise, and keep collecting that data and keep collating it across the diseases and across different labs that do different things and because each one of us sees a selected sample of the world, rather than a representative sample. So this is sort of probably a tired monologue here, but I think this panel just pushed me over the edge in a way, and I'd like to see any reaction from you.

DR. McCABE: I just would like to point out that obviously while these are estimates, the Office of Rare Diseases has made these estimates, if you have a list of 6,100 diseases that you estimate to fit the criteria for rare disease.

MS. HYATT-KNORR: Well, I can't say that we made these estimates, but we have had a contractor really look through the literature very carefully to determine whether these are indeed -- I mean, many are so rare that there's really no doubt about it, and it's really the ones that are at the edge and close to the prevalence of 200,000 where there may be an issue, but for us so far, it has not been a problem. I guess it would be a little bit different with FDA because if in doubt, we would rather be inclusive than exclusive.

DR. McCABE: One of the issues that we raised before was what if a disease is lethal and what if it's a more common disease, but the prevalence never exceeds the number? Geneticists tend to think in incidence. The law defines prevalence and that creates a problem with certain diseases.

DR. HAFFNER: Well, just to directly answer what you were addressing, we use point

prevalence. So we're looking at everything that is in existence right now, but to get to Dr. Khoury's statements, I'm really excited that you said you were pushed over the edge. We've been preaching. It's like preaching to the choir most of the time, and now we've got a new choir, but we make the statement that rare diseases are not rare in the aggregate, and if one looks around this room and asks everyone how many people have had a rare disease, you'll have an awful lot of hands being raised, and three-quarters to 80 percent of those are genetic. So you've got a tremendous number of orphan diseases. We can give you fairly accurate figures on most of them, but quite frankly, for the very low incidence, there, it's fairly easy because at least for those where cases have been diagnosed, they're followed by specific folks, and one can count them. For more common diseases, it's obviously more difficult because while the number 200,000 seems like a lot, spread out in 270 million people, they rapidly vanish. But for the figures that are 5,000 and fewer, we can give you some pretty accurate figures. Are they accurate to the 10? Probably not. Are they accurate to the 100? I would say yes. It's also obviously correct that when one gets adequate therapy for a particular disease, you do have better case finding because there's more opportunity to treat this, usually children.

DR. McCABE: Let me just comment what my plan is, and that is, to try and wrap up the discussion about 10 after 12 or so and then have some discussion by the Committee of very specific recommendations to follow up on Muin's thoughts.

DR. PURYEAR: Hi. Actually, I had some similar comments that Muin had made, but mainly because my perspective comes from being involved in newborn screening programs, state newborn screening programs, which collectively are screening for rare diseases, excluding some of those, sickle cell amongst one of them is one that would not be considered rare.

DR. HAFFNER: It is rare. Sickle cell disease has prevalence of 50,000. Now, we're not talking about the rate, but the disease itself is one of the rare diseases.

DR. PURYEAR: But some of the recommendations -- and I feel like there's a tension with the community that considers itself the rare disease community or DNA-based screening community wanting to be excused somewhat from issues around clinical validity and clinical utility as in the process of doing research. However, when our policies that are being directed towards newborn screening programs, we're calling for more clinical utility and more clinical validity in those programs and the test and technologies, we're calling for that kind of uniformity. So what you are recommending or not recommending, we'll just know that it will have some effect on this large population-based screening program that's in existence. Those are rare diseases. Most of them are testing biochemically, but in the future, DNA technology will probably enter into that.

Then I have a question for David Ledbetter. The network that you propose is actually very similar to what many of the metabolic subspecialists propose or have been proposing for years, probably for some of the same reasons, in terms of very few -- well, actually not for the same reasons, but it's small clinical expertise, small number of people with the clinical expertise, not necessarily the laboratory expertise. But I'm interested to know how you're going to -- part of the model. Is that also looking at long-term health outcomes as well as the short-term outcomes? Are you creating databases where you're collecting information over the long haul?

DR. LEDBETTER: I haven't thought that far ahead, and at the moment, it's just trying to have a coordination. The only mechanism we now have available to see who offers what test and

whether it's clinical or research is the GeneTests website, which has been very valuable, but we want to proactively encourage more of these tests to shift from the research lab to the clinical lab, and so that's the simple goal of this network. I think the example of the biochemical labs and biochemical centers for years in genetics, that's been the group that's had an informal collegial agreement that if Dave is offering one test, everybody will send their samples to him for certain diseases, and he won't set up tests that Ed or somebody else has in their biochemical lab and that's what makes sense for rare diseases. Unfortunately, in cytogenetics, my field, and molecular genetics, there's been sort of a blind culture of wanting to be a "full service" lab, and if you have a cytogenetics lab or DNA lab, you must offer all tests, and so every new molecular diagnostic test sets up CF testing first and that's why my comment was not just a joke and a tribute to Elliott and Genzyme. It would be stupid for a new molecular genetics lab to be created today and set up CF testing. We have plenty of labs doing that well, and we have this huge list of diseases that nobody's offering. So why not fill that need first?

MS. BEARDSLEY: I wanted to ask a question about how the humanitarian device exemption might apply in our circumstances, because it seems to me to be an interesting regulatory framework or strategy for all these rare disease tests. But there's one thing about it that confuses me. It sounds to me as if you can only have one test for a particular indication under the humanitarian device exemption because once the second person came in, there would already be a comparable test. So it seems like it's conferring this extraordinarily actually exclusivity. Am I wrong?

DR. LESS: There is no exclusivity.

MS. BEARDSLEY: But if no one can come in for a second indication -- well, can anyone come in for a second indication?

DR. LESS: Someone can. We have two fetal bladder stents. We said that no comparable but that does not include devices that are either under an investigational devices exemption in a clinical trial or another HDE. So if something got approved as a PMA, your HDE would go away.

MS. BEARDSLEY: But you'd be kicked off, right? You'd be kicked off the market?

DR. LESS: We would probably need to withdraw that HDE, unless we could somehow say there's a slightly different patient population or this device is different enough from the one that was approved as a PMA that it offered an advantage.

DR. McCABE: But, Dr. Haffner, in your area, is there exclusivity? That's what I recalled.

DR. HAFFNER: Yes, there is exclusivity. However, I did make an error in my comments earlier. It is correct that biologics regulate some in vitro testing. However, they are regulated as devices and hence would not have that exclusivity from a genetic testing standpoint.

DR. McCABE: So it's therapeutics that have the exclusivity?

DR. HAFFNER: Correct.

DR. CHARACHE: A couple of thoughts and then a question. First, I would like to also commend the chairs of the Rare Disease Group as well as the speakers for an outstanding broad-based discussion of issues. I thought it was also wonderful, and I'd like to strongly support Jeff Kang's recommendation. We need a CPT code to charge for the interaction between the laboratory and the clinician and that is true for a wide range of diseases but particularly for genetic diseases, where the gap is extremely great. The question pertains to the various approaches that can be used for those laboratories that are doing research testing and want to continue doing the testing. They don't want to turn it over, and the various strategies that can be used to assist them in doing this without, as pointed out by Dr. Wenger, without decreasing the quality of the information that's being provided. We have used a strategy that differs from the one which you said in that if we have such research labs, and we've got 13 of them, of which several are genetic, we don't require that a CLIA-approved laboratory, the central laboratory, repeat the test that's been done in their laboratory but, rather, we bring their laboratory up to CLIA standards without the hassle of having to apply. So the strategy we have used is to put oversight in the Department of Pathology, bring them up to CLIA standards and then include them under the CLIA license of the general laboratory. I wonder if you're aware of other groups that have done that. It's very cost-effective. It doesn't increase turnaround time and the rest of it. The main strategy which we found required is education of chairs of pathology to be willing to be collegial.

DR. McCABE: David, do you wish to comment? Either of the Davids?

DR. LEDBETTER: Well, I think as long as the intention of educating and facilitating research labs to meet CLIA standards is not intended as a minimal paperwork criteria but truly bringing

them up to high-quality laboratory testing, I have no problem with it. My experience talking to research labs is the great majority of them have no interest in continuing clinical testing. The typical scenario is they want to find the gene. They want to find the first few mutations to confirm it's the causative gene for that disease, and then a significant percentage are interested in genotype/phenotype information from 50 to 100 cases or families, for example, but in any individual family, once they've found the mutation in a proband, they're not all that excited about having to now do mutation analysis on all of the pedigree in order to identify carriers, and they get scared to death at the first prenatal diagnosis request. We're most often contacted when the first prenatal case comes up, and they say, look, we didn't want to get involved in this. We didn't want to do clinical testing, but these families helped us to find the gene. We feel an obligation. We've done analysis on everybody who voluntarily gave us blood sample. We know the carriers, and now somebody's pregnant, and they want prenatal testing help, and so for the labs who really want to do it and want to make that transition, there's no problem, if they're willing to go through appropriate training, but I suspect that'll be a small subset of the research labs currently doing genetics.

DR. CHARACHE: There being CLIA review this afternoon, and I am sufficiently confident of their competency that I'm here.

DR. KANG: If I could just follow up on kind of Pat's line of questioning around CLIA and whether CLIA should apply, I had a question for Dr. Wenger actually. For your clinical testing, how many labs are you doing a year or how many patient samples are you --

DR. WENGER: Well, we're receiving samples from about 2,600 individuals.

DR. KANG: I understand.

DR. WENGER: What you have to understand is that these people may get 12 individual tests of that one person to arrive at a diagnosis. Carriers, obviously we know what diseases to go after. Prenatals, we usually know what.

DR. KANG: Was it very hard for you to get CLIA certified?

DR. WENGER: No. I think they were rather impressed by the way we did things, that we had a lot of input into the test selection, that we had our data books in order. We had trained technicians who stay with me a long time, luckily.

DR. KANG: You don't happen to recall how much you paid for that certification for your lab?

DR. WENGER: Under the table or on top? I'm sorry. I don't remember. I'm sorry.
DR. KANG: The reason why I'm asking is, you know, I'm glad to hear that the general tone of discussion here is that we ought to maintain high quality and quality controls and et cetera. Ed, if you just bear with me, because I'm not going to be able to make the afternoon discussion. I've always been of the feeling that even if you have a rare disease, the quality of the tests and the accuracy, and we don't want to mix samples up. That should be the same irrespective for all consumers, irrespective of whether it's common or rare. I think, though, that one of the things that is fair to say with regard to rare diseases is that we should give some sort of exceptions in terms of kind of economic considerations, and in fact, when you think about it on the orphan drug

exclusivity, what they basically said is okay, you've got marketing exclusivity for seven years. They don't have to pay their $300,000 fee to go through this, and actually, in a certain sense, there is this model already in CLIA where we actually have a sliding fee scale for a number of labs done by -- performed by the lab. So it turns out the cut-off in CLIA is if you do less than 2,000 a year, the charge is 225 bucks per year for two years to get certified, while a big lab, whatever it is, that's running through -- and there's a cost shift going on. They're bearing the costs of the program, and it clearly costs us more than 225 bucks to come in a year to review your lab. So I think that those are the kinds of things I would encourage this Committee to consider, is kind of for rare diseases, in terms of kind of waiving them out of quality considerations or requirements, really thinking about how to help defray the economic impacts of those.

DR. McCABE: There are some state rules, though, that supersede Federal, and so, for example, in the state of California to be CLIA-approved, it's required that you have a med tech. Now, in fact, med techs are rarely well trained to do the kind of testing that we're talking about here, and they're extremely high paid. So that, I think that that may shift. That certainly has in our situation has shifted us more to the kind of model that David's talking about, that tuberous sclerosis, has set up.

DR. HAFFNER: I just wanted to comment that I think that incentives like you're mentioning, Jeff, are very, very important. I cannot emphasize enough, however, that people with rare diseases want products that are as safe and as effective as every other patient, and frequently, I am asked or told, you've just got to have some shortcuts here, and that would not be fair.

DR. McCABE: That'll be the last of these comments, and we'll move on to some specific recommendations.

DR. WATSON: Yes, I think this sort of links to your last question, and I wondered if each of you could suggest -- you all approached it from different perspectives. Some from sort of a research translation, some from a reimbursement based on rare diseases and, you know, not as strong a clinical validity type of database that's both reimbursement and sort of an FDA kind of perspective. Do you see specific things from your different perspectives that can be done to incent the move of tests from a research environment to a clinical laboratory CLIA environment, I mean, from exemptions that might exist for that research support or translational research support, any of a number of things that have come up in different people's talks?

DR. LEDBETTER: Actually, our personal experience is we've been advertising for the last five years that we're willing to set up genetic testing for any rare disease, and I've been shocked at how little few takers we've had, and so I don't understand the discussion that continues about it can only be done in research labs because CLIA labs aren't willing to take on this testing, and GeneDx in the Rockville area is a for-profit company, set up specifically to do rare disease testing and has been successful adding quite a large number of rare diseases. So again, my view is that there are plenty of CLIA labs who have the capacity to do this, and I don't understand why research labs aren't moving towards us in partnership even with our invitation to do so, and unfortunately, I think it's going to take IRBs and granting agencies to say this is the right way to do it. It is a human subjects protection issue. It is a quality control to provide genetic testing for rare diseases at the highest standards. You should do this.

DR. McCABE: Other comments in response to Mike?

DR. WATSON: I would only respond that, you know, ACHG and ACMG are initiating a survey of research labs now to get a sense of what they do, why they do it in their research environment, and one of the common responses has been that the clinical lab in their institution with which they try to ally themselves ends up telling them that it's just too cost ineffective for them to take that test and do it. So I mean, there's an educational issue.

DR. LEDBETTER: Well, but you have to be there, present, for the conversation to interpret the two sides. The researcher comes to the clinical lab and says I'm worried about CLIA clinical lab stuff, and I'm worried about prenatal diagnosis. The clinical lab says yes, this is what we will charge you to do the DNA isolation, do the genetic testing, and the researcher says, well, that's too much money. I'm certainly not going to spend my grant money to pay you to do that. I'm not going to pay for it. So you have to do it for free, and then they come and tell you, you and you that my clinical lab's not cooperative and not interested. Well, how are they supposed to provide this free testing service during the research and translation phase?

DR. WATSON: And you have no reimbursement issue once you take on their test?

DR. LEDBETTER: After it becomes fully transferred to a clinical fee-for-service test, and you have an expert researcher with contacts to the community or a family support group, so you have some sense that you are likely to receive most of that rare disease testing, so you can reach a break-even point, then I would say the huge majority of existing CLIA labs would be happy to do it, but when you come talk to them and say will you set this test up for free, because

I'm interested in doing research on it, and I'm afraid of the implications of an incorrect diagnosis, an error in my research lab, or I don't want to do prenatal testing. That's a silly conversation, and their conclusion that the CLIA labs are not interested in this issue is wrong.

DR. WHITTEMORE: I think the translational phase is the issue and funding for that phase, and for example, in our situation, the two CLIA labs were potentially interested in setting up the test, but they didn't want to do that in-between, between the time that the gene had been found and the time we had, say, 500 mutations or knew what the best way to do the test was, and we had the research labs could not get funding to do that mutational analysis. So that's when we had to rely on the Tuberous Sclerosis Alliance to do that sort of underwriting to get to the point where we could tell these labs what it was. In our situation, like I said, we're dealing with two very large genes, and it may be a specific situation, but I'm not sure it's all that unusual.

DR. MILLER: I've actually had the experience almost in the flip side of this of having research labs where part of the reason for that individual remaining at the institution is the institution's perception that they can provide a clinical service in the research lab, and it helps them in their internal funding, and then you have ongoing discussions about how much sense it makes for them to actually be doing clinical testing, and what kind of service they can actually provide, and they're actually providing a better service to their institution by getting the funding to do their research and not a clinical service.

DR. McCABE: The other thing I'll just comment on is that, also, in the evolution of the research, as we're moving in this direction, I'll have a family member who'll say, well, it was done for free last year for so and so. I don't really feel that I should pay for this, and so we just

have to educate people.

DR. CHARACHE: Yes, I think that the complexity here has to be sorted through, and a lot is perception and some is reality. Certainly the translational issue that Dr. Whittemore pointed out is absolutely critical. Nobody can afford it. The research lab can't afford it either, and this really must be addressed. The perception issues are very real. We've had labs at NIH in which we counseled how to do it. We chose ones that were most difficult and most adamant and taught them that it really isn't complicated, and as they saw what was behind it, it became something they wanted to do and maintain, but certainly, I mean, pathology can furnish the templates for any records that you have to keep, and they're reasonable records, when you don't have to rewrite them yourself and learn how to write them. I think even the issue of who can do the test needs to be looked at. They're high-complexity tests, but they don't necessarily have to be done by a medical technologist. There are ways of doing this with appropriate supervision. So I think that there's a lot of misinformation out there that makes it seem more onerous, including how much is charged for this. So I really think that there's an educational need. I said there's an educational need for the pathologists in terms of how to approach the labs that want to give up the test or don't want to give up the test and without losing their baby to foster care. I mean, there are ways of setting it up so that you protect their research interests while not having them go through it if they don't wish to. So I think the educational gap here interferes with policy decision making.

DR. LEDBETTER: A personal experience with funding and grants. When I write RO1 grants for my entire career, I've made a point of this quality control issue, and for my RO1 basic research, which is disease-oriented research, I clearly have a genetic counselor doing all the

informed consents and counseling the families about the purpose of the research and the likelihood that it will develop into a new genetic testing capability for diagnostics and family planning. A medical geneticist is always involved, and all of the samples are received in the CLIA lab that I run and aliquots of that sample are passed to my research lab, and anything clinically useful comes back to the CLIA lab for confirmation. That is built into my budget. It costs extra money. I explain it. The study sections say wow, that's a great idea, that's the ideal way to do it, and I get extra credit brownie points on my grant review pink sheet and score, and so, yes, it's educational, and yes, it costs a little bit more, but if you understand that and explain it, they are willing to pay for it.

DR. McCABE: One last brief question, and then I'd ask the panel to stay here for the discussion that we're going to have for your input.

DR. KOENIG: Well, the question was for Dr. Ledbetter and Dr. Wenger, and you just began to actually answer what I was interested in, was how your particular labs do deal with assuring that informed consent has been obtained, especially for rare diseases, when you may not have all that much information about clinical utility ultimately, but there may be diagnostic utility. How do you actually deal with that on the ground?

DR. LEDBETTER: Well, there are two parts. One is the informed consent, and we always have part of our faculty or professional staff on the IRB who keeps all of us informed about the latest requirements. Our consents are up to date, and we get consent on everybody whose samples come in, and we don't process or use the ones if we don't have the consent form.

DR. KOENIG: Is that just in research? Do you make a distinction between when it's a

research project and when it's a clinical test?

DR. LEDBETTER: Maybe Patti can help me out on the clinical test. We try to get the same or a clinical informed consent on all of our clinical diagnostic samples. I don't know the percent success and how long we hold the sample if we don't.

MS. MILLS: We do make an attempt, as Dr. Ledbetter said, to get informed consent on all of our clinical cases, and there is no question for research cases. They must have informed consent. For clinical cases, we do have a check box in our databases, so that when a sample comes in, and the laboratory director is reviewing the sample, if there is not informed consent, and we feel that there are specific issues that are very sensitive, then those are referred back to me so that I can contact the referring physician or the referring genetic counselor and say we will not perform this test until there is informed consent, and we have rejected samples specifically.

DR. KOENIG: But how do you verify it? Do you want to see a copy of a form? How do you get this information?

DR. LEDBETTER: We get the form.

MS. MILLS: So we will not -- informed consent must be documented, and then we simplify it in our database just as a check box yes or no, so our lab directors can have that.

DR. LEDBETTER: The second part of your question, I have to admit my personal reaction to

the discussion about clinical utility is I'm completely baffled. That's mainly because I'm not a genetic testing laboratory person and deal mainly with pediatrics and affected individuals where there's no question but establishing the correct and precise diagnosis has value informational to everybody involved in the care of the child and in talking to the family and for reproductive planning. So I guess I would just suggest that you bring in representatives of every parent support group in NORD and the Alliance, if that issue needs to be clarified to the rest of this panel. I'm just baffled by that question. It's an appropriate question for predisposition testing.

DR. KOENIG: Well, but we're making policy across all of genetic testing. So I mean, genetic --

DR. LEDBETTER: Well, but because of adult onset testing and predisposition testing, people have forgotten the value of genetic testing and affected individuals or many people get confused between those two very different settings, and it's created some problems that didn't exist prior to the notion of predisposition testing.

DR. McCABE: What I'd like to do now is move over to the discussion of very specific points and perhaps action items for the Rare Diseases Working Group to consider what might be our most appropriate response as a Committee and advise us at our February meeting. I agree with the comments that have been made. This has been a very informative, very helpful panel for all of us and can certainly impact on the recommendations that we make.

Two of the points that I heard, the two that I wrote down that we need to consider strongly, is reimbursement for the clinical interface between the patient and the laboratory, however that is

described, the Pat Ward Model, but having some knowledgeable professional who serves that interface and makes sure that there's appropriate transfer of information. I'll point out that this is not unique to genetics. The radiologists, every radiologist I've ever met in my career has always been very concerned that they're being asked to look at films not knowing what they're supposed to be looking at, so that it's a more general problem, but here, because of the complexity of the information and the fact that you may not even look in the right place, if you don't know the right information, I think it's important that that was brought up.

The second thing that I have written down is a discussion of the translational phase and the funding for the translational phase. We heard that consistently throughout all three days of this meeting, starting with the roundtable, the Education Roundtable, on Wednesday afternoon, and this is a consistent problem, that NIH funds basic research. There are other groups, like HRSA and AHRQ, that look at reduction to practice pilot projects, quality assessment, those sorts of issues, but in fact, I really feel that this has been a major hole in the organization of clinical research in this country, that we have not had the funding to reduce the science to practice. So those are the two points, and I think if others heard other points that we need to emphasize back to the work group.

DR. BURKE: I agree completely with your two points. It does seem to me that it's also worth stating how strong an endorsement we have heard about the current policy that requires that genetic tests done for clinical information going back to patients or docs should be done under CLIA certification, that even in the circumstance of rare diseases, where there are extra hurdles to getting testing done, that that policy is a good policy and guarantees good testing.

DR. McCABE: Yes, I'd like to just comment, that it is in our recommendations that there needs to be technical assistance. Now, those recommendations were developed a year and a half ago. I think we've evolved in our thinking. I think the whole field has evolved over that period of time, but I think that your point is consonant with what the Committee has recommended previously as we've gathered additional information.

DR. HAFFNER: Just a brief comment. You talked about lack of funds for translational approaches. Our grants program does provide those kinds of funds. We call them bridging grants, but it's the same idea. Needless to say, with our $12.5 million a year, we can't do a whole heck of a lot, but we get a lot done.

DR. McCABE: Could perhaps you share that information with the Committee, just so we could have it as part of our records?

DR. HAFFNER: Sure.

DR. McCABE: But also, if you could give us perhaps, and I don't know if these figures are readily available to you, but the number of projects that you're able to fund?

DR. HAFFNER: We fund approximately a hundred projects every year total. About 20 of those are new. Our funding is done the same as NIH funding. We have an RFA that closes twice annually, and we award grants in January-February, and in August-September. The grants vary from $100 up to $300,000 per year, three years, and then competitively renewed. Those are direct funds and indirect is on top of that. Most of those are very early projects,

Phase I/Phase II. At the very latest, some Phase III, but most Phase I/Phase II. We have had 27 products that began in our grants program that have gone on to full marketing approval, and we do fund devices as well as drugs, biologics and foods in that program.

MR. HILLBACK: I just wanted to ask her a direct question, if I could. Have any of those been diagnostics or all therapeutics?

DR. HAFFNER: I think they're all therapeutics, but I don't know.

MR. HILLBACK: Right, and for diagnostic, there would be a home brew where you're really just supporting getting the test out that would never come back through FDA. Would that limit your --

DR. HAFFNER: That would be limiting because you have to have either an IND or an IDE to get funded.

MR. HILLBACK: Thank you.

DR. WHITTEMORE: I just wanted to go back to something Muin pointed out and that I think is important for the committee to also think about or consider, which really starts during the translational phase but continues then when you have a clinical test, is the information gathering, developing a database for ongoing genotype/ phenotype, and I know there are several lay advocacy groups that either have put something in place or are in the process of doing that, but what would be ideal from our perspective, I believe, is to have some sort of template that eventually these databases could also interact, so that we're not working with something that

could not then interact with other databases, and it would help us out, also, in putting something useful in place. So some sort of consortium to at least think about or consider these larger database issues would be important.

DR. KANG: The only thing I would just add on the reimbursement issue, I'd be happy to help on the Rare Disease Work Group to think through that a little bit. I'm not convinced tactically that a CPT code is the right way to go but we can have that discussion.

DR. McCABE: So we've just added a new member to the Rare Disease Working Group. Thank you very much. A new ad hoc member. Thank you for volunteering.

DR. WATSON: Elliott actually asked half my question when he asked about the home brew side of this, but I think it's important to think about the fact that our testing is so heavily home brew-based, that the system has now essentially established the home brew test as a product that will be regulated by FDA as it would a device, yet in definitions throughout, it's not dealt with in that sort of a context, and I think it's something we'll have to focus on a bit.

DR. McCABE: So in summary, then, we have three topics that we would like the Rare Disease Work Group to address and get back to us with specifics regarding recommendations. The one is the reimbursement for the clinical interface with the laboratory, looking at funding for the translational phase of research, and also looking at ways that we can enhance the move of testing from research labs to CLIA-approved laboratories. Everyone in agreement with that charge back to the group? Is it reasonable to ask for you to convene at least a conference call of your group and address these very specific issues in a focused way and then give us some

guidance at our next meeting in February?

MS. DAVIDSON: Yes.

DR. McCABE: Thank you very much to the panel. We really appreciate it. It's been very enlightening to all of us and probably we will be in touch. I doubt that you will get off this easy. Thank you.

DR. McCABE: We will start at 1:15 with the afternoon session.

(Whereupon, at 12:27 p.m., the meeting was recessed for lunch, to reconvene at 1:15 p.m.)

AFTERNOON SESSION (1:17 p.m.)

DR. McCABE: We begin the afternoon with a public comment session, and one of our commentators could not be here and asked me to read his comments into the minutes. So I'll start off the afternoon doing that. These comments are from Chris Palatucci. Dr. Palatucci is Director of Business Development, Athena Diagnostics, Inc.

So his comment is, "This is a comment on yesterday's discussion about submissions to FDA for approval of genetic tests. One aspect of the discussion centered around what would happen in a case where 100 labs across the country were testing for the same genetic alteration and

whether this would necessitate 100 separate submissions. There was also a suggestion that labs would be able to piggyback on the original submission."

"This raises some issues that I would caution the Committee and the agency to be mindful of. First, in a scenario where some form of FDA approval is required in order to market a test, a commercial organization has a very strong incentive to be the first to receive such approval. However, many times, the methodology used is proprietary, and there would have to be a strong assurance that the details of such a proprietary method are not made available to potential competitors in their attempt to show equivalency."

"In addition, allowing labs to piggyback on the original submission removes the incentive for a commercial organization to devote the necessary resources to be the first to submit if potential competitors will be allowed to get a 'free ride' on their efforts. This discourages innovation and will have an impact on submissions, particularly for rare diseases."

"The agency also needs to carefully consider exactly what level of sameness constitutes equivalency; that is, two tests could have the same clinical and analytical sensitivity and specificity using very different analytical methodologies or methods that vary only very slightly. It would be difficult for a lab making a piggyback submission to argue equivalency of method without seeing the original method which would be problematic for commercial laboratories."

"Finally, the Committee and the agency need to consider how the submission process would work in the reference laboratory setting. Would improvements in methods, such as redesign of primer sets, require a new submission? These kinds of improvements are frequently carried out

as new developments allow for greater accuracy or other enhancements or, as was brought up this morning, suppose a test is approved for particular alterations that have been shown to be pathogenic? What happens when the new pathogenic alterations are discovered? Does it require a new submission? If each improvement required a new submission or an addendum to the original, I would predict an enormous bottleneck at the agency and delays in putting these types of technical improvements in the hands of practitioners."

Again, these are the comments of Chris Palatucci from Athena. So with that, our next public commenter is Katherine Schneider, President of the National Society of Genetic Counselors.

MS. BEARDSLEY: Can I just say one thought? It seems to me that the issues that he's raising are important ones and maybe we should refer that -- I don't know if we have a mechanism to do this, but somehow refer those thoughts to FDA as they continue to develop their system.

DR. McCABE: I have a written document here which I will give to Sarah, and she can get a copy to you then, and you could consider those. Do you want a response back, Kate?

MS. BEARDSLEY: Well, maybe in the overall context of what you're doing. I don't know that we want to separate these from all the other ones, but they certainly belong in the mix.

DR. McCABE: Right, and I think there was some discussion about this in a slightly different vein yesterday and that's what prompted Chris to get more specific. I'm glad you didn't ask me to respond to that.

So I'm extremely pleased to introduce Katherine Schneider, President of the National Society of Genetic Counselors.

MS. SCHNEIDER: My name is Katherine Schneider, as you all heard, and I am the President of the National Society of Genetic Counselors, and it's my pleasure to speak on behalf of NSGC, which represents nearly 2,000 genetic counselors in an array of medical specialties and is the leading voice, authority and advocate for the genetic counseling profession. We commend the SACGT on its accomplishments to date and appreciate the opportunity to comment on the Committee's continuing activities. At this point, the NSGC would like to raise three specific points.

Point 1. The informed consent process and education of providers is closely linked. We support the SACGT's efforts to create educational materials for consumers regarding genetic testing and informed consent. Developing these brochures should obviously include input from all relevant stakeholders, including genetics professionals, clinical laboratory directors and consumers, and please let us know if you would like the NSGC to review these materials formally. We would like to remind the Committee, though, that the process of informed consent will only be successful if providers are appropriately knowledgeable about genetic tests. Recent studies assessing the genetics knowledge of health care providers have found deficiencies in the understanding of appropriate eligibility criteria for ordering a specific genetic test and that point was certainly brought home this morning by the laboratory directors and also in the interpretation of both positive and negative test results. Thus, the education of health care providers needs to remain a high priority. The NSGC remains committed to educating both health care professionals and the general public about genetic testing issues. We need to ensure that pre-

and post-test education and counseling by properly-trained health care professionals is widely available. This is the only way to ensure an adequate informed consent process. As a quality assurance measure, high-risk genetic tests should require discussions with a genetics professional or specialist similar to the way in which patients with specific medical concerns are referred to the appropriate medical specialist.

Point 2. Genetic non-discrimination legislation is vitally important. We urge SACGT to support the Genetic Discrimination in Health Insurance and Employment Act. Studies have shown that patients and families are very concerned about possible genetic discrimination and that this fear keeps some people from pursuing testing and in certain cases from genetic risk assessment, despite the potential value of this information. The public's fear was heightened by the recent case involving the Burlington Northern Santa Fe Railroad in which genetic testing was being performed without scientific validity and in the absence of appropriate consents or counseling. The benefits of the Human Genome Project will only be realized if the appropriate safeguards are in place. Forty states have now enacted some type of protective legislation on behalf of individuals who have undergone genetic testing. SACGT is charged with developing appropriate oversight strategies to protect the public and thus should strongly support genetic non-discrimination legislation on the national level.

Point 3. Medical providers and patients rely heavily on the lab test report. We support SACGT's efforts to streamline the laboratory report. Standardizing the information required on a genetic test report would be extremely helpful to both medical providers and their patients. Although the responsibility for accurate interpretation of the test result rests with the referring health care provider, labs could certainly make this task easier by using a standardized format,

providing complete information and minimizing technical jargon. Given our experience in reading genetic test reports and discussing results with patients, NSGC suggests that genetic test reports include at minimum the patient's name, date of the report, type of testing performed, references for the assays being utilized, the exact result obtained, accuracy and limitations of the result, and implications of the result for the patient and other blood relatives. It would also be useful to include, with positive test results, penetrance figures and resources for further information or follow-up.

In closing, the National Society of Genetic Counselors enthusiastically supports the efforts of your Committee. I would be happy to continue the dialogue about any of these points if there are questions. Thank you.

DR. McCABE: Are there questions? If not, thank you very much. We've enjoyed having NSGC make frequent presentations to our group at almost every, if not every, meeting of SACGT.

Next, we're going to look at the role of the laboratory report and ensuring appropriate interpretation of genetic test results. The quality and completeness of information conveyed between the genetic testing laboratory and the referring health care provider is crucial in ensuring appropriate interpretation of test results. The communication often occurs through a written report, and the written report is thus a key tool in the communication process. CLIA regulations address reporting content to some degree. CLIAC has emphasized the need for additional criteria for genetic tests. Also, a number of professional organizations have developed some reporting guidelines and recommendations but wide variations exist in test reporting, content and format.

Through a cooperative agreement with the Association of Teachers of Preventive Medicine, CDC is supporting the development of recommendations for preparing test results. This collaborative effort is being led by two investigators from Tulane University, Dr. Marie Krousel-Wood and Dr. Hans Andersson, two scientists at CDC, Dr. Ira Lubran, who's a board-certified clinical laboratory molecular geneticist, and Dr. Eunice Rosner, an education specialist with expertise in evaluation. The investigators began by examining variability in test result reports issued by molecular genetic laboratories for cystic fibrosis and Factor V Leiden. Data from the study in turn has been applied to the design of an assessment method that determines how useful specific report components and formats are to non-geneticist physicians. Everyone involved in this project is hopeful that it will contribute to the design of report formats that facilitate and enhance patient management decisions.

We are very pleased that Dr. Krousel-Wood and Dr. Andersson could both be here with us today to present the findings of their research on this important topic. Dr. Krousel-Wood is Clinical Associate Professor, Director of Preventive Medicine Residency Program, and Assistant Dean for Graduate Medical Education, at Tulane University Health Sciences Center. She's a Diplomat of the American Board of Preventive Medicine. She also serves as Director of Clinical Outcomes Research at the Ochsner Clinic Foundation and in that role has carried out a decade of health services research. Dr. Andersson is an Associate Professor of Pediatrics, Hayward Genetics Center, Tulane University School of Medicine. He is an Associate Laboratory Director for the Hayward Center Diagnostic Genetics Laboratory and serves as Course Director and Lecturer in Medical Genetics. Dr. Andersson is a Fellow of the American College of Medical Genetics and the American Academy of Pediatrics. Dr. Krousel-Wood and

Dr. Andersson are the principal investigator and co-PI, respectively, for this project. We'll have about a half-hour presentation on their study findings and then that much time for discussion of the implications of the study for enhancing the quality of test reports and, most importantly, for the interpretation of test results. I think that this presentation will flow very nicely from the discussion that we had this morning.

DR. ANDERSSON: Thank you very much. My thanks to the Committee for inviting us to present this data. You've heard the key members of this group. I want to just acknowledge that Kelly Jackson, our genetic counselor, had a significant role in this work as did Janet Rice, who's one of the institutional statisticians at the Tulane Public Health School.

I should say at the outset, for anyone who'd like a copy of this PowerPoint and handout, we didn't make it in advance but we'd be glad to provide that, if you'd like to have it. I don't think I need to give very much introduction to this group, especially after the last day and a half, and I think this flows, also, very nicely from Ms. Schneider's comments a few moments ago.

Genetic tests are increasingly being ordered. They're increasingly being ordered by a broad variety of physicians, and genetic testing, whether it's DNA-based or not, has a significantly-higher degree of complexity, we would agree, than many other types of testing. Some of that complexity includes the application of the results of the test to other family members, which distinguishes it, I think, from many more standard lab tests. The fact that negative genetic test results don't necessarily preclude disease nor do mutations predict a clinical phenotype. Additionally, these tests are often being developed and are performed exclusively, in some cases, in research laboratories.

I want to mention that the focus of the Division of Laboratory Systems at CDC has a particular interest as well as in quality assurance of laboratory practice. So our interest is particularly in, exclusively in the post-analytical phase of the testing that we looked at. So we won't discuss at all the pre-analytical or analytical phases of this, but rather how does the test result get conveyed to the physician, and how useful is that for the physician?

Now, there are a number of guidelines which have been alluded to previously, and I'll just reinforce the fact that CLIAC as well as NCCLS, the American College of Medical Genetics, CAP, the American College of Obstetrics and Gynecology, have all weighed in on this set of issues, and there are some unified general guidelines which have been recommended, but there's no specific, shall we say, proficiency testing for the outcomes of this test reporting, and there is significant concern that there may be variability in reporting practices between laboratories for a certain type of test. So there's not ever been, that we're aware of, a survey of all the laboratories that perform a given test and to see how they actually report this and whether they are in accordance with the guidelines that have been discussed.

So just to give you some background on some of the guidelines for post-analytical reporting, CLIAC has suggested that a molecular test report should include the list of mutant alleles tested for, the detectability with that particular panel. There should preferably be a revised risk assessment based on the results. There should be important implications mentioned for other family members based on the test results. Variables that affect the test interpretations, such as ethnicity, and other variables should be specified preferably in the report, and that there should be a mention of the limitations of that test report. So these are some CLIAC general guidelines.

NCCLS, on the other hand, have included a number of other pieces of information, specifically data on specimen collection, and we talked a lot about that this morning with Dr. Wenger and others. Collection issues. The date of the report, the date of collection, indication for testing, tests performed, whether or not there's an adequate description within that molecular test of methodology, of course the test result, most people do provide that, the resultant interpretation, so what does the test result mean, and whether or not there's a signature of the lab director.

So the results you're hearing this morning are the result of two years of work that Dr. Krousel-Wood and I did as a result of the CDC collaborative effort. I'm going to present to you Year 1, and she will present to you the second year of data.

So the objective in Year 1 was really to identify variations in the current DNA-based testing for all labs in the United States and Canada that perform cystic fibrosis and Factor V Leiden on a molecular basis, and specifically, we asked in cystic fibrosis only for DeltaF508 reports, so as to simplify that issue. We chose these two tests because we thought that they were relatively more straightforward. There was a fair amount of experience with many of them, and they didn't get into a number of the complicating factors that you see in some other disorders, not to say that they're also simple either.

The design was to basically solicit reports from all of the laboratories in America and Canada and then to evaluate the presence or absence of a certain set of critical elements that were based on the guidelines that we just went through. These reporting elements that we looked for in each of these forms were organized in basically four groups: administrative elements, patient-specific elements, test-specific and post-test-specific elements. I won't go through each one of

them with you, but there are the administrative ones that we mentioned before, specimen information. For instance, did the lab report confirm whether or not that lab had CAP and CLIA certification? It doesn't say whether or not that lab is CAP or CLIA certified. It's simply whether or not the lab form mentioned that. So many of these lab forms may not have mentioned it, but in fact those labs were CAP or CLIA certified. Patient-specific elements would include things like clinical indication, ethnicity, the gender and the date of birth, and the test-specific elements, everyone gave a result. We didn't bother scoring for that, but we scored for interpretation, whether or not there was a reasonably adequate description of the methodology of the test, which mutations were tested for in a battery, if there was a battery, the detection rate of that battery, and then the post-test had to do specifically with an adjusted risk and whether or not there was a recommendation for genetic counseling.

So here are the laboratories that we identified primarily by GeneTests but also through sort of the network of laboratories which we're aware of. We could identify that there were 44 total labs doing cystic fibrosis molecular testing, 72 labs doing Factor V Leiden, and we broke them down into lab types. Most of them were academic-based labs and then hospital-based and independent for each of these.

Our response was on the whole, 64 percent actually for both groups of disorders of reports. You can see there's a bit of difference, although it was not statistically significant, between the types of lab for CF. The Factor V Leiden data was significant at the .03 level. So there was some significance in terms of the difference in response of those types of labs for Factor V Leiden. This simply gives you the breakdown of how many labs were U.S. and how many were Canadian.

The summary then of their response or their inclusion, I should say, of these critical elements is on the next couple of slides. This is for cystic fibrosis and then for Factor V. Medical director signature is clearly on almost all of them, but whether they were CAP or CLIA listed is on almost none of them. You may notice board certification wasn't listed for many of the lab directors. That doesn't mean they weren't board certified, but it certainly wasn't mentioned on the form. The specimen collection date was listed variably in about half of them, a little bit better for the date of receipt, and the result date was on almost every form. If we look at patient-specific elements, the clinical indication for cystic fibrosis was given in a greater number of cases than was given for Factor V, but there were a number of cases where there was no clinical indication given whatsoever. Ethnicity was only included in 21 percent of the lab forms for cystic fibrosis, and we didn't look at that for Factor V because there's no good evidence of ethnic-based diversity with regard to that mutation. Gender, about half. If we look at test-specific elements, the interpretation was reasonable in almost all of the test reports, but only 64 percent of cystic fibrosis lab forms gave a reasonable sense of the methodology used to arrive at the result, and some of them gave absolutely no mention whatsoever of how the test was done. The mutation listing was there in almost all forms for cystic fibrosis. Adjusted risk. If we look at the post-test-specific elements, and I think this is really important, 71 percent gave an adjusted risk for the cystic fibrosis patient based on the data, whereas 61 percent gave any indication whatsoever that there should be genetic counseling or that this has implications for other members. That's a strikingly-low number in my opinion. Because we could, we tallied the number of mutations which the different laboratories were looking for, and you can see that there's a broad variety from single, you know, one or two or three mutations, in a given lab to greater than 60 or 80, and most labs do something in the 26 to 40 range.

So in conclusion, I would tell you that we found remarkable variability between the different laboratories that responded. I think we had a reasonably good survey with 64-percent response rate. We would recommend that these laboratories consider going back to their reports and potentially revising them based on the NCCLS and the CLIAC recommendations to include some additional information, and certainly additional study in the future, I think, of perceived usefulness of the laboratory test report form is very important. I'm going to turn this over now to Dr. Krousel-Wood, who will give you the Year 2 data.

DR. KROUSEL-WOOD: Yes. Thank you again for having us here today. We certainly look forward to presenting the Year 2 data as well. As you can see from Year 1, we did document that there was significant variation in lab reporting for cystic fibrosis and Factor V Leiden. The next question was, did the variation in lab report have an impact on the physician's perceived usefulness of the variations in the report? So the Year 2 objective was to determine the usefulness of medical genetic mock test reports for both cystic fibrosis and Factor V Leiden in a representative sample of U.S. physicians. We also hoped to identify barriers and opportunities for improvement for the use of medical genetic test reports.

The way we went about this is we did a cross-sectional survey. We did this from April to October of 2001, and we selected a random sample of U.S. physicians in the different specialties that were relative to the disorders that we were studying. Where we got the data or the sample was from Axciom. This is one of the providers to the American Medical Association. We targeted office-based physicians. We know that this particular data source contains both AMA and non-AMA members, and from this source, we obtained a random

sample of a thousand physicians in each one of the relative specialties that we were looking at, and from this, we drew our random sample.

You can see here that for cystic fibrosis, we included the specialties, family physicians, pediatricians, pediatricians with a secondary in pulmonology as well as pediatric pulmonologists. Initially, when we were doing this study, we were told by Axciom that they didn't have a designation of pediatric pulmonologists. So we selected all of their physicians who were listed as pediatricians with a secondary in pulmonary, and there are only 81 in their database. After we received the database, we realized there was a second specialty of pediatric pulmonology, and so we selected that sample as well. For Factor V Leiden, the physicians included family physicians, internists, as well as hematologists.

What you can tell here is for cystic fibrosis, we wanted to get a representative sample from the U.S. You can see all the regions represented here, and you can tell that for the majority of our sample, they were from the Mid-Atlantic, Southeast as well as the West, although we had representation from all regions of the U.S. We had also representation from all of the age groups of physicians that are involved with this. However, you can tell from this particular slide, the majority of the physicians were between the ages of 41 and 50 years of age. For cystic fibrosis, 411 physicians were surveyed. We had a 36-percent response rate, and when we compared our responders to our non-responders, there were no demographic differences with regards to the region they were located, birth decade, or gender. The majority of the physicians were males in the range of mid-60 percent. For Factor V Leiden, again we have the distribution of the regions, again the majority being from the Mid-Atlantic, Southeast and the West. With regard to age range, again the majority of our sample was between the ages of 40 and 50 years

of age. Here, we had a sample of 353 physicians. We had a 25-percent response rate for Factor V Leiden, and again we found no differences with regards to demographics between responders and non-responders with regards to region, birth decade, or gender.

Now, when we went to develop our survey, we did develop this using a focus group that we held in Year 1 involving physicians from the representative specialties. We did pilot test the study and the survey on a sample of physicians from the relevant specialties in New Orleans, and we modified the survey based on those responses and our analysis of the pilot study.

When we surveyed the physicians, we did it as follows. We had an introductory letter explaining what we were doing. We included a brief clinical scenario, one relative to cystic fibrosis and one relative to Factor V Leiden, and each of the physicians selected got one of three mock reports. Now, we developed the mock reports as follows. The first one was considered the most comprehensive, and it included all the recommendations from NCCLS and CLIAC as well as perhaps a few other variables, and we called that Report A for cystic fibrosis, and Report D for Factor V Leiden. Then, of course, we had our least-comprehensive report that only had bare minimum, and that was Report C for cystic fibrosis and Report F for Factor V Leiden, and then, of course, we had an intermediate report that had somewhere between the least and the most. All the physicians only got one survey and that's important to understand. We were afraid that it would be too much of a bias if they got all three. They would gravitate to the more comprehensive report, and therefore our results may not be valid. So they only got one report, and they got a one-page survey to respond to.

Now, the survey, we won't go through each one of these in detail, but as you can tell from Dr.

Andersson's presentation, a lot of these questions that are on the survey are relevant to the CLIAC and NCCLS recommendations, and they mapped to the reports that we developed. The first set of those recommendations, you can see, deal with the test. What test was performed? What methodology? Were there limitations? What's the result? The test result format. The second group of questions dealt with more the clinical decision-making components. We asked them how useful is this with regards to these components, to include genetic counseling and these other areas. Then we had other questions that dealt with the laboratory itself. What contact information, the laboratory accuracy and reliability, and the last two questions on the Likert scale were their overall satisfaction with the report. That was important to determine reliability. If we had poor usefulness and high satisfaction, we would have wondered if our responses were reliable. We also asked the question, how often do you order the test? Those who never ordered the test may respond to the survey in a different way from those who actually order the test frequently. We also had three open-ended questions, and these were designed to give us our barriers and opportunities for improvement. We are currently doing the content analysis of these questions, where we asked them what additional information, what deletions, what modifications, would the physicians want to actually improve these reports, and that data will be presented at a later time.

Now, as we go into our results, for cystic fibrosis, I mentioned earlier, we had an overall response rate of 36 percent. You can see the range from each of our categories here of the specialties that we surveyed, and you can see the highest response rate were from pediatric pulmonologists.

Now, this seems sort of like a busy slide, but you can see here, we have the survey questions

listed in the first column. I have the mean score, and again these Likert scales went from 1 to 5. A higher score or the closest the number was to 5 indicated more usefulness. So this column deals with the most comprehensive. Then we have the intermediate. We have the least comprehensive. We have a P value, which you all know we're looking for Ps less than .05 to detect significance, probably less than .05, significantly less than .05 when we're looking at multiple comparisons, and, of course, here gives us the Neuman-Keuls which tells us the direction of the difference. Which report was really rated as being better? As you look across this, and I won't go through every one, but you can tell that the mean scores in general are higher for the more comprehensive report. Intermediate, a little bit lower than the more comprehensive, and for the least comprehensive report, the means are lower. We had significant values P, less than .0001, and what you can tell in the last column is that the more comprehensive reports, that's A and B, are significantly considered to be more useful by our physicians than the least comprehensive report. You can see here, with the exception of the test report format, again we're having significant differences. It is interesting for cystic fibrosis, that the way the results were reported, the format was similar, perhaps had more information or less information, but we did not pick up significant differences in the report format for cystic fibrosis.

For the ones dealing with the clinical usefulness of the report, again you can see significant differences. Those reports that complied more with the CLIAC and NCCLS recommendation were given considered more useful than the least comprehensive reports, and for the last bit dealing with contact information, lab result accuracy and reliability, you can see the results here, with only contact information not showing any significant differences.

Now, with regards to overall satisfaction, we did find that there was significant differences

between satisfaction and the version. Again, this added to the reliability of our test results. Version A, of course, being the most comprehensive, B intermediate, and C being the least comprehensive. What you see is a trend here, that for the most comprehensive, a higher proportion of our respondents said that they agreed or strongly agreed with the statement, "I am very satisfied with the enclosed report." For the intermediate report, you see the results go kind of intermediate. They either agree or they're not sure, and for the least comprehensive, we're seeing a higher proportion of our respondents saying that they disagree that they are satisfied with the report.

We did note that there were differences among the specialists with regards to the frequency of ordering a test. We assumed there might be, but we wanted to be able to quantify it. What we can see for those who responded is that the majority of the family physicians never ordered the test. What was wonderful is that they actually answered the survey and that they gave us responses. A little over half of the pediatricians never ordered the test and only 4 percent of the pediatric pulmonologists indicated that they never ordered the test. We did a regression to detect whether or not controlling for the frequency for which they ordered the test would get rid of the specialty differences, and in fact, for cystic fibrosis, it did, for their satisfaction.

Now turning to Factor V Leiden, our overall response rate was 25 percent, as indicated here. You can tell we had similar response rates from the family physicians and the hematologists, not quite what we had for cystic fibrosis, but still we were able to detect significant results. Again, we have the test information represented in this first slide. The most, intermediate and least comprehensive report, our P values, and the Neuman-Keuls, and you can see from here, the P values are not as small in some cases for Factor V Leiden as they were for cystic fibrosis. You

can again see a pattern that the reports that are more comprehensive are considered more useful than the least comprehensive reports. The exception here is for test limitations. There were no differences. Again dealing with the test report format as well as some of the clinical history information provided, we have seen significant differences. More comprehensive reports are more useful to physicians than the least comprehensive. More of the clinical decision making, we're seeing a similar trend here, and for the laboratory-specific information with regards to contact, reliability and accuracy, for two of them, we're seeing significant differences, and for lab result accuracy, we found no differences. Again for overall satisfaction, we identified a very strong relationship between satisfaction and the version. As you can see, it's the same pattern that we saw with cystic fibrosis, except for the most comprehensive report, a higher proportion of our physicians reported more satisfaction or agreement with the statement that they were satisfied. For the intermediate report, we had agree and not sure as the higher proportion, and for the least comprehensive, more of them disagreed with these reports they were satisfied with. As with cystic fibrosis for Factor V Leiden, there were significant differences among the specialists with regards to the frequency with which they ordered the test. Again, 72 percent of the family physicians who responded never ordered the test, only about a third of the internists indicated they never ordered the test, and very few, 3 percent, of the hematologists reported that they never ordered the test.

So what did we determine from this component of our study? That even with a fair response rate -- we would have liked it to be a little bit higher, and we did three mailouts and received this particular response rate, but we were able to get a sufficient sample size to detect significant differences with regards to physicians' perceived usefulness for genetic test reports as it relates to how comprehensive the report version was and that, you know, correlated with some of the

other things that we looked at in Year 1.

We did note that there was significantly-greater satisfaction and higher perceived usefulness for the more comprehensive reports, those reports that comply with the CLIAC and NCCLS recommendation, when compared to those reports that provide bare minimum information. Although it did vary by the item number that we looked at, the trend is certainly there. We also note that there are differences by specialty with regard to the number of tests ordered and their perceived usefulness and overall satisfaction with the reports. However, the trend across specialty was the same. The physicians, regardless of specialty, felt that the more comprehensive reports were more useful.

It's very interesting, and we will report this at a later date, but even our focus groups, although usually the primary care physicians reported that they wanted more information, and our subspecialists said we don't need so much information, we need a very simplified report. Overall, when we surveyed the physicians, giving them a single report, we saw that the more information was perceived to be more useful, and, of course, this can translate very positively. If the physicians find it more useful, that the quality of care given to patients may also be improved, if the reports are provided in the information they need for clinical decision making, and so that's an interesting next step for us.

The barriers and opportunities for improvement. We are identifying by specialty any open response questions. That will be reported later, although there are some trends that we have identified already, and I think that some specific recommendations back to laboratories will certainly be an outcome of this particular activity.

So we have a lot to do. This is preliminary data. We finished getting surveys in late October, and we're continuing to analyze it. We are hoping to compile a specific list of barriers and opportunities as well as specific recommendations for laboratories. We think there are opportunities for future research with regards to looking at what physicians would actually do with different types of reports, by-version differences, also looking at different disorders as well as exploring specialty differences. It could be that primary care physicians with less genetic testing may need a different sort of educational strategy than those who have had specific training with regards to these tests. Thank you.

DR. McCABE: Thank you very much. Perhaps Dr. Krousel-Wood and Dr. Andersson could join us here. Dr. Lubran, do you care to join us at the table here, also, or any of your other colleagues in the audience?

DR. LUBRAN: No.

DR. McCABE: Well, why don't you just join us up here, please?

DR. BOUGHMAN: I wonder if you might clarify a few things for us, not having seen the lab report format and not having seen the survey. When you say more comprehensive, you simply mean more from your list of variables but not more content per variable. Am I correct in that?

DR. KROUSEL-WOOD: That is correct.

DR. BOUGHMAN: So when you say test results, could you tell us how that was reported? Was it reported? DeltaF508, yes/no, plus/minus? The list of mutations with all of the pluses and minuses? Was it in sentence format?

DR. KROUSEL-WOOD: It's actually the way that you stated it, that it was for each one of the mutations tested. There was a pos/neg. It was using sort of the standard nomenclature. It is interesting that on some of the open-ended responses, many of the physicians in the various specialties noted that the pos/neg nomenclature was somewhat confusing but that's exactly how we did it. We did it in this report.

DR. BOUGHMAN: And the people, the physicians that you had fill out the survey were sent along with that a patient --

DR. KROUSEL-WOOD: A clinical scenario, yes.

DR. BOUGHMAN: So in fact you're asking them a question, how useful was this lab result format given the paragraph or page of information you had, and there could have been variability on some physicians saying, well, if I got this result back for one of my own patients, I would have known many of the date drawn, the date sent. I know the qualifications of the laboratory, so I don't need it on the lab report. So that is not something that the way the study was designed would have picked that up one way or the other?

DR. ANDERSSON: No, but if I could comment to that. One of the important features of a test report is that it is a medical record. The physician who takes care of the patient or in fact may

receive that test report may not be the ordering physician and that's a really important piece of this whole puzzle about what should be in a test report result.

DR. BOUGHMAN: And just a couple more content questions. You talked about the adjusted risk. The way the data were presented, for example, in the CF case, this was a diagnostic situation, I would assume, for a child that had some symptomatology. You didn't look at it from a carrier perspective.

DR. ANDERSSON: No.

DR. BOUGHMAN: So when you talk about an adjusted risk, it would be adjusted risk for the diagnosis?

DR. ANDERSSON: For that clinical scenario.

DR. BOUGHMAN: Okay.

DR. BURKE: Very interesting data. I appreciate your reporting it to us. It does seem to me that one of the implications one might be able to read into your low response rate, and I think there are other data to support this, is that doctors are busy, and in that context, I think it may be extremely important to do some content analysis that includes looking at those responses where A and B seem to be both better than C versus A was clearly better than B because I think a breakdown of those or looking through and particularly mapping those results with what you actually had in your high content and intermediate content may help to determine where

additional information isn't necessary, where you've gone as far as you need to go, where, in other areas, it's clear that the A was distinctly better, and I think making those distinctions may be extremely important.

DR. KROUSEL-WOOD: That analysis is underway. Thank you.

DR. LEWIS: This is really interesting and very helpful, and I just had a couple of methodology questions. First of all, on the first part of the study, did you identify any differences among the labs that responded and the labs that didn't respond in terms of volume? Because I think sometimes there can be a difference in a respondent and a non-respondent.

DR. ANDERSSON: I'm sorry. In terms of volume, did you say?

DR. LEWIS: I mean, you listed the labs by the types of labs they were, but I would presume even among those labs that -- did you capture most of the tests that are being reported? I mean, sometimes you have one or two missing, and you're missing a large proportion of the tests that are being done.

DR. McCABE: In other words, if you had three labs that were doing a test, and the majority, 90 percent, were done by two or one laboratory and that lab didn't respond, you'd have two respondents, but you'd be capturing a minority of the testing that was being done.

DR. ANDERSSON: Boy, I got in early this morning, but I'm sorry, I still haven't captured this concept yet.

DR. LEWIS: Say, for example, there were four labs in the country that do a test. One lab does 75 percent of all the tests in the country.

DR. ANDERSSON: I have no idea what the volume of any of the labs that we selected is.

DR. LEWIS: Okay. So you have no sense as to whether the labs that responded were different than the labs that didn't respond?

DR. ANDERSSON: I only know the name of the laboratory and the report that they sent me.

DR. LEWIS: And then, my second question is on the second year of the study. In your questionnaire, did you do things, like Cronbach alpha, or any reliability tests on your particular items in terms of looking at the validity of your two, the reliability of your two?

DR. KROUSEL-WOOD: I'll tell you what we have done. In Cronbach alpha, I know what you're talking about, it looks for internal reliability with regards to their response. We did a couple of things, and we have other things underway. One was correlation. We correlated each one of the items, the first 14 items, with overall satisfaction to make sure -- because if they said it's useful, it should correlate with satisfaction, and we found high correlation. It usually ranged between 0.6 to 0.7 on correlation between those reports, and we did that for overall, for all of our responses, and what we're going to do is look at it by report type, by report version, because I suspect satisfaction will be higher for the most comprehensive. That's what we already reported, and the correlations may also be higher with regards to that.

DR. LEWIS: But in terms of the actual instrument itself and the ability of the instrument to detect significant differences is what I was looking at.

DR. KROUSEL-WOOD: Well, we did some of that in the pilot testing, and we didn't look at Cronbach alpha per se, we looked more at the correlations between the different questions to determine which ones had differences in content validity, and some of the other things that we're looking at now in the correlations and the models, we're predicting, will help add to that and provide more information on our method section.

DR. LEWIS: And again, other than looking at age of the respondents who replied versus those that didn't reply, do you have any other way of knowing whether or not the sample is representative of the population?

DR. KROUSEL-WOOD: Well, we did look at region, we looked at age, and we looked at gender, which are the items that we had on all of our sample. Now, with regards to the other things and their practice if they didn't respond, we couldn't get that type of information, but at least we weren't getting just from one region or one age group or from one particular gender.

DR. LEWIS: I guess what my concern is, is that I would expect those differences to be randomly distributed, but people who respond to a survey like that are usually people who are more interested, and the people who really didn't give a rip are the people who don't respond. So that's what I'm trying to sort out.

DR. KROUSEL-WOOD: Sure, and I understand that, and it's hard to evaluate, but what was very interesting is the family physicians, which in both cases, over 70 percent of them never ordered the test, which I would say perhaps they're not interested in it if they're never ordering, actually responded to our survey, and we do have a range, and we looked at the frequency with which they ordered the test, which is a possible surrogate for their interest in the disease, ranged from people who never ordered the test to those who ordered it more than five times a year.

DR. LEWIS: And you had no information whether or not these people treated those kind of patients in their practice and maybe had taken care of those patients but had referred them for test ordering?

DR. KROUSEL-WOOD: That was not a specific question. The only way we could tell is if they never ordered the test, they probably didn't take care of those patients and referred them out. The same thing for all the specialties that we looked at, but within each specialty, we had a range of physicians that responded from those who never ordered it to those who ordered it greater than five times a year.

DR. LEWIS: I think it's really interesting, and I was just trying to get a --

DR. KROUSEL-WOOD: Well, with the lower response rate, the thing you worry about is selection bias, and are we getting a true representative sample, and so we had some of the same concerns that you do and as many variables as we can look at to compare them, we're trying to do that, but the only variables that were similar with the respondents and non-respondents were the variables that we reported to you.

DR. LEWIS: Well, one of the things might relate to one of the questions that Wylie asked, which is, I don't know the physician community. Maybe they're just not folks who never return surveys versus --

DR. KROUSEL-WOOD: They are.

DR. LEWIS: So it would be interesting to look at the response rate on this versus the response rate on other surveys. I sort of thought that might be the case.

DR. BURKE: Oh, I think this would be not an unrepresentative response rate.

DR. KROUSEL-WOOD: And we did look at other studies, and there are a few that may have gotten higher response rates, depending on different mechanisms. One of the studies that we sort of modeled our methods after was the one that developed with the resource relative value scale, and, of course, physicians had a vested interest in responding to that because it was going to determine their payment. So they got closer to a 50 to 60 percent response rate, but for the others, it's been reported in the literature that physicians sort of are in that much lower range, even actually lower than the response rate that we got, with an overall response rate of 31 percent.

DR. PENCHASZADEH: I have a question for Dr. Andersson. On the first year of the study, I'm not clear about the methodology. You got a sample report?

DR. ANDERSSON: That's correct.

DR. PENCHASZADEH: One sample report? What were the actual indications you gave to the labs, to send you what, and what did you analyze?

DR. ANDERSSON: So we wrote to these laboratories, sometimes numerously. We wrote to them saying we would like to have an anonymized report form for your cystic fibrosis test relative to a DeltaF508 study. So whether you did other mutations or not wasn't of interest to us. We wanted to see what the lab form was, and when we got those lab forms, we collated them and then analyzed them piece-by-piece for what was in that form.

DR. PENCHASZADEH: So was the form without the natural report?

DR. ANDERSSON: I'm sorry. It was a report form. It was the report that they --

DR. PENCHASZADEH: Without the particular result, I mean. It says positives versus negatives.

DR. ANDERSSON: No, it would have the -- there were two forms requested. One was for a negative result, one was for a positive result.

DR. PENCHASZADEH: Thank you. And the other one is a comment on the second leg, because I guess that one of the most important things is not so much -- of course, the data are very interesting in terms of the physician's assessment of the validity or the usefulness of our

report system. The question is in which way different reports make with regard to different actions from the physicians for their patients. I mean, in terms of whether a particular complexity or comprehensiveness of a report may be, a better translation into an action order with respect to a patient. In other words, if you have a full interpretation, are you planning to look at actual physician responses to different types of reporting in terms of what they would do with a patient? I don't know if my question is clear.

DR. KROUSEL-WOOD: I agree with you. I think one of the next questions is, so what?

DR. PENCHASZADEH: That's right.

DR. KROUSEL-WOOD: So now we've identified there's variation. Now we've identified the physicians, rate them differently with regards to usefulness and satisfaction, and the next question is, what would they do with the different information? We do not have funding for that portion of the study, although we have laid out part of that and probably will submit that.

DR. ANDERSSON: Yet.

DR. KROUSEL-WOOD: But that is the next question, and we've already discussed that that would be the next place to go.

DR. McCABE: Thank you.

MS. BOLDT: Thank you so much for that. I can tell you as a genetic counselor, I've seen the

variability in test results a lot. So one thing you didn't address, but I am concerned about, is there's more intermediary labs now where the provider is ordering, it goes to a lab, and then they send it out to the lab that's going to provide the test, and then the report gets back to the intermediary lab, and then they transfer all that information on to another letterhead, and I'm concerned about that, and I don't know if that's something you're looking at. I mean, I know that there's chance for error and things don't always then transfer. So it's a concern, and it's a concern for the provider then to know who actually did the testing, so that you can get follow-up or talk to the person in that lab. So I know you didn't address it in your talk here, but are you aware of that, and is there any way we can --

DR. ANDERSSON: That's a very good point. I'm aware of it. It's difficult to capture without making a great deal of communication with the laboratory in general that's sending you the report form, at least from the Year 1 point of view, and we were trying to keep as much distance from the laboratory as possible, so as not to cause any sort of concern about regulatory or why are these people looking at my lab forms? Just send me the lab form, I'll leave you alone, please. Thank you very much. It's a good concern. I wonder that there isn't a requirement to actually include on the lab form who performed the studies.

DR. McCABE: There is a requirement.

DR. ANDERSSON: And so I didn't come across, at least in the reports that we got, a suggestion that my hospital sent this test to X company, and they did it for us and here's the result, but I'm aware of what you're saying.

MR. HILLBACK: Yes, I just on the second year had a question. When you sent these things out to the physicians, did you send out the actual forms or did you homogenize them? You just abstracted the data and put them on a common format?

DR. KROUSEL-WOOD: You mean on the mock reports?

MR. HILLBACK: Yes.

DR. KROUSEL-WOOD: No, we had a full form that looked like an official form.

MR. HILLBACK: But they were three different forms. In other words, you didn't take all the forms you got from the various labs and --

DR. ANDERSSON: We sent them three different forms as if we were doing the lab.

MR. HILLBACK: Okay.

DR. KROUSEL-WOOD: But based on and including variables that were actually present in real lab reports that we got back from other places.

MR. HILLBACK: So the point I was getting at is you didn't really look at the organization of a form or how the form reads or whether it's hard to find the facts because yours were organized in a way that the facts were easily findable and probably similar, from A to B to C.

DR. KROUSEL-WOOD: They were similar for the content that was similar. However, on the

content analysis, the physicians had some very interesting comments and even in our focus groups --

MR. HILLBACK: We couldn't find this or --

DR. KROUSEL-WOOD: -- or the print's too small.

MR. HILLBACK: Yes.

DR. KROUSEL-WOOD: I want you to have more pages. That would be the primary care people.

MR. HILLBACK: Because if yours are that way, just think about how --

DR. KROUSEL-WOOD: The subspecialists wanted fewer pages.

MR. HILLBACK: Right.

DR. KROUSEL-WOOD: Instead of the pos/neg, they wanted you just tell me the result is positive, it's a carrier, and then put all the other stuff in little --

MR. HILLBACK: So there's a lot of richness behind that, and there'd be even another layer of richness if you'd sent out with the name of the labs crossed off all the actual reports that were complex, simple, whatever, trying to lump them together, because I think there's a lot of issues

about the forms being really hard to read separately from what's contained in them.

DR. KROUSEL-WOOD: That's true. Even though we tried to keep the format very consistent across it, so we weren't measuring multiple things at the time and not knowing what they were evaluating, it is interesting that we did get comments back on the open-ended questions about just what you're talking about, and we will categorize those and provide that in a summary report.

MR. HILLBACK: Thank you.

DR. CHARACHE: Yes, I was interested, as I saw the list go by, incidentally I thought it was very helpful, if you could give us the slides you showed. I thought it was wonderful. But the NCCLS list is essentially that which is already required by CLIA, and then the CLIAC ones are those things which were thought to be important in addition. Now, with that in mind, as I jotted it down, only 46 percent of your labs' examples had the collection time and that's very telling because if that is correct, if I understood you correctly, that's an essential quality assurance/quality control measure. You can't tell otherwise whether the sample's good or bad by the time it arrives in your laboratory. It does suggest that maybe how the labs are being reviewed has some gaps in it, whether it's CAP or Joint Commission or HCFA that's doing the reviewing, if they're not picking up the fact that more than half the labs have essential things missing, and there are other things that were missing that are CLIA requirements. So I think this is a flag, also, for the group.

DR. McCABE: Thank you very much. Thank you very much for presenting this information to

us and as it progresses, if you can keep us updated, we'd appreciate it. Thank you.

DR. BOONE: I just wanted to add that we don't have the funding to continue with this. I think we're on a very productive track, and if anybody else would like to pick it up, I'm sure that they would love to have a source of funding to continue.

DR. McCABE: Thank you.

DR. ANDERSSON: Thanks for that plug.

DR. McCABE: Next, we're going to talk about the status report and the discussion of information request to the agencies. At our meeting in August, we had an extended discussion about the critical importance of supporting ongoing data collection and analysis of genetic tests from the premarket phase to well after the marketing of tests begins. We actually realized this early in our deliberations on the oversight questions, and we included recommendations about the need for coordinated efforts in data collection in the July 2000 oversight report. Since then, we have been working largely through the efforts of Dr. Burke and the Data Work Group to understand in greater detail and depth the challenges and opportunities to achieving this goal. An outcome of our deliberations in August, which were benefitted greatly by the feedback of the August 16th Outreach Meeting that Wylie organized, was a commitment to find out more specifically what the HHS agencies represented at this table are doing to support the advancement of knowledge of the clinical validity and utility of genetic tests.

You will find at Tab 9, behind the Work Group Progress Table, a copy of the correspondence I sent to each of the agency heads in late September. You will see that we have requested a fair

amount of information from AHRQ, CDC, CMS, FDA, HRSA, NIH, and just to be sure we have covered all the basis, even OHRP. Specifically, we asked for information about HHS efforts to increase knowledge of the validity and utility of genetic tests, both before and after a test is marketed, in the following four types of core activities: primary research studies, secondary analyses of existing data for multiple studies, projects involving the development or updating of information, summaries for clinicians, laboratory personnel and policymakers, patients, consumers and the general public, and information dissemination projects for professionals and the public. From each agency, we also requested a mission statement, a description of the agency's specific role in increasing the knowledge of the validity and utility of genetic tests through the four core activities, summaries of all projects or, if this is not feasible, a representative sample of projects underway for increasing knowledge of validity and utility of genetic tests, the total number of projects underway in each of the four types of activities, the amount of resources devoted in fiscal years 1996 through 2000 to these activities, coordination of core activities with other agencies, and the extent to and mechanisms by which the agency shares relevant information with other agencies in order to increase knowledge of the validity and utility of tests, the extent to which professional and consumer organizations and/or individuals are involved in carrying out the agency's efforts to increase knowledge of the validity and utility of genetic tests, the agency's future plans for increasing knowledge of the validity and utility of genetic tests.

We also asked FDA to address a number of additional questions related to the regulation of home brew tests. We had initially hoped that the information from this request would be available by the time of this meeting, but given how much detail we are looking for, particularly about specific projects and resources, we understand that the need for more time is required to

gather the information. I know that the effort for NIH in particular, given the scope of its relevant research activities, has been especially time-consuming.

We understand as well that the agencies are planning to meet in December to review the data gathered and to discuss together the question we have posed about information sharing and the coordination of activities. We will look forward to a presentation of this information at the February meeting.

Are there any questions from members of the Committee or points of clarification or amplification from any of the agency liaisons? Did we not ask enough questions?

DR. McCABE: Anything else? Okay. So we will look forward to some information in February. At each of our meetings, we usually ask Dr. Pat Charache to report on relevant proceedings of CLIAC. The last scheduled meeting of CLIAC was canceled due to the September attacks. Pat does, however, want to provide the Committee with a very brief update on one of the issues that she covered in her report to us in August. Before we do that, we'd also like to ask Dr. Joe Boone from CDC to provide an update on the Notice of Proposed Rulemaking to augment the CLIA regs, the CLIA regulations for genetic testing. So Joe, do you have a comment on that?

DR. BOONE: Well, we are making progress, and I've gotten my CLIA vest out that has the big target on it, and I'm going around to various professional organizations and trying to make sure that everybody understands that we are going to have a proposed rule, and we would like to get comments from everyone and trying to relate specific areas that we think specific organizations

will want to make comments. So I'm making those rounds. I'm going to the AMP meeting this weekend and that's going to be part of it. We are making progress in developing the proposed rule. There are a lot of issues that we're trying to work through, and we are going to be working very closely with our colleagues in the Department to try to resolve some of those issues. So I think we're on track as far as we're meeting the Department's expectations. My boss had an expectation that we would have something to deliver to the Department by the end of this calendar year, and we will meet that deadline.

MS. CARR: Yes, I wanted to ask a question, I guess, of the Committee and maybe of Joe as well about whether or not we would want, once the proposed rule is published, whether this Committee would want to comment on it. Of course, the Committee has recommended that augmentation of CLIA regulations for genetic tests occur, but we've never commented on the specific provisions or recommendations or suggestions that were laid out in the Notice of Intent, and I think there's some issues where it might be appropriate. There may be some provisions in the proposed rule related to clinical validity, and so I'm just wondering of the appropriateness of our doing that from your standpoint and also whether the Committee will have an interest in doing that, and we should probably gear up for that and least be aware that we want to do that.

DR. McCABE: So Joe, how would you see that?

DR. BOONE: I would see that as an appropriate response. I'm sure that our CLIAC members will -- because we're not going to necessarily adhere to every recommendation that the CLIAC provided us last. So I think it's important to get as broad an input as possible.

DR. BURKE: Yes, I would endorse that the Committee looks and responds, and I think it's helpful for us just to ensure that we're fully informed about that process, and it's possible that our couple of years of discussion about these related issues will enable us to make some useful comment.

DR. CHARACHE: I would also think this would be extremely helpful because the quality of the testing that goes on isn't a two major parts, and one is FDA ensuring appropriate tests, and the other is CLIA sharing appropriate use of those tests in the laboratory and covering some FDA doesn't do. So I think getting both pieces would be extremely helpful.

DR. McCABE: Okay. Any other comments on that before we move on? Pat, do you want to then make your presentation to update us?

DR. CHARACHE: This will be very brief because the issue is a bit peripheral but extremely important, and it's the one that we talked about in August on waived testing. Just a brief update. At that time, we pointed out that the waived test is the lowest category of tests compared to high complexity and moderate complex, and that any test that is waived is relieved of any further oversight by CLIA, so that it's very important that tests that are waived be done properly. I also presented data from Judy Yost that showed that the accuracy of the waived test is dependent on following manufacturer's directions. A third of the waived test labs that were surveyed showed that they had no directions from the manufacturer and another third showed they weren't following them, and there was a lot of other errors made in the tests that were reviewed, both by HCFA in 10 percent of the labs of eight states and by the two other groups that looked at the same thing. There's only one test currently that would fit our genetic category that's waived, but

there's a lot of pressure on FDA to waive a great deal more. I reported that CLIAC had established a waived test working group which had serious reservations about some new guidance documents from the FDA that were thought to be perhaps too permissive. FDA has since withdrawn that guidance document and has been rethinking and participating in a rethinking of how tests should be categorized as waived, and I understand that at the present time, the decision of who is going to be reviewing those tests is further under flux as well as how they will be reviewed.

DR. McCABE: Any questions or comments for Pat? Steve?

DR. GUTMAN: Well, anything is possible, but Pat is correct. FDA has signaled its intention to withdraw the draft guidance on waiver. That withdrawal actually was talked about yesterday. That withdrawal has actually not formally happened, but it is the intention for that to happen, and in the interim, we're certainly not following that draft guidance, and Pat is also correct that there is a fairly intense tri-agency discussion over how to proceed in the interim.
FDA continues to review waiver submissions, but we are reviewing them using the 1995 proposed rule initially developed by CDC and also using the concepts in the statutes since you're not able to bind yourself to the proposed rule. At this point in time, there is no intention in moving the administrative program out of FDA. So what is at stake is perhaps not the administration of the program but the rules of the game, but again this is a somewhat awkward and fluid state. So I don't wish to suggest that anything is impossible.

DR. McCABE: Is that something that you might be able to update us on at our February meeting? Thank you. Any other comments? Questions?

DR. McCABE: If not, I want to remind all of the members of the Committee who have comments on the information brochure to send them to Sarah as soon as possible but no later than close of business next Wednesday, the 21st. If there are no further questions or comments, I want to thank all of you for a very intensive and a very productive meeting. Please have a safe trip home, and the next meeting of the Secretary's Advisory Committee on Genetic Testing is scheduled for February 13th and 14th in Bethesda, Maryland. We may be having an educational summit, or we decided we'd put that off till May, right? So that will not be in association with that meeting. Thank you.

(Whereupon, at 2:33 p.m., the meeting was adjourned.)