SECRETARY'S ADVISORY COMMITTEE ON GENETIC TESTING

Thirteenth Meeting

Wednesday,
May 15, 2002

Constellation Ballroom E-F
Hyatt Regency
300 Light Street
Baltimore, Maryland

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Chair

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C O N T E N T S

C O N T E N T S

PROCEEDINGS (8:08 a.m.)

DR. McCABE: Well, good morning, everyone. For the National Human Genome Research Institute and the NIH, we have Barbara Fuller sitting in today. Barbara, do you want to introduce yourself, please?

MS. FULLER: Good morning. I'm glad he didn't say I'm replacing Francis Collins, because that would be too much pressure on me today. But I am branch chief at the Genome Institute, and my areas are education, outreach, and policy. So I'm very pleased to be here today. Thank you.

DR. McCABE: Thank you very much. This morning, Dr. Burke, chair of the Data Work Group, will lead a session on three case studies that were prepared to elucidate the steps involved in the development and application of the genetic test. Background information on these case studies is at Tab 6 of your briefing book. The case studies are part of the second phase of SACGT's assessment of HHS efforts to support the advancement of knowledge of the clinical validity and utility of genetic tests in both premarket and postmarket phases.

You'll recall that at our last meeting we reviewed a compendium of projects supported by the agencies around this table in primary research, secondary analyses, summary information development, and summary information dissemination. We were very impressed with the totality of the HHS efforts in advancing knowledge of the clinical validity and utility of genetic tests, but we did have questions about whether sufficient support was being provided for the translation of genetic tests into health care services, whether HHS had a clear vision and plan for its role in genetics and genetic testing, and whether coordination and communication among the agencies were adequate to foster the cross-cutting collaborative efforts required to advance knowledge for the appropriate use of genetic tests.

Before coming to final conclusion about these matters, we decided to gather

additional data in several selected areas to gain further insights about the ways in which the agencies have worked together and with the private sector to advance the validation and integration of genetic tests.

Dr. Burke has guided the conceptualization and development of this entire enterprise and has worked closely with the Data Work Group members. Dr. Puryear and Dr. Khoury have volunteered to help with phase 2.

Wylie, thank you for your work on this important project. We all hope that these case studies will put us in a better position to formulate policy recommendations to the Secretary in this area.

Wylie?

DR. BURKE: I'm going to start with just a couple of introductory comments. Can you hear me okay? I just want to remind you that the issue we're really addressing right now is postmarket data collection, the idea that tests become available and there are still many questions about them, and that one of the ways in which we can assure the best use of genetic tests is to make sure that needed data is acquired. So, as Ed just reminded us, we asked the HHS agencies to give us a picture of what their research efforts currently are, and we got a lot of data delineating different types of projects.

The important point about this slide and subsequent slides is that those research elements that are most in the direction of studying the application, the actual what happens when a test comes out into clinical use, tend to be the smallest part of the research portfolio.

Here's a little bit of a breakdown by agency and type of study. We made a distinction between primary and secondary research, the idea being that primary data collection is often basic science and that a very important element of understanding what a test means, and particularly its utility and the validity of test results, comes from secondary analysis, pooled and meta-analyses looking at studies together, et cetera. Then we looked at information development and information dissemination as separate elements that we thought were

important.

I do want to remind everybody that the distinction of thinking of primary data collection as mostly not translational research is a little bit artificial. As we found in our case studies, some primary data collection is directly related to the translational process. So this is a little bit of an artificial distinction.

But you can see two things from this slide, which is that NIH does the most of everything, and that the most activity is in the primary data collection column. The profile is different in other agencies because of differences in agency missions. This just shows you the same data in terms of funding. So the really important point here is that even though NIH is exactly as we would expect, the primary funder of primary data collection, it is also the primary funder of all other types of research, just because of the difference in budgets.

The other important observation here is that project funding has increased over time, but that increase is seen predominantly in primary data collection and not so much in secondary analysis, information development, or information dissemination. So, in fact, one of the important questions is what kind of ratios do we want here, and another important question is how much primary data collection is, in fact, addressing central issues of translation?

Again, in terms of the breakdown, we see what we talked about last time as the pyramid, with the vast amount of funding going into primary data collection and much less into other elements that are more directly related to translation of genetic test information into public use. But the discussion around the table was is this the right shape of the pyramid. In other words, is this a good thing or a bad thing? We actually don't know what the ratio should be, and our feeling was that we could get a better handle on that if we looked at a few specific examples of genetic tests that have become available and look at a timeline and the trajectory of accumulation of information about those tests, particularly around clinical validity, clinical utility, and the development of good information sources.

So we're going to now present to you information about three case examples. We're going to go in a slightly different order. Muin Khoury is going to start and

talk with us about HFE mutation testing. Then we'll hear from Michele Puryear, and then myself. Michele will talk about sickle cell newborn screening. I'll talk about BRCA1/2 testing.

Our goal in presenting to you the information that we've gathered is just to give you a picture of what we found and create the platform for discussion about what conclusions we can come to.

Muin?

DR. KHOURY: Thank you, Wylie.

You have in your folder a 10-page case study that Dr. Paula Yoon from our office put together. I think this came late last week, so it was probably not in your package. The credit for this goes to Paula Yoon, who is an epidemiologist in our office. She put together both the whole 10-page timeline and these slides. What I'd like to do very briefly this morning is review some of the timelines of development of the test around hemochromatosis, give you some of the major issues along those lines, but also the public and the private sector, and then assessment of the process itself and the gaps that this has revealed.

I'd like to start off by saying that this was a good process. Hemochromatosis was not a bad process. But before we get there, I'd like to very briefly go over this fairly complicated slide that Paula put together just to illustrate our thinking around this transition from gene discovery to application.

Briefly, you have gene discovery that starts with mapping and sequencing and then family studies, and there are two things that have to go on simultaneously once you discover a gene. You have to understand the gene disease biology, protein function pathways, pathophysiology, et cetera, and you also need to do the population work around the epidemiology of the gene and the relationship to disease before you get to the development of tests, and you really cannot bypass these two steps, although you can try. But I think you run into trouble, because when you bypass these two steps, you'll find those gaps will come back and haunt you later on.

Once you develop a test and the usual parameters of validity and utility and

ethical/legal issues, as SACGT has outlined many times before, those tests increasingly will be used not only for diagnosis but for prediction of future disease. I think the case studies that we have here are a mixture of both diagnosis and prediction.

But the clinical utility of these tests will be defined by what to do with interventions, and there are roughly four types of interventions. Gene therapy, of course, is reserved for situations when you're trying to fix a gene product, and that's too futuristic right now. Modification of the environment, a la behavior modification or diet, et cetera. Targeting of interventions, like screening and prophylactic surgeries. And then drug therapies and pharmacogenomics.

What happens after you go through this initial assessment phase and you figure out the clinical utility, then you put the test in the real world, and I think we have a sort of a loop that, for lack of a better term, I call surveillance. Somebody needs to sort of keep track of how the test is behaving in the real world, evaluate the data that comes out, and then possibly modify the interventions, because as you evaluate the data in the real world, you're not only refining those estimates of your parameters of the test, but you're also finding more about the epidemiology of the disease. So this is sort of a schematic idealized way of transition from gene discovery to applications.

There is one arrow here I'd like to tell you about briefly. Not all the applications will have to necessarily go to develop a test. Sometimes you bypass that step altogether. So, for example, you find that there is a relationship between a certain gene and a certain disease that is modified or affected by the environment. Sometimes you can develop the policies right away that apply to the whole population, like occupational exposures where you're trying to protect workers, and there is really no need for genetic testing. So this is sort of a bypassing of the loop, and not everything will have to be funneled through a genetic test.

So this is a quick intro, and I realize this is too dense for a slide show but I thought it was a useful representation of what's going on.

So what is hemochromatosis? It's an iron overload condition. Many people

think about it as the poster child for genetics and public health in the 21st Century. It is a single-gene disorder, kind of a single-gene disorder, but also a genetic risk factor. Basically, there is a problem with iron metabolism that may lead to iron accumulation in the front organs and potentially organ damage over many, many years.

Diagnostic tests. There is biochemical as well as now a DNA-based testing. Basically, the first thing you need to find out is whether you have excess iron in your body, and serum transferrin iron and iron-binding capacity will be the first way to find out whether you have excess iron. Liver biopsy has been viewed as a gold standard. The good news is that there is a therapy. So by getting rid of excess iron on a regular basis through phlebotomy, you can reduce the risk of complications.

The gene was discovered in 1996. It's on chromosome 6. The function is still unknown, although there is progress being made along those lines. Again, it's an autosomal recessive condition, and there are two main mutations, although now more have been described, the C282Y and the H63D variations.

Now, hemochromatosis is an attractive condition for population screening because of several factors. It's highly prevalent. It's one of those conditions that may be two orders of magnitude more common than PKU, not in the 1 in 10,000 range but maybe 1 in a few hundred range. There is lack of clinical findings early in the disease, so there is a long latency period. Initially, the clinical manifestations are very non-specific. People get fatigue, neuralgias, many different manifestations. There is low cost of diagnosis and treatment, and there is efficacy of early treatment, and also high cost and low success for late diagnosis and treatment.

This is a brief timeline of the whole field of hemochromatosis, which was first described in the 1800s as a triad of bronze diabetes. I guess it was thought to be a very rare condition. People were manifest with diabetes, heart disease, and a bronze discoloration of the skin. The genetics was first described in the '30s and linked to HLA in the '70s. As a matter of fact, for about 20 years, the only diagnostic work was done through family linkage

with the HLA loci, until 1996 when the gene was discovered.

So afterwards, the College of American Pathologists had a pronouncement for enhancing diagnosis, sort of a diagnostic algorithm and clinical management guideline. I think what happened soon after that is that the CDC and the NHGRI got together and we came at it from two points of view, both from the clinical side, the gene discovery side, as well as the public health side, because we at the time were evaluating guidelines for iron supplementation. Believe it or not, in 1996 the CDC was working on guidelines to supplement the whole world with iron, because iron deficiency is still a major public health problem, and the staff who were working on this stumbled upon hemochromatosis.

The idea was if we put out guidelines to fortify the food chain with iron, won't we be hurting some people at the time? So together we came as two institutes, two agencies within the federal government and held a workshop that Wylie Burke was a major leader in, and you will see some of the products of that. She continued to lead the effort in hemochromatosis even until now. We asked the question was screening for hemochromatosis warranted? What are the relative merits of biochemical tests versus DNA tests?

To cut a long story short, the meeting was a great effort to put together what we know and what we don't know about hemochromatosis, and we examined the issues around screening from the U.S. Preventive Services Task Force perspective, which led to a JAMA article that Wylie is the first author on, and we realized that there were some gaps, basically some issues that need to be learned about the prevalence of the condition in the population, and very importantly the penetrance of the mutations. In other words, if you carry one of these two mutations, what is the likelihood that you're going to be developing disease, and at what age? Therefore, if there is to be screening, what is the appropriate age for screening?

Very shortly after that, a bunch of groups got together. The AMA had a directive on hemochromatosis to try to work towards routine screening for iron overload. Among its membership, the proceedings of the workshop came later on. I'll talk about the publications later on. But in 1998, NHLBI solicited proposals for a big epi study of about

100,000 adults, and that study is still ongoing, and they have some preliminary data that will be coming out soon.

The FDA in 1999 weighed in because there was an issue around whether or not you can use the blood from hemochromatosis patients, which is a major deal if you're going to tilt the cost/benefit equation. If you should pay for phlebotomy, then the cost/benefit analysis will go one way. If the phlebotomy is free, the cost/benefit might go another way. In Europe, the Europeans and WHO got together in 1999. There was an international consensus conference on hemochromatosis. I think Wylie was there too. It reaffirmed basically what the NIH and CDC workshop came up with.

So basically, the absence of data, the uncovering of the gaps led to major grant proposals, a solicitation of grants through NIH, and the CDC in the meantime, as a public health agency, decided that even though there is no data, there is enough evidence to basically move forward with the idea of early detection of hemochromatosis. So a major educational campaign was launched to educate primary care providers. In 2000 there was the meeting of experts to begin to develop educational materials. The Office of Genetics also started our work in 2000. We funded the Foundation for Blood Research in Maine to develop a model approach for how we can continue collecting data on hemochromatosis and other genetic tests, and this work is still ongoing.

In 2001, the World Congress on Iron Metabolism was held in Australia. We visited population screening. I don't think they came up with a different conclusion. The Iron Disorders Institute, which is a consumer-driven organization, came up with their own guides for parents and patients and doctors. In 2002, earlier this year, there was a lab study sponsored by the CDC to evaluate the quality assurance and proficiency testing around the analytic methods for measuring iron. This is a lab round-robin involving 15 or 16 labs. Then a booklet was published earlier this year.

There are major publications that inform the process, the famous Wylie Burke article in 1998 that summarized the meeting of CDC and NHGRI. The Annals of

Internal Medicine published nine papers from that same proceeding, with more in-depth analysis of key issues, and AHRQ, which at the time was AHCPR, funded a couple of studies that were published in 1998. GeneTests and GeneReviews published also a review of hemochromatosis, and Karen Steinberg from our lab at the CDC published the first population-based estimate of the prevalence of the mutations in the U.S. using the NHANES specimens at CDC.

There was an epidemiologic review of hemochromatosis in 2001, and recently a paper published by Ernie Beutler from Southern California was published earlier this year that attempted to look at the issue of penetrance in hemochromatosis by looking at more than 40,000 healthy people who go to Kaiser in Southern California and found that very few of these people with hemochromatosis had any signs or symptoms consistent with long-term damage. There were some methodologic issues with that paper, and we don't have time to go through them today. I will be happy to discuss them.

Now, John Merz earlier this year published a lab survey that determined that some labs are not performing DNA tests because of the charges that GlaxoSmithKline is imposing.

Again, I'd like to summarize some of the issues that were uncovered in the development process. Many of them are good.

Soon after the gene was discovered, federal research and public health agencies came together to address the issues. It included academia, clinical medicine, and private companies. Other groups met, like WHO, and reached similar conclusions. A series of articles were published that essentially identified the research gaps. Funding was driven, both intramurally and extramurally, from mostly NIH, a little bit from CDC and AHRQ.

These are from the CRISP database, and thank you, SACGT staff, for helping put this together. These were most of the NIH studies published since the gene discovery. You can see the numbers are going up over time, from 18 to 45 in 2002. Most of them, however, are still in the molecular realm, less in the natural history, and less in testing,

treatment, and physician education. This is sort of our attempt to classify these kinds of studies. So we need more in the different areas.

The existing abstracts now are the natural history, penetrance, clinical course, other genetic contributors to the disease, role of non-genetic factors and the environmental interactions, the public health impact on the disease burden need to be more identified. Screening and genetic testing issues, course and efficacy of DNA versus the biochemical tests, impact on primary care, post-test follow-up, some of the ethical, legal and social implications. But I suspect many of the ongoing studies two years from now will leave answers to cover some of these gaps.

Really, the issue around clinical utility is the efficacy of early treatment versus late treatment. So should we pick up -- I mean, what's the advantage of picking up hemochromatosis in the asymptomatic stage versus early in the disease versus late in the disease? Most of the clinical utility studies have done usually later in the disease.

So forgive me if I spoke too much, but this is sort of a quick overview.

Wylie, do you want to add anything to this?

DR. BURKE: No. What I'd like to propose is that we go through our three case studies and then kind of have our discussion, having looked at them in the aggregate. So why don't we go ahead to the sickle cell.

DR. LLOYD-PURYEAR: I'd like to thank Sarah's office, Suzanne Goodwin and Susanne Haga, for these slides, if they appear.

DR. BURKE: While we're waiting for the slides, if anybody has a question just for clarity of the facts, why don't you ask?

DR. LLOYD-PURYEAR: Actually, I can begin.

Sickle cell disease, the case study that I'm going to present is actually a case study of the development of a test and the development of a screening and treatment program that's already in place. I agree with Muin's schematic. Actually, I liked it a lot. That's why we put Muin first. But I was thinking about it and I think one thing that's missing from that

schematic, and sickle cell disease is a good example of that, is that you need to have an overlay or an intersection of families, of the community, and health care providers.

So just briefly, a description of the disease. It's autosomal recessive. The mutations cause sickle hemoglobin in the red blood cell. There are four genotypes that are common in the U.S., sickle cell anemia, sickle-hemoglobin C disease, and two types of sickle beta-thalassemias.

The genotypes are characterized by marked and largely unpredictable variability in clinical expression and severity. I think it was Elliott who said a single gene is not a simple gene, and I think we're discovering that with many of the single-gene diseases.

There are about 2,000 newborns identified each year with sickle cell disease. Sickle cell disease is a clinical condition with multisystem manifestations and therefore requires considerable expertise in the care of individuals with sickle cell. We feel that it's essential that every child with sickle cell disease receive comprehensive care that is coordinated through a medical home with appropriate expertise. The latter phrase is absolutely essential to remember.

Most infants are identified by routine neonatal screening. There are 44 states that screen. The District of Columbia, Puerto Rico, the Virgin Islands, and Guam and Saipan all provide universal neonatal screening for sickle cell disease. Screening is available by request in the other remaining six states -- Alaska, Idaho, North Dakota, South Dakota, New Hampshire, and West Virginia. Last year Utah was presenting a targeted screening, and they began universal screening this year. Two of the infants they identified through the program were not African American, which I think makes the case for universal screening.

Sickle cell disease is most prevalent in populations of African, Mediterranean, and Middle Eastern and Indian backgrounds, and in people of Caribbean descent or from parts of Central and South America. So I think with the diverse population in America, that's important to keep in mind.

Confirmatory testing requires hemoglobin separation by electrophoresis,

isoelectric focusing, or high performance liquid chromatography. DNA analysis as a secondary screening tier has been shown to significantly decrease the time to definitive diagnosis and treatment. Solubility testing has no place in the confirmatory diagnosis of sickle cell disease. It does not distinguish between sickle cell disease and sickle cell carriers. Because of the high fetal hemoglobin concentration and low sickle cell hemoglobin concentration, there are considerable false-negative results.

So going through the milestones, I think it's important also to remember that although we using a medical model often think that the discovery of disease comes with the discovery of a medical case, sickle cell disease has long been recognized in Africa and the Middle East and can be traced back for three centuries just using family histories. But it was recognized as a definite disease entity in 1910 with Herrick identifying it.

In 1949, Pauling and others designated sickle cell disease as the prototype of a molecular disease and demonstrated that hemoglobin acid and hemoglobin A were distinguishable from one another by electrophoresis. In 1957, Ingram identified the substitution of valine for glutamic acid in the beta-hemoglobin molecule.

In 1930 through 1960, we began to see some newborn screening in isolated trials, and during the same time we began to see the advent of sickle cell disease screening programs in some states. Those were in general targeted screening in New York City to the case studies there, using targeted screening in New York City hospitals. But Georgia began universal screening in the 1960s. It became targeted later and then has gone back to universal. But initially, it was universal screening.

And then in 1973 you actually had the ability to -- and Guthrie was involved with this -- actually detect sickle cell hemoglobin on dried blood filter paper. So with this capability we began to see the incorporation of detecting sickle cell disease in newborn screening programs.

At the same time, from 1970 through 1992, you had significant federal funding for the detection of sickle cell disease. This funding came through two acts, the 1972

Sickle Cell Disease Act and the 1978 National Genetic Disease Act. Under the 1972 and 1978 authorities, the National Institutes of Health, which was responsible for the implementation of the Act, transferred funds to the Maternal and Child Health program to develop community-based sickle cell education, screening and counseling services, and there was actually a significant amount of funding put forward during this time.

This funding contributed to projects to improve follow-up services for newborn screening programs. You had the application of DNA technology in the diagnosis of sickle cell disease, a large development and dissemination of educational materials, regional conferences and training workshops in sickle cell screening and diagnosis, projects to improve the newborn screening system as a whole, including technical assistance for screening for sickle cell disease, and the establishment of comprehensive sickle cell disease centers. These sickle cell disease centers were largely funded through NIH.

Over $50 million was put forth during this 20-year time period, and I've broken this down by the types of funding, the types of projects that were funded. Sickle cell clinics for a little over $30 million, counseling couples for about $2.4 million, psychosocial support for patients and families of almost $2 million, newborn screening for sickle cell disease of about $17 million, newborn screening follow-up of about $4 million, and then programs for young adults with sickle cell disease, and those were focused on the transition from pediatric to adult care.

Also, separate from the NIH funding that was transferred to HRSA, HRSA also increased grant funding to newborn screening programs to encourage special emphasis on sickle cell disease, and that totaled about $12 million. At the same time during this time period, with NIH funding, there were large collaborative clinical trials. Marilyn Gaston headed up or wrote the paper that brought all the clinical trials together, and the recommendations out of those clinical trials indicated that we should be screening infants during the newborn period for sickle cell disease to decrease the mortality and morbidity associated with the disease, and those infants that are identified in the screening programs should receive oral penicillin

prophylaxis.

Shortly after the publication of the material from the clinical trials, there was a consensus development conference on sickle cell disease which was sponsored by NIH and HRSA which confirmed the above recommendations.

Later, clinical practice guidelines were developed by AHCPR, AHRQ now. Federal funding continued on a smaller level throughout the past 10 years, and this is approximately $1 million per year that we've been funding different sickle cell disease projects, and I've listed the priorities. Again, there's been a focus on the coordination of follow-up with the state newborn screening programs, the transition from pediatric to adult health care services, and the integration of the sickle cell disease programs into managed care health plans.

From 2002 onward, because I think it's related, it's going on, implementing the Newborn Screening Task Force Report. We spent a considerable amount of time educating state legislators and health officials on the need for universal screening, which was a need that was pointed out by the Task Force Report. We helped put forth management guidelines for the care and treatment of sickle cell disease, and this year we received $4 million to enhance the sickle cell disease program. There are two components to this program. One will be a cooperative agreement with the large National Sickle Cell Disease Association, and we're funding 15 community-based projects.

The purpose of these projects will be to enhance the state sickle cell disease and newborn screening programs through the provision of outreach and counseling efforts.

There were many pitfalls, and also many positive things happened during the development of screening programs for sickle cell disease. Actually, with the development of the technology, screening programs were developed quite rapidly. Newborn screening for sickle cell disease, along with federal funding to encourage it, was integrated pretty rapidly into the existing newborn screening programs. However, one of the pitfalls came with well-intentioned, probably enthusiastic screening for many people for sickle cell disease with inadequate follow-up and inadequate counseling and a lot of misperceptions about the carrier

status. Actually, sickle cell disease screening was incorporated into EPSDT programs, so anyone under the age of 21, in some states it was mandated that screening take place, and this is often done without counseling and, in general, probably without permission. I think some people like Ed, who were probably around during those time periods, can answer some of those questions more precisely.

That's often not published, and I couldn't find a lot of the details of what was involved there. But during the development process, another significant problem was the absence of national universal screening. This was recommended by a consensus development conference in 1987, and to date we haven't achieved that.

There's also an absence of programs for consistent family and community-based and culturally competent genetic counseling. Often, parents get the child identified with the sickle cell trait or having the carrier status are left to fend on their own and very little connection with any ongoing genetic counseling is offered. Some of that is left over from the stigma of what went on during the '70s and having a hands-off stance in it. But quite clearly, I think it's a good example of the need for genetic counseling no matter how trivial the test may seem to some.

There is still a lack of consistent adherence to national guidelines for follow-up and treatment, and there's a lack of a readily available hemoglobinopathy reference lab for hemoglobins not readily identified by screening techniques and about which no functional information is available. There used to be a reference lab that was supported by CDC at the Medical College of Georgia, but funding for that, because of other CDC priorities, has disappeared, and the community still identifies that as a need.

NIH studies, you can find those on the back of your handout. That came from the aid of Susanne Haga, and according to the database, NIH has had numerous grants related to sickle cell disease since the year 2000. Research is still ongoing in the areas of gene and protein function, disease epidemiology, and treatment and therapies, and NIH is still actively funding the comprehensive sickle cell disease treatment centers.

The gaps that are identified are the education process, both for general public and for health professionals, public health as well as health care professionals, and education and counseling for affected families; follow-up programs that aim toward a coordinated integration with early intervention programs; adherence by health professionals in state programs to national screening, such as universal screening and treatment guidelines; and again, the establishment of a hemoglobinopathy reference laboratory.

DR. BURKE: Well, I'm just going to quickly review our third case study, which was susceptibility testing for breast cancer, and the specific test is a sequence analysis for mutations in the BRCA1 and BRCA2 genes, these mutations being associated with an autosomal dominant inheritance of a markedly increased risk for both breast and ovarian cancer, often referred to as hereditary breast/ovarian cancer syndrome.

The discovery of the genes occurred in the early '90s. Linkage analysis identified the gene that subsequently was identified as BRCA1 in 1990, and the gene was sequenced in 1994. Linkage identification of BRCA2 occurred in the same year, and sequencing the following year for BRCA2. A scant year after, we had the introduction of the commercial test for BRCA1/2.

One of the themes of BRCA1/2 is intense interest, and I think this rapid timeline reflects that.

These are just a few highlights for commercial test development, and there are more details in the handout that's in the book, in the background materials that we provided in the book. I do want to acknowledge the amazing amount of work and high-quality work done by Susanne Haga in gathering this information together.

Really very shortly after the genes were sequenced, a test was available. In 1996, Oncormed was the first company, but followed very quickly thereafter by Myriad Genetics, and Myriad Genetics, in fact, successfully fought for patent rights. So that's the bottom line story here. Myriad Genetics is now the exclusive provider or has exclusive licensing, I should say, for this test and owns the patents.

Another milestone that is worth mentioning was that in 1999 a story hit the front pages, and this was the story of a woman who had initially gotten a test result indicating that she had a mutation. She came from a family where a mutation was likely. She underwent prophylactic surgery, and only after her surgery had been done was it discovered that there had been a lab error and she, in fact, didn't have the mutation. So that obviously attracted a great deal of interest because of the intense interest in this kind of testing, but it also is a reminder that I think always needs to be there, that human error is always a possible source of lab error, even when we have very specific and highly accurate techniques.

The growth of the use of this test is best evidenced by the data that Myriad provides us because in recent years it is the primary source for testing, and you can see that there has been over several years a rapid increase. Every year we see more tests being done. In fact, Myriad recently reported on the results of 10,000 tests performed.

There are other testing laboratories that offer tests for BRCA1/2 mutations. GeneTests identifies 14 laboratories that offer clinical testing. However, the majority of them are offering a specific test for three mutations that are relatively common in people of Ashkenazi Jewish descent, whereas what Myriad labs offers is a full sequencing test, or so described full sequencing test. It's a detailed analysis of the majority of exons in both BRCA1 and BRCA2, looking obviously not only for known mutations but for sequence variance that may not previously have been described. That's considered at this point the gold standard approach to testing, and the reason why is because there are many, many different mutations in the BRCA1 and BRCA2 genes, literally hundreds and hundreds identified already, and we're still finding, as women from candidate families go through testing, the identification of further additional new mutations.

There have been many clinical guidelines and position statements starting as early as the identification of the gene in 1994 and continuing on to the present day. They tell a very interesting story that may be worth reflecting upon, and that is that many organizations, both public and private, rapidly made statements after the genes were identified suggesting that

we should delay the development of a clinical test, and the primary reason for making that argument was that even though the genes had been identified, we had many questions about clinical validity and clinical utility.

The argument was that we should try to keep testing within a research setting while we worked those problems out. So despite those many statements of that sort, and all generally consistent with one another, the commercial test in fact was developed, I think one could say, as rapidly as it was possible technically to develop it. In response to that we began to see a different kind of position statement and guideline statement, which was who is a candidate for testing.

So there was a community response that said let's delay this and keep this in the research sector, the test became available, and the response shifted to let's try to figure out who is a reasonable candidate, and then there were a few consensus processes that tried to look very carefully at what would be reasonable to offer in the way of preventive care management once a mutation was identified given all the uncertainties we had about what to offer to women who were so identified.

Another major theme, and I think it reflects the tremendous interest in these particular genes, has been what I think would be best described as a very robust response from the federal government in terms of funding research. So there has, in fact, been a lot of awareness of the questions and a lot of funding made available to try to address questions about BRCA1 and BRCA2 mutations.

NIH is the major funder, and you can see the graph of steady increase. There's an apparent drop in fiscal year 2002, and I don't know if that's just a plateau effect. We'll have to see what happens over time. Interestingly, and I think it reflects very powerful advocacy and concern about breast cancer research, another major source of federal funding has been the DOD, actually starting in fiscal year 1994. There were special arrangements made to put some DOD funds specifically into breast cancer research, and a whole review process, an RFA process was developed in order to spend those funds in that way.

There have been, in addition to federal funding, a number of federal initiatives that directed funding, tried to promote certain kinds of research approaches. I've noted some that are the most prominent. The Cancer Genetics Studies Consortium, which was a multi-institute RFA directed at funding studies that looked at ethical, legal, and social implications of cancer genetics testing; breast cancer family registries, funding for bringing in families and studying families related to genetics, breast and others; Breast/Ovarian Cancer SPOREs, which are dedicated centers for a wide array of breast and ovarian cancer-related research, not just focused on BRCA1/2 or genetics; the Cancer Genetics Network, an NCI-funded network involving, I believe, eight centers presently around the country that is focused on cancer genetics. I've already mentioned the Department of Defense Army program, and I'll talk more about CancerNet PDQ, which is an information source in just a moment.

Let me give you a little bit more detail about some of these research initiatives. As you can see, the Cancer Genetics Studies Consortium, which was focused on ELSI issues, involved primarily NCI and NHGRI, but two other institutes as well. An initial 11 projects were subsequently joined by five others and has been very productive, and actually remains probably our primary source of information about ethical, legal and social implications of testing, and in particular psychosocial outcomes of testing.

This consortium, in addition to funding research in this area and publications coming forth from that research, has sponsored some consensus processes that have generated recommendations, for example about follow-up and about informed consent procedures.

Cancer family registries. There are currently six breast centers within this funding initiative, and as you can see at the bottom of the slide, these cancer family registries are focused on a variety of issues all around familial cancers, so again not exclusively BRCA1, but they include epidemiology, modifying factors such as diet and exposures, and involve the collection of biologic samples.

I spoke with the project officer for this initiative, and she said that amongst

the breast studies she would estimate that about two-thirds of families enrolled come from population-based sources, and another third come from clinical sources and tend to enrich for higher-risk families. Thus, this particular funding initiative creates an opportunity to investigate hypotheses from both population-based and enriched high-risk groups concurrently.

One of the issues here is that there is not routine BRCA1/2 testing. So this initiative involves enrolling families and looking, therefore, and collecting populations in which there is a familial clustering of cancer, and it would be extremely valuable to then gather BRCA1/2 data on those families and try to begin to correlate clinical characteristics and familial characteristics with testing, and they're just beginning to figure out how they might be able to do that.

SPOREs, Specialized Programs of Research Excellence. There are several breast SPOREs, currently nine sites. There will be additional solicitations. These SPOREs are focused on translational research, but not specifically on BRCA1/2. Obviously, genetics is a very prominent issue in any study of breast cancer research.

Then there is the Cancer Genetics Network. The Cancer Genetics Network is a national network. It creates infrastructure. The idea is the infrastructure created by Cancer Genetics Network creates a framework in which people can be recruited, either people who have had testing and can be recruited so that you develop populations, or families could be recruited. These networks vary in the degree to which they use specialized populations, or referral populations, versus population-based samples. They vary in their focus on breast cancer. Some are not primarily focused on breast cancer. Others have that as a very prominent research goal.

There is not at this point, at least as far as we could gather, a clearly defined mission in clinical validity or clinical utility of BRCA1/2 tests. But clearly, this kind of infrastructure creates the opportunity or the site where such research could go.

Now, I said I wanted to talk about the PDQ system. The National Cancer Institute for some time has had an online information system providing information about a

broad range of issues related to cancer, including prevention screening, et cetera, and starting in 1998 created a cancer genetics section of their PDQ system. They've changed the Website name and the Website name is now cancer.gov. It's very easy to get to. Within that is what they call the PDQ system, which is a system that provides information both for health care providers and for consumers.

They do have a very detailed summary of breast/ovarian cancer genetics. So that represents a very available source, and a lot of effort, I should say, is put into keeping that source current and up to date.

I do want to mention that the GeneClinics site also has a breast cancer summary.

So that's just a quick overview of where we are particularly in terms of federal initiatives. I want to take that background and then briefly summarize for you based on that funding effort where are we in terms of different elements of translational research.

Well, in terms of analytic validity, there are very limited data in terms of publications. In fact, there's only really one major publication comparing different kinds of testing methods. We consider the sequencing method the gold standard. There are other technical methods to look for mutations in BRCA1/2 genes. There's one paper that has compared a variety of methods in terms of their sensitivity and specificity, but there really hasn't been a lot of work, and how much work there will be is quite unclear since most of these other methods are primarily used within research studies and are not used for clinical purposes.

In terms of clinical validity, I think it's fair to say that it represents a major focus of research, and that is true both for initiative-based research -- that is, research that is funded through, for example, SPOREs or family registries. In fact, clinical validity is a primary concern of the family registries and investigator-initiated research. This reflects the fact that this was a big concern from the time that the genes were first discovered. We don't know the penetrance of these genes. We actually have discrepant data. Population-based data suggests, for example, that lifetime risk of breast cancer might be around 40 percent. Studies of high-risk

families suggest that the lifetime incidence is 85 percent, suggesting modifying factors, suggesting that it's a complex issue to determine what the penetrance of these mutations is, and clinical validity data are extremely important.

Clinical utility. I think it's fair to say that current and recent studies have addressed a lot of psychosocial issues, at least in terms of short-term follow-up. Usually the follow-up as been up to a year. We're seeing an increasing number of studies in the funding pipeline that are looking at outcomes of current preventive options, so outcomes of mastectomy, outcomes of oophorectomy, the effects of hormone therapy both in the form of oral contraceptives and estrogen replacement therapy, the effects of tamoxifen. There have been publications on all of these points, and more data is forthcoming.

These data continue to refine our knowledge about what current preventive efforts do, but they tend to confirm what we've suspected from the beginning, which is that the current preventive efforts are imperfect. They provide some preventive opportunities, but they certainly don't provide the very definitive preventive care that we'd like to offer to women at high risk.

In talking to some of the project officers involved, the point was made to me that that's why we need to focus on clinical validity studies, because the clinical validity studies, as well as the basic biology studies, are likely to provide clues about modifying factors and therefore may lead to the innovative therapies that we really want.

In terms of secondary analysis, each of the guidelines processes, and there are a number that are listed in your handout, have done some degree of secondary analysis as they've tried to come up with guidelines. In addition, the CDC-sponsored ACCE project is focusing on BRCA1/BRCA2, so that will be a source of data. I've already mentioned that we are pretty rich in terms of online information sources. We have the PDQ, we have the GeneTests summary, and we also have a number of educational tools that have been developed particularly as part of those ELSI studies.

There are some remaining issues, and I'm just summarizing highlights here.

What's the role of the test offeror in ongoing research? If Myriad has done 10,000 tests, wouldn't it be nice to do prospective follow-up of everyone that had a positive test result? Well, how do we do that? What is the responsibility of the lab offeror, and how might we incent some sort of research process that would develop that prospective follow-up? Who funds it? How do you deal with the human subjects issues, that are considerable, in terms of perhaps offering participation to participate in a prospective follow-up study to women as they get their test process done? Does that, as a question, lead to reevaluation of current research strategies?

We have, as I've shown you, quite a bit of infrastructure. We've got the SPOREs, we've got the Cancer Genetics Networks, we've got the family registries. Should they be linking up in some way? Should they be coordinating in order to get large samples and good power? Is there a way to link one or more of these infrastructures to the lab in some way to create the ongoing follow-up data that we'd like? And what's the role of the government in trying to make this happen? Because research collaborations of that sort could always happen, initiated by investigators if those investigators were willing and able to go through the considerable work to talk to all the players and figure out how to work together. But the question is, is there a role for NIH or other places in HHS to provide leadership to help promote that kind of activity?

I just offer as an example that efforts of that kind might be the best way to study what we currently have as a very important apparent discrepancy of much lower penetrance when the mutations are found in population-based samples versus when they're found in high-risk families in referral centers, again speaking powerfully to modifying factors that we need to understand.

There is no established body for ongoing secondary analysis, and that's a question. Do we need that? Would that be helpful in terms of directing where the research initiatives should go? If we fund an ELSI study for three years, we're going to get a one-year follow-up. Is there any way to get much longer follow-up, and perhaps follow-up that looks

much more broadly at social issues?

So those were questions that we identified.

I'm going to finish, and you've heard three case studies. I think what we want to do at this point is just open it up for reactions, comments, reflections on these three case studies.

I have David and Joann.

DR. LANIER: First of all, I would like to thank you for these case studies. It really helps make more concrete in my own mind the issues that we're dealing with in terms of particularly accumulating the evidence that will be required to develop evidence-based guidelines.

I've got a couple of questions. The first one I think is mainly for Wylie, because I'm interested in more DNA-based testing. You sort of gave a nice picture of the accumulation of evidence increasing over the last year or two in terms of clinical utility and validity. I'm thinking about the U.S. Preventive Services Task Force and the level of evidence required for making recommendations there.

My question for you is are we at a point, knowing what you know about the U.S. Preventive Services Task Force, where we would come up with anything more than a C-level type of recommendation for BRCA1/2 testing for population screening?

DR. BURKE: Oh, for population screening? No, I wouldn't think so. I think there's more a question of what you might call a cascade screening, where what we might recommend is a routine assessment, a family history to a certain level in order to identify people who might benefit. Whether a recommendation would rise to a level of B, I'm not sure. Maybe.

But I think the question you're asking might lead to a different question, which is should we have some monitoring system in place? I mean, I think that's part of the ongoing secondary analysis issue. Should there be a monitoring system in place that triggers the point at which U.S. Preventive Services Task Force ought to do a review? My sense of it is

probably not quite yet, but the larger question is how could we monitor a question like that and identify the triggers, the point at which it really is time to do it?

DR. LANIER: The second question I have is probably impossible to answer, but I just want to put it on the table. If you look at the chronology here, I think you said that the BRCA1/2 testing became commercially available in 1996. Most of the studies in terms of clinical utility and validity it seems to me may have been inspired by the release of this commercially. Do you think that if it were not released commercially we would be at the point we are now? Has that somehow inspired us to do the research more quickly?

DR. BURKE: I think that's a very important question, and I think that's also a generalizable question. In other words, we can look back retrospectively and say was it a good idea for all those people to be saying no, let's not do this test yet, we're not ready. Is it the reality that we do the test and then understand? Is that part of the natural history?

DR. LANIER: Right.

DR. BURKE: Joann?

DR. BOUGHMAN: My questions are actually somewhat related and come back to the fact that in our meeting on Monday, the U.S. Preventive Services Task Force was also mentioned, and this may be my ignorance of the way that group operates, but it's also related to that conservatism that scientists tend to show.

In working with policymakers in a lot of the work that we've done in teaching judges, the stunning difference in mindset for policymakers and in the courtroom, where there comes a point where somebody has to vote yea or nay given the data they have, whether it's enough data or not, versus the mindset that we often have as scientists, that the answer is always we need more data.

It seems to me that, related to David's question now, and even in these three very different scenarios that have been presented, there is a huge amount of federal support being used in various ways on these disorders.

I was on the sickle cell comprehensive centers parent committee for 10

years, and that was a long time ago. The amount of time and effort that's already gone in, and if we say we aren't to a decision point now, I think it may be that this group or some other groups do need to change our mindset and come up with at least some criteria, because if we don't, other policymakers and the courts will. As frustrated as we might be that the commercialization decision was made when we thought we needed more data, it would be worse to have the whole system being driven by those who have less understanding of these things than we do.

So I think these three case studies really demonstrate that we're going to have to bite the bullet sooner rather than later.

DR. BURKE: Ed?

DR. McCABE: Two points. First of all, I just want to point out from Dr. Puryear's presentation that there was a study done in 1986 by Marilyn Gaston showing that there was a need for universal screening. There was a consensus development conference in 1987 headed by Doris Wethers out of the NIH that said that there needed to be universal screening, and we still have six states that aren't doing universal screening.

So while we can establish policies, we can do the studies that are clearly definitive and establish the policies, because of the nature of our state-based public health programs, sometimes these aren't implemented. I've stated publicly before that it's a tragedy that there are still approximately somewhere between 75 and 100 kids who are not going to be detected this year, 15 years after those studies came out, because we don't have a system that will put our policies into practice. So whatever we come up with in terms of evidence base, we then have to have a system for establishing the policies.

Second is more of a question, and it's sort of an extension of the question about when is it appropriate to trigger a U.S. Preventive Services Task Force study. But even before that, when is it appropriate to determine that we need large population-based studies? That's been done for hemochromatosis, it was done for sickle cell disease, it's being done in various ways for breast cancer, but do we need some sort of a triggering system as we get more

and more diseases that reach that threshold where we need to think about large population-based studies, and where would the funding come from for that? Because we need those data to then trigger the assessment of whether the evidence base is adequate.

DR. BURKE: I have Mary, and then Pat.

MS. DAVIDSON: Thank you. I was really struck by the degree of collaboration between private and public sectors, and in particular the consumer organizations. But I would like to just ask you to describe or to quantify the contributions of the Iron Overload Institute's Sickle Cell Disease Association and the National Breast Cancer Coalition and other groups that might have been involved. I'm trying to understand the kinds of resources and support that those family service-based organizations, disease-based organizations bring to the process in looking at this from the research and the registry stage all the way through the development of information resources.

I guess tied to that is a related question again. I'd like you to help me understand better the development of lay information resources, and the collaborative role of all the partners, but in particular the role of the disease organizations.

DR. LLOYD-PURYEAR: I'll speak to sickle cell. There is one large national organization. That's the Sickle Cell Disease Association of America. It has about 60 affiliates all over the nation, sometimes with a relationship with the comprehensive sickle cell treatment centers in that area, and sometimes a relationship with a state newborn screening program. But by and large -- and Ed or Victor can speak to, if they know, the earlier history but as of now, the history now, that from hearing from them, because we've had recent meetings, they're very disconnected in general from the state newborn screening programs and from the sickle cell treatment centers.

They really feel a need for family participation in carrier counseling and have been the big impetus to institute that counseling and are going to be very much a part of -- I don't know organizationally, but at least very much a part of the new initiative that we have. Whether or not the states are going to collaborate or not, that remains to be seen, but that's part

of the initiative, that ongoing collaboration.

But they really have been left out. I think sickle cell disease shows that if things are following a medical model and remain in academic centers and are not community-based or family-centered and culturally competent, the implementation of any of these programs will be a big disconnect and they will not necessarily be well received. I think sickle cell disease is a good example of that.

If you compare it, actually, to what happened with Tay Sachs screening or cystic fibrosis screening, I think you'll see some differences in the input from those family organizations and the organizations themselves.

DR. KHOURY: Just some comments on the hemochromatosis community. There are at least two groups, consumer groups, the Island Disorders Institute, and I think the other one is the American Hemochromatosis Society.

DR. BURKE: There are actually four.

DR. KHOURY: Four groups? Okay. Wylie might know more.

These groups have been at the table from day one in each one of these discussions that I laid forth in the milestones, from the NIH CDC workshops to the roundtable discussions to the development of educational materials, and even to some of the things I didn't show, which are the HHS efforts. At one point we had a data working group. So we're always involving the community.

Now, whether or not they get specific funding from any of the federal agencies, I can't tell you. I'll be happy to check on that. I don't know about NIH or anything. But they are equal partners.

That kind of raises the bigger issue in my mind, that while we've presented three conditions here, these may not be the way genetic testing is going to look in the future, because these are, by and large, single-gene disorders, and for each one of them there happens to be consumer organizations owning the disease and behind it, and I think when we start looking to the future for testing for a combination of SNPs or polymorphisms, like MTHFR or

Factor V Leiden and things like that, I don't know who will own that disease or group of diseases.

I just wanted to open this up because it's an issue that I don't think we covered in the three case studies as to the future of genetic testing.

DR. BURKE: I think some comments on breast cancer might be relevant here.

DR. McCABE: The breast cancer story is the story of a very sophisticated group of women who went to the Hill and started meeting with their members and senators and said, "We're taking names. You're either with us, you either support this research and you recommend that funding be identified for it, or we will see to it that you don't get any funding for your survival on the Hill." So it was a very strong political message that went out. It was a unified group that was able to show that they had clout, and that's part of why the funding went up so strongly at that point in time. It was a political effort, pure and simple, and it worked.

DR. BURKE: I suspect that as the genetics of common disease becomes more apparent, we might see that kind of model more. As another point, a lot of the advocacy in breast cancer is led by women affected by breast cancer relatively young. Many have had breast cancer in their families, and so the genetics has been front and center as a very important issue, and they have been sitting pretty much on every consensus process. I think they've been involved.

I have Pat, and then Joann.

DR. CHARACHE: Two thoughts as they pertain to some of these laboratory issues that Wylie raised.

The first pertains to the issue of laboratory reporting of results. I think we recognize the strength of having Myriad be a focus for identifying populations, particularly because among the questions a lot of people have is which allele changes are associated with likelihood of disease, and particularly in the population without the familial profile being obvious.

The challenge here -- and this was discussed a lot with the Genetics Working Group -- is what the laboratory is in a position to do, noting all the issues that pertain to confidentiality and what have you. We know that this is the only way to reliably trap the positive and negative populations that you want to see, and we know this from all the public health reporting. Less than 10 percent of the reports of salmonella or anything else come from the physicians who, by law, have to report it. They come from the laboratories, and by law, they have to report.

But I think this is an issue which should be thought about in a very thoughtful way. Should the laboratory notify the clinician and have on their report a form that they send in if the patient agrees to be followed, or something of that type, some reminder? So I think there are a lot of things that can be done if we think through how to trap that population, with the concordance of the laboratory group.

The other is just a reminder, and I'll try to make this the last time I say this today. But I think what we've seen here with the release of the BRCA1/2 testing, is the fact that all of the public health and scientific community said we need to know which of these positives are meaningful. Yet, for commercial reasons, that didn't happen. Now, the scientists will never be happy when something is released, as Joann pointed out. But what we need is an objective decision, do we have enough data to release this.

We know perfectly well from this example that with the familial story with 80 percent penetrance, that there was only a 20 percent likelihood that people were harmed. But we know that more than half the people that got a positive with the random testing were harmed. They thought they had cancer or would likely develop it. That was not the case.

The point I'm making in questioning whether there's anything that this group would want to do to reinforce our concern is that the only way that this can have an intervention is if an objective group like the FDA is making the decision, yes, we know enough to put this out, and this is what your report should say in terms of the limitations of our knowledge base.

I think it's a beautiful example of a laboratory developed test that caused harm for a lot of people. If you have a group that doesn't have a conflict of interest, a commercial desire to make money in a hurry, making that decision and not the person who developed the test, it seems to me that's the only safe approach that's going to be increasingly critical over time.

DR. BURKE: I just want to comment on a couple of things. First of all, I did have a conversation with Mark Green at NCI just in a very general way about how could you link a lab that's doing tests to the kind of prospective follow-up, and he made a few points that I want to convey. But also, I would say we generally agreed that that is a research strategy that should be explored. The question is how could one incent a lab to be involved in the offer to the people that are getting the test of voluntary participation in prospective follow-up, and what kind of research infrastructure do you need to have in place to then make the research work and make sure that appropriate confidentiality and so on are protected?

The point he made was that he thought exploring those points would be an extremely positive thing to do, that there might be a lot of interesting discussion, there might be a role for HHS leadership in creating the structures for this kind of research, that he would view it as rather negative if it came as a regulatory imperative but very positive if it came as a research strategy to be explored with appropriate attention to voluntariness of the participation.

It sounds like you've got a comment on that, and then we'll go to Joann.

DR. CHARACHE: Just a very strong support. I think you would have support, and I think it would be most critical for the places you're most likely to get support, and that is the academic laboratories that are testing for rare diseases. I think that this is a critical area that otherwise will be very difficult to approach.

DR. BURKE: Joann?

DR. BOUGHMAN: We in fact focus a lot of our effort on the ethical, legal and social implications, and sometimes we remind ourselves and sweep in the psychosocial implications, which would be more individually based. Being one of those people in one of

these categories and it having changed my life as a genetic counselor in changing my own perception of risk and what risk really means, I'm encouraged to suggest that we assign ourselves the same process that was done with the Endocrine Society, and when we come to our meeting in August, each one of us come with a different scenario attached to us and just see for yourselves how the implications really play out.

I would raise that as it applies to another set of issues now being studied from NIDCD and the newborn hearing screening and the Connexion 26 and some of the very nice studies that are now out there on the timing of the pre- and post-counseling and the individually based psychological effects, which brings me back to the scientist's view that BRCA1/2 release of the test was too early for all of the data, and maybe some of the women were harmed, or maybe their psychological perception of their risk changed, although their actual change did not.

They are all still at some risk for developing breast cancer, whether it's BRCA1-related or not, because they're adult women. So somehow, even the challenge I'm providing here I think is to gather data on the individual psychosocial implications and not just the population-based issues, and I think we do have a model out there that is going to get at some of that with the NIDCD studies.

DR. BURKE: Michele, and then Vence.

DR. LLOYD-PURYEAR: This is a follow-up on Pat. It's not just a problem of whether or not you have a clinically valid test. Sickle cell disease is screened with a clinical valid test, and you still have many, many, many problems in the implementation of that as a screening and follow-up and treatment program.

I think the problems, actually, if you separate out the research from the actual implementation or the actual health care provider community, the public health community, and the society at large, many of the problems with sickle cell disease screening -- i.e., the lack of universal screening -- I think happen to be because of misperceptions about who's who in America.

So I think what we need to do is develop a model, a paradigm that reflects the need for an ongoing process and also reflects the need for relationships between families, communities, and also public health and health care providers, so that you can both develop a test and implement it, because it is an ongoing process. I mean, to accumulate the kind of knowledge you need still about sickle cell disease, even more about hemochromatosis and breast cancer, is going to take those kinds of relationships. You cannot separate out research from the health care community from families.

DR. BURKE: Vence, and then Pat.

MR. BONHAM: As we think about our agenda over the next couple of years and our role and function of oversight of genetic testing, I think these case studies can provide us helpful information in thinking about what we should be doing. As we think about sickle cell disease and really the whole question of access, that is an access question when we have six states that are not providing universal screening. So I think it's important that we think about all three case studies as we think about our focus and what we should be doing as a committee.

I think this was excellent, and I think it clearly identified a number of gaps. So I guess I hope we continue to think about this as we move into our next meeting in August and the focus of the committee over the next couple of years.

DR. BURKE: I just want to follow up. I really support your statement. It seems to me that we've identified gaps, and we then have this big question of what can HHS do, what should HHS do, and that's a complicated question.

Pat?

DR. CHARACHE: I just wanted to emphasize that I 100 percent agree with the last three statements. What I'm suggesting is that among the ethical issues that should be studied is what happens to people who are told that they have a likelihood of cancer, or think they do, and who do not, because I've seen mostly with HIV testing lives destroyed with information that was not valid.

DR. BURKE: Ed?

DR. McCABE: I just wanted to follow up on what Vence and Wylie said. I think these case studies are very helpful in focusing our attention. They're different. They complement each other. I would suggest that we revisit them at least at annual intervals to see the progress that's made and see if we can learn more, and then I think we ought to try to identify other informative cases that we should address and then track, as well.

DR. BURKE: Thanks. I just want to say that I actually feel that I now have new questions that I can go back and ask about this case study based on the discussion. So I think there will be a utility to ongoing research.

Dr. Baumiller?

DR. BAUMILLER: I think we all recognize how quickly things are moving in some of these areas. Certainly with sickle cell, the use of hydroxy urea now, studies taking it down to age 5, and we've been waiting to get the experiments underway that would take it down to 5 months of age in order to try to save the spleen and kidney function in these children. So it's not just a matter of screening identifying, but the broadness of treatment for some of these are growing very rapidly and need to be.

DR. BURKE: Thanks. In fact, I think your comment suggests that clinical utility is always a moving target and that one of the things we may want to watch and think about is how people respond to new information about clinical utility and what potential role HHS might have in promoting an effective response.

DR. BAUMILLER: Right. The Heart, Lung and Blood Institute ought to be alive to what we're talking about with certain diseases, et cetera.

DR. BURKE: Tracking it and thinking about how to get the message out.

Cindy, and then Ed.

MS. BERRY: Perhaps the committee has already addressed this in years past and this is more of a question to educate me. Is there a role for the committee in making recommendations with regard to health professionals and their counseling in light of the fact

that some of these tests perhaps raise ethical questions and there's the potential for harm? Has this been done in the past? Has the committee worked on this, or is this an issue that we might look at?

Rather than trying to put our finger in the dike of commercialization of technology and new tests, maybe since we can't really avoid that, is there something we can do on the provider end that would help prevent some of these problems?

DR. BURKE: I think you've just articulated the line of thinking that led to our conference on Monday, exactly that, which is that one part of safe and effective use of genetic tests is having a health provider population that is ready to make wise decisions about the use of tests, and in terms of our role, I think we have seen our role as that, which is identifying what the issues are and then stepping back and saying, okay, here are the issues in this case, provider education, what is HHS' role, which obviously dominated our conversation yesterday.

MS. BERRY: Maybe to get to even more specifics, because I know we've talked a lot about that we need to have counseling accompanying these tests and we need to make sure that there's reimbursement so that people have access and things like that, but are there specific -- much like the brochure on informed consent, are there things, real targeted, specific recommendations that could be made and disseminated by HHS to the health professions?

DR. BURKE: Ed, did you want to comment first?

DR. McCABE: No.

DR. BURKE: Judy?

DR. LEWIS: I was just going to comment on that in terms of the fact that I think it's a real interesting question, but part of what we have to focus on is the role of advising the Secretary about public policy, and then also encouraging professional societies to raise their awareness of issues. But in terms of developing professional practice guidelines, I'm not sure that that's our role or whether it's the role of the various professions who look at these in the

context of legal roles and scope of practice, which is different for the various health care professionals. Each of us has a different scope of practice.

So I think that we've encouraged the groups to come together and talk and collaborate, but I'm not sure that we've seen our role as dictating professional practice.

DR. BURKE: I have Ed, Michele, and Victor.

DR. McCABE: I think that Dr. Boughman's group is going to be coming back in August with some general issues about this. But certainly, if we feel that we should advise the Secretary on more specific issues and could determine a way in which we could do that and how we could bring the efforts of the various agencies together to develop that, that might be something that we want to focus on. I don't think we've gotten as specific as you've suggested in the past, but it doesn't mean that we couldn't in the future.

I wanted to also follow up on what Bob was saying in terms of looking at some of these issues. When I was in Texas, one of the things that we tried to look at was sickle cell disease and whether there was really any impact on the death rate among children. Looking at penetration of screening, certainly I'm someone who is very concerned that we don't have 100 percent penetration of screening. But it's really not the screening for screening sake that's important. It's what's the impact on health.

So certainly one can look at death rates and try to see if it makes a difference if you really do screen and then can begin penicillin prophylaxis. There was a study that was done a number of years ago that showed that none of us are good at staying on medicine every day for prophylaxis. But because the penicillin was in the house and the parents were educated, then they would start it very early, so it was good to have it there.

But we need to look beyond just the testing at the follow-up, even for a disease like sickle cell disease, and see if the testing is having an impact.

The other thing that Bob mentioned was kidney disease. We looked at the cost of some identified genetic diseases in the State of Texas, and as a pediatrician I was surprised. The major cost was because of renal failure that began in the 30s and 40s in

individuals with sickle cell disease. Then again, this is something that we could ask HHS to begin to collect data on at a national level. That was Medicaid data that we were using in the State of Texas that was able to identify this for us.

DR. BURKE: I have Michele, and then Victor.

DR. LLOYD-PURYEAR: Actually, HHS, both NIH, CDC and HRSA, have many, many efforts focused on educating health care professionals. There's a severe lack of funding to do large-scale education, and part of the debate is whether or not that's necessarily the federal role to take that on. I think adding to what Judy said, I know you're not asking us to dictate guidelines, but having professional societies recognize the need for this has been slow in coming also, and if they were taking a more active role, then probably the efforts that HHS is taking would be complemented.

Then second, just to let people know, we're on the sickle cell advisory committee for the National Heart, Lung and Blood Institute, and we are going to present the little report that we did and talk about what SACGT is doing.

DR. BURKE: Victor, and then Muin, and then we'll start wrapping up.

DR. PENCHASZADEH: In trying to wrap up, I want to commend the work of the data group because you really showed us the fragmentation and the complexity of gathering data to know what all this gene testing is doing to the population.

My concern is that you showed us all the complexity, the problems of funding, the problems of different agencies, the different groups, the commercial sector, et cetera. My concern is, is the Data Working Group, what are the next steps of your agenda in the sense that are you planning to try to come up with some recommendations to streamline somehow a system for data analysis for clinical validity and clinical utility of different tests? Because I think that this is the crux of the matter.

If we are to end up recommending something to the Secretary out of all this myriad of groups and agencies and data in different sectors, do we need to develop some consortia? Do we need to come up with some super-agency concentrating all the information

and try to come up with validity studies long-term? What is the main strategy that you foresee in the near future?

DR. BURKE: Muin?

DR. KHOURY: Actually, I was going to begin to start moving us towards the wrap-up, and I think Wylie will pick it up from there.

It was interesting to me because I listened to the other two presentations as I sat down, and I think I just want to highlight a few themes that hit me here in relation to what SACGT is doing, and I want to keep our eye on the ball of what SACGT is doing.

SACGT is trying to advise HHS what it needs to do in moving genes from discovery to genetic tests and assuring the safety and effectiveness of these genetic tests. We've seen three diseases -- maybe they're the outliers, maybe they're not. I think we need to see a few more examples. But I'll put that aside.

SACGT has come up with this oversight paradigm or framework, like the FDA, the CLIA process, and the third arm, which is this process. You've uncovered very quickly how complicated the third arm is, which is this ongoing data collection so that people know what we know and what we don't know at any given point in time. This is an iterative process to the nth degree.

But a few themes that emerged in my mind. You can't do this alone. No single agency can do this alone. This is truly a multi-HHS effort, and the feds have to coordinate, collaborate, and get together. That could be one of the recommendations you make. It may be different for different diseases because there are different homes for different diseases. Chronic disease is different from maternal and child health. Infectious disease is different from environmental health.

Second, as a theme, you can't do this alone. The government can't do this alone because the test developers want to sell their products, and if the FDA process eventually works in its conceived notion of a light touch effort, a lot of gaps in our knowledge will still be existing even as the tests move into the real world. Therefore, we have to work with the private

sector. Working with Myriad is an interesting possibility. I don't know if you've seen some of the email traffic in your binder around Myriad sharing some of its data with a group that's doing the second re-analysis. This is the Foundation for Blood Research that Wylie alluded to around BRCA1.

What the ACCE project is trying to do is figure out what we know and what we don't know around BRCA1 in terms of clinical utility and validity, and analytic validity as well, and there is a whole host of data around Myriad. They've approached them to share that data with them, and there is still an ongoing negotiation with that group. It hasn't worked out yet, but it's sort of an experiment in progress.

So we need public/private partnerships. I mean, government alone cannot do this. We need that partnership.

The third theme that emerged in my mind is that this is a state by state by state activity. The sickle cell showed us that, even despite consensus conference around the need for universal newborn screening, there are six states that don't do it, and this is a test in the public health domain for which there are programs at the state level that do newborn screening, maybe not the follow-up but the actual newborn screening. But how about the many, many tests that are in the clinical domain? There is a question of reimbursement and access in state policy, so we need to bring in the public health community into this discussion.

So this whole thing is intimately tied with the other two components, the CLIA process and the FDA process, and if one of them weakens a little bit, this would highlight the need for that third element to be even stronger, because if the FDA process weakens, then there is really no safeguard for effectiveness, sort of who is going to be the watchdog for this to make it happen.

So a lot of research needs to be done, and maybe there is a creative way to incorporate research with practice at the same time, where data continues to be collected on an ongoing basis through these consortia, driven partly by federal funding but also driven by the private sector that's in it to make money, of course, but they might benefit from that.

The final thing is that we need somehow this coordinated information system, whatever we call it. Right now there is GeneTests, there is GeneClinics, there is the National Library of Medicine, there is the CDC Website, there is the Alliance Website, there is the MCH Clearinghouse, and we have to figure out a way for consumers and people, as a gate maybe, to go to one side to figure out what we know and what we don't know quickly using accepted criteria that would help and inform the consumers and the health care providers what they need to do in the face of incomplete knowledge.

Let's face it, there will be incomplete knowledge in genetics for many, many years to come. So it's a question of how do we manage that incomplete knowledge and what kind of advice you'd like to give HHS to help guide us through this process. These are my themes here.

DR. BURKE: Thanks.

Let me pick up on this. Although we have not convened our Data Working Group, I'm going to throw out some possibilities, and in addition to Muin and Michele, Pat and Steve can comment on whether this sounds reasonable, and we can go out to other members of our working group that aren't here.

I want to pick up on Muin's last point. It's clear that when a test comes to commercial availability, questions remain, and I think we can say that is a generalization that we can make. There will always be a need for a careful consideration of what we should do given what we know now -- i.e., good guidelines -- and some sort of process for gathering data. It seems to me we've heard that there are some important tasks, and the question is how might HHS leadership make those important tasks go more smoothly.

The need to promote collaboration among different agencies, between public and private entities, perhaps using HHS' very powerful convening capacity, to make sure that collaborative approaches to guidelines are developed, to make sure that the key questions, the major things that we don't know, are identified so that we can then figure out how to deal with them. We've got to identify them first. That sounds like, from the discussion we've been

hearing, that that means the leadership ought to address innovative research strategies that get best and quickest to the answers, and innovative strategies perhaps to implement when we have a good sense of what to do. Implementation came through.

So if that all sounds like getting at the important issues, what I'd like to propose is that the Data Working Group take up the suggestion of continuing to think about these three case studies. In light of this discussion, I'm interested in figuring out what kind of insurance guidelines are being created for who is a candidate for BRCA1/2 testing. I know they're out there, and Pat's comment made me realize that that's important.

So we can continue thinking about these case studies and perhaps crystallize more fully what we've learned from them. We've already had some discussion about the fact that there's at least one other kind of case study that we think we need to take on, and that is the fact that there are now a couple of examples of direct-to-consumer or direct-to-physician offers of multiplex tests to create risk profiles for chronic diseases, and that might provide an interesting different example.

I think also the data group could meet amongst themselves by conference call to pursue that idea, continue discussion about these three cases, and try to focus and crystallize some thoughts to bring back to the committee in August about what kinds of steps HHS could take. Does that sound reasonable?

DR. McCABE: Yes, I think that sounds very reasonable, and it would be good to have very clear and specific recommendations that we could then see if we were ready. But I have a feeling, given the information that you have as background, that you will be ready for us then to transmit to the Secretary.

Thank you very much. I think this was very helpful and very informative.

We will now take a 15-minute break, or about a 12-minute break, and reconvene at about a quarter after. Thank you.

(Recess.)

DR. McCABE: Let's go ahead and get started again.

We're extremely pleased to welcome Ms. Kate Gottfried, the executive director of the National Human Research Protections Advisory Committee, or NHRPAC. This is Ms. Gottfried's third appearance before the SACGT. At our last meeting she was accompanied by Dr. Mary Faith Marshall, chair of NHRPAC, in presenting the committee's statement about the status of third parties in human subjects research.

Since we had hoped to hear about some of NHRPAC's other work but couldn't because of the press of time at our last meeting, Ms. Gottfried has kindly returned to brief us on the activities of NHRPAC's Genetics Work Group and the ethical issues in genetics research that it plans to address.

Kate, welcome, and thank you for taking time from your busy schedule to come over to Baltimore to be with us today.

MS. GOTTFRIED: Thank you. I'm delighted to be back, and I want to just fairly quickly bring you up to date on where we are.

This is the work group that was formally known as the Third Party and Genetics Work Group, and now we're just known as the Genetics Work Group, and that, of course, is a momentous event for us because it means that we dispensed with the first issue, which was third parties. I'll come back to that at the end of the talk about what other priority issues we're looking at.

I do want to let you know that we reconstituted to some degree the work group. We rotated some people on and some people off. We added some additional genetics experts to our work group: Wayne Grody, who I'm sure many of you know, out in California; Rodney Howell, who is a genetics pediatrics specialist down in Florida, where Dr. Shalala now resides at that institution as well; and Stephen Warren from Emory, who is an expert in bioinformatics.

You may recall that we talked a while ago about some priority areas that actually Francis Collins had outlined at our meeting in April of 2001. So what we've done as a work group is looked at those areas and looked at what we've done thus far and taken stock, and

I think that there's a pretty strong consensus that the issues, although Francis himself acknowledged that there could be other issue that we could take up as well, but that the five issues Francis identified in April are the issues we ought to be focusing on, with the caveat that we put something at the head of the list, which is the chapter in the IRB guidebook or handbook that OHRP is working on on genetics.

So the first area that Francis had identified was, in fact, the third party issue, and he talked about the VCU case, et cetera. As you all know, we took a lot of time, as did the NIH, to look at this issue. I should say that since that time, since I was actually here last, we did modify based on our discussion that Francis had pointed out an inconsistency in our language, and I think we came to a resolution that works well. That simply is that we've changed it to state the following, at the end of our discussion, and some of this is the same, but I'm giving you the entire context of the last couple of sentences.

"Nevertheless, investigators, in designing and proposing research projects in IRBs, and considering and reviewing research projects, and in conducting continuing review, should consider how the research design might focus not only on the identified human subjects but on other persons. In cases in which a research project's design," and this is where we've changed the language to be concordant, "requires the collection of information about third parties, the investigator and IRB should consider the following factors, among others, in considering whether the information is private and whether the third party is identifiable, and thus, by definition, a human subject."

Then we go on to enumerate the four areas that were in the prior document. I know that's a lot to digest right now. Suffice it to say it is on our Website. Sarah can give you the site, or I can give you the site. I actually didn't have a chance to bring new copies for you.

But with that having been said, this document, along with another document done by our Social and Behavioral Sciences Work Group, was forwarded to the Assistant Secretary for Health in April as a final document and recommendation to the Secretary, Assistant Secretary, and OHRP.

So, having dealt with that, the other issues that were raised by Francis were community consultation issues, and the whole issue of getting entire groups, communities, populations involved in research design and implementation and how that ought to be addressed, and how we should examine it, and how we should incorporate or not incorporate various communities, and what the potential stigma might be, et cetera. That's number two now on our list.

Stored tissue research. There's been a lot written about that, and it's actually become a very big business, obviously, and there are a host of recommendations out there. But the fact is that it seems IRBs are still pretty confused. So that's on our list as number three.

The following issue, blanket consent for use of samples in research. This is important with respect to whether or not it's really ethical to give somebody a blanket consent form and say, okay, now we have carte blanche to go ahead and use your biological specimens for any purposes for an indefinite period of time. Given the fact that you will state that to the person, the question still is, is that an ethical approach to dealing with research, and does that meet the standard essentially of what we know as the informed consent standard? That's something that we're going to have to look at as time goes on.

The final area is the disclosure of research results, and under what circumstances should research results that might have very little meaning in the immediate stage of carrying out a particular project be disclosed to the participant, and under what circumstances is it legitimate to not do so, providing that the investigator has in fact informed the participant up-front that he or she is not going to provide this information? So that's an issue that we need to take a look at, as well.

Having said that, our number-one priority has been determined to be this guidebook chapter. I'm sure many of you are familiar with it. It came out in 1993. It's not a bad guidebook, but it is somewhat outdated, and I have to say with the tremendous assistance both of Sarah on your committee and Finley Austin, who is very well involved in our work group, we've put together I think a really strong outline for that chapter, with the caveat that

gene therapy will not be addressed in this particular chapter and that the work group had asked Sarah to check with the RAC and see whether they would work on that facet of the guidebook.

The guidebook is multi-chapters and definitely in its very formative, preliminary -- the revision of the guidebook is in its formative stages. I'm hoping it will be an electronic guidebook, but I don't know that for sure.

Just to give you a flavor of the chapter, and this is not set in stone yet, so I'm not distributing a copy to you at this point, but the overall sense of the chapter would be basically an introduction and definitions, general considerations for IRBs, approaches in genetics research, looking at family studies, monogenic disorders, multigenic disorders, applied research and development, bioinformatics and data sharing, genetic counseling and psychosocial issues, children and adolescents – this is the bulk of the chapter -- collection of race and ethnicity data, subject access to data, disposition and secondary use of tissue samples, and then a section on research that's exempt from review or eligible for expedited review, which would be information from deceased persons, cell lines, and de-identified samples, and then a section that looks at some of the applicable laws and regulations, relevant publications, and a glossary.

Now, having said that, I know this is an issue or a theme that comes up a lot in your discourse on genetics in general. The work group recognizes that many of the issues that we're discussing in genetics really pervade all research issues and that they're not peculiar to genetics. So the way in which we intend to deal with that is have a section sort of up-front in the guidebook that says a host of these issues, and then delineate them, really apply to all facets of research, not simply one area or another, and then when we come to those issues within the chapter, we'll refer them to either the chapter where it's discussed, such as informed consent, which I know you had a very good discussion on yesterday, or wherever the pertinent issue is in the guidebook.

So we're trying to streamline this as much as possible and not be duplicative but give really important information to IRBs vis-a-vis the issue of genetics.

I think that's about it. Let me just check on one other thing.

Oh, just one other comment with respect to informed consent. This is a very, very critical issue for our committee, and we have in fact two work groups on it, one that deals with informed consent with those who are decisionally impaired, and another one that looks overall at the informed consent process. The way in which we've configured that work group is -- we have about six ongoing work groups, and we've identified an individual from each work group to be a liaison to the informed consent work group. So they'd participate on that work group.

So those work groups where people feel, for example, like social and behavioral sciences and possibly genetics, where people feel there are some particular issues related to their area with respect to informed consent, that information can be funneled through to us in the work group by the liaison.

DR. McCABE: Thank you very much.

Any questions for Kate?

MS. CARR: I just want to remind the committee that the guidebook chapter that Kate reviewed the new outline for that the NHRPAC work group is developing, that was a recommendation that the committee made a number of years ago, actually, that that needed to be updated, and the committee thought that OHRP or NHRPAC would be the appropriate locus for that kind of work. So I think it's commendable that NHRPAC has taken up that charge, and I don't think we were alone in that others recognized the need for that to be updated as well. But I want to thank, on behalf of the committee, your committee taking that up.

MS. GOTTFRIED: Well, thanks. That means we're two for two, since you also shifted third parties our way.

DR. McCABE: We just recommended that it was a topic that needed to be addressed. But thank you for taking it on, and thank you for completing the task also. That was very impressive that you got it done so quickly.

Any other comments for Kate?

(No response.)

DR. McCABE: If you would keep us informed as you proceed through with the chapter, that would be very good.

MS. GOTTFRIED: No problem.

DR. McCABE: Thank you.

At this time, we have time built into our schedule for public comment. We have two individuals who have registered for public comment, Dale Halsey Lea and Debra Schutte. Is that right? If anyone else wishes to register, please do so at the table outside.

So, Dale Halsey Lea is assistant director, Southern Maine Regional Genetic Services Foundation for Blood Research and is here representing the American Academy of Nursing to present the AAN's position statement on integrating genetics competencies into baccalaureate and advanced nursing education.

Thank you.

MS. LEA: Thank you very much.

Is this on, and can you hear me all right?

DR. McCABE: Yes, we can.

MS. LEA: There was a more detailed summary passed out to you. I'll just be speaking on the highlights.

I'm very pleased to speak to the committee on behalf of the American Academy of Nursing. This is an organization of 1,500 nurses recognized nationally and internationally for their outstanding achievement and leadership roles in the profession. The Academy is responsible for the vision and leadership to improve health outcomes and inform policy. As a member of the Academy and representing their expert panel on genetics, and also in response to the committee's ongoing discussions and work regarding health professional education in genetics, I will be speaking today on the importance of incorporating genetics into nursing education, which will enhance the nursing contribution to genetic testing and overall genetic health care regardless of health care setting.

Nurses and other health care professionals have an expanding role in the management of genetic testing and counseling services, in monitoring the effects of genetic testing, and in using genetic information as the basis for medical interventions, pharmaceuticals, and nursing biobehavioral interventions. Nurses and other health professionals support individuals in their decision to have a genetic test or therapy and in understanding the application of new genetic testing for selection of treatment options.

Clients and families expect nurses to clarify, interpret, and reinforce information gained from genetic tests and decisions about health management. They also expect nurses to help individuals and their families comprehend the health implications and to make informed decisions. These activities take place not only in hospitals and clinics but also in a variety of other settings where nurses practice -- for example, public health agencies, schools and workplaces.

Nurses are often the first providers to whom clients will turn with questions about their genetic risk and will seek guidance regarding the application of genetic testing in treatment decisions, interpretation of test results, and implications for their personal health and the health of their families. Thus, all nurses, regardless of practice level of specialty, need to incorporate genetics into everyday practice and care.

The American Academy of Nursing is a member organization of NCHPEG, and through its representative participated in the development of the core competencies. Various nursing organizations have already specified competencies in genetics. The International Society of Nurses in Genetics, or ISONG, recognizes nursing practice in genetics at both basic and advanced levels. Advanced practice nurses in genetics are now acknowledged by a credential from ISONG, the Advanced Practice Nurse in Genetics Credential, and practice at this level in all areas of nursing practice.

Nursing organizations must work with the SACGT, NCHPEG, ISONG, other professional organizations, and federal agencies to bridge the knowledge gap of health professionals regarding integration of genetics into practice to improve the public's health. It is

the position of the American Academy of Nursing that, 1, organizations or institutions that are responsible for curriculum development or curriculum standards in nursing education adopt the NCHPEG recommendations for integration of genetics content and the NCHPEG core competencies into both baccalaureate and higher ed degree programs of nursing; second, that organizations or entities that approve or certify basic and advanced education programs in nursing include the NCHPEG core competencies in their criteria for approving or certifying baccalaureate and higher degree nursing programs; 3, that organizations that are credit hospitals include NCHPEG core competencies as a part of their continued competencies for health professionals, including nurses; and fourth, that jurisdictions that license registered nurses establish policies for the special acknowledgement of nurses who have competencies in genetic care nursing as specified by NCHPEG, and also the ISONG Statement on the Scope and Standards of Genetics Clinical Nursing Practice, as follows: "Nursing appreciates the limitations of its, his or her genetics expertise, understands the social and psychological implications of genetic tests and services, knows how and when to make a referral to a genetics professional, and manages genetic information and educates clients, other health care providers, and the public about the nature of genetic testing and protection of genetic information."

In summary, the American Academy of Nursing wishes to communicate to the committee that leaders in nursing recognize the need for integration of genetic knowledge and skills at all levels of nursing education and at all levels of practice. The Academy affirms that the knowledge and skills for professional nurses are the same as those recommended by NCHPEG for all health care professionals, and endorses the ISONG Statement on Scope and Standards of Genetics Clinical Practice.

In particular, the Academy wishes to acknowledge that it values interdisciplinary collaboration in the establishment of genetic core competencies for health care professionals while recognizing that nursing has unique aspects to its professional practice. We appreciate the work of the committee and we remain available to offer our support and expertise to the committee as it continues its work.

Thank you.

DR. McCABE: Thank you.

Any comments or questions from the committee?

Yes, Joann?

DR. BOUGHMAN: Just on behalf of the Education Work Group, I'd like to thank you for actually bringing it to our attention in a formal way that the Academy has, in fact, been appropriately responsive, so that we can add that to the database, basically. By your coming here, that allows us to do that more quickly and efficiently.

MS. LEA: Thank you. I think the Academy is using one of the milestones we talked about in your group, which is certainly taking leaders and using an expert panel to infuse the whole concept into the leadership of the Academy. Thank you.

DR. McCABE: Thank you very much.

Our next speaker is Debra Schutte, who is president of the International Society of Nurses in Genetics, Inc.

DR. SCHUTTE: Good morning, and thank you. It's my privilege to offer comment this morning on behalf of the International Society of Nurses in Genetics. ISONG is a professional specialty nursing organization that comprises 300 members representing nearly every state in the United States, as well as eight other countries. ISONG is dedicated to caring for people's genetic health through excellence in the provision of genetic health care services.

The majority of ISONG members are nurses functioning in advance practice roles who directly intervene on a daily basis with clients who are seeking and managing genetic information to inform their health decisions. On behalf of ISONG, I'd like to offer the following comments for the committee's consideration and primarily in response to yesterday's discussion of access to genetic services.

The ultimate goal of genetic testing is to improve the health and well-being of individuals, families, and communities. ISONG believes that the use of genetic technologies and information to meet health goals should be a possibility for all. Reimbursement for genetic

testing and those health interventions that accompany genetic testing by both public and private payers are essential to equitable access. Strategies to remove reimbursement obstacles to care should be pursued concurrently with the equally important strategies to promote effectiveness research for genetic health care services.

ISONG strongly concurs with the Secretary's Advisory Committee's recommendation that education and counseling are critical to the appropriate use, interpretation and understanding of genetic test results. We believe that these interventions, therefore, must be considered in discussions of reimbursement, and we concur with the Access Work Group's recommendation to expand CPT codes to do so.

We would also draw the committee's attention, though, to other standardized language, such as the Nursing Interventions Classification system and the Nursing Outcomes Classification system that both currently include interventions and outcomes relevant to genetic health care services. For example, genetic risk identification, genetic counseling, risk counseling, health teaching, decisionmaking support, promotion of family integrity, and emotional support are all interventions delivered in the context of genetic testing and are all present in the Nursing Interventions Classification taxonomy. These intervention types must be reimbursable for genetic testing to be fully beneficial and accessible.

To further assure consumer choice and access, reimbursement needs to be available to all specialty genetics services providers working within their state practice acts and professional scope and standards of practice, whether they're advance practice nurses in genetics, masters prepared genetic counselors, medical geneticists, or Ph.D. geneticists.

As the extent of the impact of genetic research expands, some level of genetic testing interventions will likely and appropriately be provided in the primary care setting by primary care providers across disciplines. To achieve this flexibility in health care delivery, we believe that recommendations from the committee to the Secretary related to billing and reimbursement should focus on the intervention or service rather than the provider or setting.

Finally, collaboration between health care disciplines and the promotion of genetic services is essential and can only improve outcomes. However, reimbursement for genetic testing services that require direct supervision by a medical geneticist will ultimately impede the cost-effective appointment of providers and will decrease access to services, particularly in traditionally underserved populations and geographic regions.

In summary, adequate reimbursement for genetic testing services, including concurrent education and counseling, available from a full array of health care providers is essential in order for all of our citizens to benefit from new genetic information and technologies. I thank you for the opportunity to offer these views. The International Society of Nurses in Genetics is eager to continue dialogue with the committee on these important issues. Thank you.

DR. McCABE: Thank you for your comments.

Any questions or comments?

Yes, Judy?

DR. LEWIS: That's very helpful in terms of some of the deliberations and discussions that the access group has been having, and thank you very much for that.

DR. SCHUTTE: You're welcome.

DR. McCABE: Other comments? Questions?

(No response.)

DR. McCABE: If not, thank you very much.

Any other public comment?

(No response.)

DR. McCABE: If not, let's move on, then, to the next section.

In the SACGT's July 2000 oversight reports, the committee made two recommendations related to CLIA, that the current regulations be augmented with specific requirements for genetic testing laboratories, and that technical assistance be provided to ensure that all laboratories engaged in genetic testing for patient care, including research laboratories,

are in compliance with CLIA.

Ms. Yost, who directs CMS' CLIA program, will now briefly review the high-priority provisions of CLIA and plans underway to develop a Frequently Asked Questions document about CLIA certification. A preliminary version of the document appears at Tab 7. Efforts to explain the major provisions of CLIA, the elements that are considered high priority in ensuring quality assurance, and the flexible approach CMS surveyors take in compliance review will be very useful in helping laboratories achieve CLIA compliance. The Rare Disease Work Group has been tasked with being of service to this effort.

So, Judy, thank you for being with us today, and we commend the educational approach CMS is taking to enhance compliance with CLIA and your efforts to develop outreach and information tools.

MS. YOST: While we're searching, good morning, everyone. I'm the other part of CMS that just does quality. We don't talk about the dollar part, at least in context of reimbursement.

There are a couple of new faces in the group, as well as I thought it might be important to help orient them by providing a very brief overview of the CLIA requirements to orient them, and also to refresh the other members of the group that obviously don't do this for their daily living.

Also, I thought it might help us to be able to dispel some of the concepts that some folks have that these requirements are very onerous standards. CLIA was intended to be minimum standards for quality. They were not developed in a vacuum. A lot of laboratory professional people who are experts in laboratory medicine, as well as states that already have laboratory programs, provided a tremendous amount of input into the development of these requirements. They represent a balance between quality and access, even though sometimes I guess people have a question about that.

My first boss when I started working for the feds back in 1992 said that if both sides of an issue are unhappy with us, then we've probably done our job because we got

people engaged.

Just as background, the impetus for CLIA was deaths from inaccurately read pap smears and the proliferation of blackbox technology with no oversight in physicians' office laboratories. Congress passed the law in 1988, ironically on Halloween. The CLIA law regulates all testing on humans for health purposes using minimum quality standards. They are intended to ensure accurate testing regardless of where the test is performed. It also includes research when the results are returned.

When CLIA was first published, there was a tremendous amount of anxiety out in the United States because it was going to cover many facilities that had never, ever had any oversight or any visitors from anywhere before. We actually went from 12,000 labs that were the traditional hospitals and independent laboratories to where we now are, at 175,000 laboratories covered under CLIA.

This anxiety did cause a lot of misperceptions, and I think that there's the possibility that some of those may still exist. If you look again at Mike Watson's survey results, I think that gives us some evidence that some of those are still around. I have some good news, at least from our perspective, in that we kind of went head-to-head with AMA because a lot of the physicians' offices did not want intrusion into their practices because they felt we were invading their patients' privacy and so forth. But I can tell you at this point in time that AMA admits,even though it’s reluctantly, admits that CLIA is really just part of doing the physician laboratory operation.

There are currently 95,000 physician office laboratories enrolled in CLIA, so the numbers at least are somewhat telling. We actually do kind of like you do here at the Hyatt. You get a little survey that says how was your visit. We do that with our surveys just to get an idea of how the process is working or whether the laboratory had any particular problems with the visit, because we really do want to do an educational-based program, and I can tell you that about 85 percent of the responses we receive -- and they can do it anonymously, so they can say whatever they like without any fear -- give a positive review of

the survey.

The final regulations were published in February of 1992. I can't take credit or blame for them because I came two weeks before I came out, so they were there when I arrived. The regulations have five major quality standards, and they are based on the complexity of the test -- that is, how sophisticated is the test and how difficult is it to perform. The more complex the test, the more stringent the requirements. The stringency resides primarily in the areas of personnel qualifications and in quality control.

Genetic tests, as they are defined generally, are mostly high complexity tests, so that's the highest level of complexity. The CLIA certificate is to be obtained for the highest level of testing that the laboratory performs. Generally, it's one certificate per site of testing, because we regulate the testing, not the people per se, but there are exceptions for hospitals and universities that allow them to achieve cost savings if they choose to. They don't have to.

The program is funded entirely by the laboratories that we regulate. We get no money from Congress, so it's got to be effectively and efficiently managed in order to ensure that the funds stretch as far as they need to. We have based the fees, however, on the level of testing that the laboratory performs, so that the annual test volume dictates what the fee will be. That again is to ensure that the smaller types of laboratories aren't killed by large types of fees. For example, for a laboratory that does less than 2,000 tests a year, the certificate fee is $150, and the survey fee is about $300. That's $450 every two years.

The program is actually administered by CDC, FDA and CMS. So the labs get the benefit of three bureaucracies, not just one. Each agency has its own discrete roles, but they overlap tremendously. We collaborate and work together. The benefit to the laboratories and the program is that you get the best approach and best perspectives and expertise from each agency to combine into the program. So, to me, it's a very positive experience.

The surveys are biennial, every two years, for the moderate and high complexity laboratories. Because cytology was an impetus for CLIA, there are very detailed

cytology standards. The test complexities, very quickly, are waived and moderate, PPM, which is provider performed microscopy, a sub-category of moderate, and high complexity. The waived tests are the real simple things, like the glucose meters that are used oftentimes in nursing homes to do glucose levels, urine dip sticks, cholesterols that you see in malls, those kinds of things. The moderate tests are things like the complete blood count, automated chemistry profiles and so forth.

The PPM are tests done under a microscope, like a KOH prep or urine microscopic.

The high complexity tests are things like cytology, toxicology, pathology, and genetic testing. These are the tests that are much more manual. They're not automated. They require more expertise and training to perform. Oftentimes, the results need interpretation, it's not just a number that you can take action on. So these, again, have the most stringent standards.

That leads me to standards. That's my segue into the applications of CLIA. The quality standards are five essential ones, and they include personnel qualifications and responsibilities. So it's not just the fact that you need to have education and training and experience. You need to actually have responsibilities where you help to ensure the quality of the testing and the lab, depending on what your position is.

Under CLIA, it was determined that the director would have overall responsibility for ensuring quality in the laboratory. One of the reasons for that is that a lot of the other qualifications for some of the other required positions are not as high or as stringent. So it's giving this responsibility to the director, and then the director can determine what the level of individual is required for that particular laboratory.

Again, the director cannot be in name only. They can't do any drive-bys. It has to be someone who is actively involved in the laboratory; that is, not reading the revenue but truly looking at what's happening in the laboratory. That doesn't mean they have to be there every minute, but they clearly have to be involved.

Under quality control, that's a mechanism to ensure that the test is working, very simply. In a situation where there aren't commercially available controls, then the laboratory can certainly take patient specimens with known values and re-test them for quality control. So there's no additional cost there.

Patient test management is just a fancy term for a record system, what kind of audit trail do you have to ensure that you can identify the patient specimen all the way through the testing process and make sure that the test gets to the right person. It includes a unique identifier. It doesn't have to be a patient name, because when you get to genetic testing, you obviously get into very important confidentiality issues. So a unique identifier is all that we require.

For proficiency testing, that's really just an external type of quality control, meaning that you can buy it from an organization who will sell you some specimens where they know what the answers are for, or the laboratory can again, if there isn't commercially available proficiency testing and genetic testing -- we know that there's not a whole lot out there right now. So the laboratory can determine on its own, using its own creativity, what type of way they want to provide and ensure that there is accuracy. They need to do it twice a year under these circumstances.

An example is they can take a specimen and split it, and they can send it to somebody else and compare answers. I know that a lot of the genetic testing labs actually do that now.

Quality assurance is essentially the summation of all the other requirements. It's what the lab actually does to ensure quality. It's their plan to monitor and ensure accurate and timely results, how does the laboratory communicate, how does the laboratory solve its problems.

The CLIA surveys, and I'm going to provide you a CMS perspective, because obviously we administer the program. But I do want to make it clear that there are two routes for the laboratory that is eligible for inspection to take in order to be CLIA certified, and

the laboratory can choose. It is their choice. They can either use an approved accrediting organization, such as the College of American Pathologists, or they can be certified by CMS. CMS uses the state health department, and they hire medical technologists with laboratory experience, and then we train them to do CLIA surveys. So again, the laboratory has a choice. Either one of those options will meet CLIA as long as the accrediting organization has been approved by CMS.

As far as the approach, again it's outcome oriented, outcome in this case being results, since laboratories don't traditionally see patients. The surveys are educational, and it's a quality assurance focus. So again, it's more a big picture type of approach. CMS does not use a checklist, but we use surveyor guidelines, questions that can be asked of the laboratory, and decision trees based on the information the surveyor finds.

CAP, in conjunction with ACMG, has developed excellent genetic testing checklists and I think is on an ongoing basis updating those standards. So there are two different approaches, and both work quite successfully.

Again, I guess the good news is that the data that we have collected over the years, over the 10 years that CLIA has been in place, indicate that there is improved lab performance over time based on the educational approach. When we first visited laboratories, we found that somewhere between 30 and 35 percent of the laboratories had some quality issues, not paperwork but strict quality issues. Now we're down to 6 and 7 and 8 percent of the laboratories having problems. And the whole concept that everybody was going to leave and go out of business has also proven false in that there are now more laboratories than ever enrolled in the program.

I'd like to talk a little bit, because that was actually the purpose why I'm here, so I'm finally getting there, about CLIA compliance for genetic testing laboratories. But this is really our approach for everybody. It really isn't much different.

Laboratories have to enroll in the program. That's not educational. That's either you do it or you don't. They need to meet all of the five major quality requirements

under CLIA, and they're listed here as we just went through them.

The place where CLIA light, or if you want to call is a kinder, gentler CLIA comes in, is in the flexibility in how the laboratory can meet the requirements and the time frames that we allow to meet those requirements.

So there are no essential giveaways. But, for example, we don't prescribe how the laboratory can meet the requirements. We leave that up to the laboratory because we still do believe that every laboratory is unique and has its own situation. So we allow them that flexibility.

As far as the time frames to meet something -- for example, say that a high complexity laboratory director requirement requires a board certification, a Ph.D. with a board certification, if the laboratory director that happens to be in place hasn't quite yet achieved their board certification, we recognize that there are prerequisite experiences required before you can even take the test for board certification, and we will, within reason, allow the laboratory a time frame to achieve that certification.

We are reasonable as far as how we apply the standards. In a case where a standard is not applicable to a particular situation, we certainly aren't going to hold the laboratory accountable for that particular situation. A real quick example is a requirement under CLIA quality control that says you have to record the time that a specimen arrived in the laboratory, and that makes a lot of sense. You want to ensure specimen integrity so that you get a good result. You also want to be sure that there's no mix-up for, say, a sequential test, like a glucose tolerance, where multiple tests are collected. You want to be sure they're in the right order.

But in a case where you have a single research lab or a physician that's doing the testing themselves, then they're going to collect the specimen, they're going to do the tests, and they're going to report the results and take whatever action is necessary. It isn't necessary to document the time that specimen arrived in the laboratory, so we will not hold the lab accountable for that requirement. That's the type of flexibility and reasonableness that

exists with the requirements.

I also wanted to point out again, for all of you who are friends and colleagues, that there are no penalties at this point in time for not enrolling in the program. We realize that people are still uncertain about where they stand, whether or not their research constitutes requiring CLIA enrollment, so there are no penalties. However, once we identify a facility doing testing that should be covered under CLIA and it does not want to enroll in CLIA, then we need to take some action. Obviously, we cannot let someone just go by, or everybody would.

The key point here, however, is the last one, and that is that CMS wishes to provide whatever technical assistance, either through our own resources or through experts that we could retain, to ensure that laboratories can meet the requirements.

Just a little bit about the surveys, because that's always the biggest point of concern that scares people. The first survey we do for any new laboratory is always information sharing, because we have to see what they're actually doing and they need to tell us about what their operation is. So we need to talk about what the requirements are to help educate them, as well. So it is a two-way exchange of information. Clearly, if there's risk to patient safety, then obviously we need to help that laboratory fix whatever problems are causing that.

The survey process, again, looks at outcomes, that is results. Problems that are found that affect test quality are the things that we are interested in. The things that directly impact the quality of the testing result for that patient are the items that we are going to focus on in our reviews. So if we find something, we offer customized guidance to correct the problems, we'll help the laboratory set priorities if they have multiple problems, we will suggest resources where they can get additional help or information, we will provide time frames and a contact person for correction of problems. If we find some minor infractions that we feel are not as significant, we'll even give them verbal ideas to help improve those problems, as well.

Our goal is to do this with a very positive approach. The lab is given credit

for what they do right because we feel, for the most part, everybody wants to do the right thing.

Our survey process, again, is very simple. We don't sit in a closet and read procedure manuals or data. We actually walk through the laboratory, we talk to the laboratory people, we observe testing. We want to make sure that they're actually following the procedures that they have. We do review data and information and records. We look at outcomes again, and then we determine compliance. So it's an iterative process, actually, where we do some decisionmaking based on what our findings are.

We will tell the laboratory at the conclusion of the survey what we found, give them a second chance to come back with any new information, and then the laboratory, if they do have problems, does need to provide a written plan of correction.

The CLIA surveyors, just for folks who know, they're not just folks out of the states but they are actually medical technologists. They're professional. They have been trained in CLIA. They have tremendous laboratory expertise, and they know quality assurance. They will look at the lab's overall ability to provide accurate results rather than just individual standards. We do have periodic reviews and refreshers of training, and if we feel we're out of our league, we'll bring in experts to help with that training.

As I have said before, and I have committed to do this, the surveyors will receive specific detailed training when new and updated genetic testing regulations are published. We plan to enlist nationally recognized experts -- so all of you in the room can leave your phone numbers -- as well as any professional organizations who would like to join us in that effort, because I think the more we work together on this, the better off we are.

Just to dispel another misperception, I think that folks feel that because a surveyor may come in that's not specifically an expert in genetic testing, that doesn't mean they can't find problems or they can't look at the laboratory's operation. I just wanted to point out that there are clearly a number of things that the laboratory can do that are going to give them tips and clues about what problems might exist there. Yes, they may not know the exact technology that's being utilized by the laboratory, but they can sure tell whether the people

doing the testing are competent, whether they're following their own procedures, whether they have good recordkeeping and so forth, whether they have a plan to correct their problems. So I just thought I'd throw that in there.

We have had some experience already with some research laboratories doing genetic testing, and I thought again that I would provide you some reassurance. You can say, yes, that sounds wonderful, but show me the money. So I realize that this is really just words, but we have found that we have been able to work very closely and successfully without putting anybody out of business with laboratories doing genetic testing research, because we still feel that based on the IRB protocol that that lab is using, much of what they do to verify that the test actually works, that validation process, whatever that is, of repeating the test over, comparing the results, that helps that laboratory to meet CLIA. That's part of proficiency testing. That's really all that is, just checking your own system, and also to make sure that the results are correct.

So those items that the laboratory is already doing will facilitate meeting those major requirements that I just talked about. Again, existing documentation and data are useful in that case.

Again, I mentioned the IRB protocol. There are professional standards that can be used. For example, CMS actually uses NCCLS, we had a discussion about NCCLS yesterday, the act uses NCCLS standards in microbiology, so that all the laboratory has to do to meet certain requirements is to follow the NCCLS professional standard and they're fine. That helps the laboratories because they don't have two sets of standards, and it helps the manufacturers because everybody is on the same page. So it is certainly an approach, and we do accept that.

Again, when a research laboratory may be part of a larger organization, organizational types of materials for the administrative CLIA requirements, like job descriptions and safety plans and all that stuff, you can use the organizational stuff. You don't have to create your own necessarily.

So again, this is obviously a very simplistic view, but I'm trying to give you at least a clear message that we will work with you.

Again, CMS does consider that every laboratory is unique, and where there are problems identified in the laboratory, we will then focus our priorities for that laboratory on whatever those problems are. However, if we have a laboratory that's starting from scratch, here's a possible priority order that the laboratory might consider, because I can understand that for some folks it could be overwhelming to say, well, here's CLIA, all 200 pages of it that I've just condensed into five slides, and you have to meet it. We'll help you with setting priorities so that you don't have to do it all at once and feel that you're spinning your wheels.

Personnel qualifications are absolutely critical. Obviously, the people who oversee and do the testing have got to be qualified and be able to be competent.

Quality control. On a day by day basis, you've got to do something that shows that that test is working. Proficiency testing, again, is an external measure. It's a long-term measure to make sure that your accuracy is okay. Then once you have all those things in order, you can talk about quality assurance because that's really just the lab's own assessment of how it meets CLIA and how it ensures quality. So if you take it in that context, I think it is a simple viewpoint, but at least it will help you to be able to focus and prioritize in meeting CLIA requirements.

For quality assurance, by the way, the best quality assurance to us -- and it may be possible in a research setting -- is actual correlation of patient results or information with their history and their test results. I mean, that's real quality assurance. It's your patient and what is your diagnosis versus what are you seeing, what are the symptoms and signs. If you have that opportunity, you may use that as your quality assurance, or at least a major piece of your quality assurance. It may not be possible, obviously, with genetic tests that are predictive or presymptomatic, but clearly there are cases where it might be applicable.

So anyway, I just felt I would come in to say that I've sat through most of the 13 SACGT meetings, and I heard nothing to contradict the mandate that genetic tests have

to product good quality results. I think that CLIA is clearly the vehicle to do that.

Again, I want to make it clear that the message is that CMS is willing to work with all of you, as well as professional organizations and standards organizations, to do whatever it takes to ensure that new and updated genetic testing standards are published and implemented effectively and efficiently, and that any laboratory that has any hesitation is provided whatever it needs to meet CLIA effectively.

That's it. Any questions?

DR. McCABE: Thank you very much, Judy.

A couple of things. One is that back in February, I think it was, Mike Watson talked about the preliminary data from the ACMG/ASHG survey of laboratories. One of the things the respondents asked for at that time were workshops with CMS, and I was wondering if either Mike or Joann Boughman from ACMG and ASHG respectively would comment on any plans.

If you would want to comment on that, Judy, if there are any plans to develop these workshops.

MS. YOST: Could I comment first, and then I'll let you guys follow.

Part of that umbrella statement I made at the end about working with anybody includes the fact that we would be happy to go to and participate in any of -- because I know there are a lot of professional society meetings already, so we don't need to create another one, but we would be happy to work with whomever, whatever organizations, whatever meetings, attend, present, provide advice, at whatever level is necessary to provide guidance to help out. So not a problem from our side at all.

DR. McCABE: I don't know if either Joann or Mike wish to comment.

DR. BOUGHMAN: I would just say that the timing for this year's American Society of Human Genetics meeting was not ideal. Our schedule is usually set by February for the following fall. However, I will be talking to Judy Yost and others about the possibility. We've made slightly different accommodations this year for non-profit

organizations and having space to display and interact with the folks at ASHG, and I think that might be an entree into that group of people.

DR. McCABE: And ASHG this year is --

DR. BOUGHMAN: It's here in Baltimore. We're in the Headquarters Hotel. It's going to be in the Convention Center, so it's not --

DR. McCABE: It would be convenient.

DR. BOUGHMAN: It would be relatively convenient, at least for CLIA to be there for a day or two.

DR. McCABE: I think the issue, and we've always been concerned about the rare diseases where people who are doing it as research may not be aware that they need to come into CLIA compliance. We certainly don't want to shut down the testing for rare diseases, but it will take some work to transition.

DR. BOUGHMAN: Well, in fact, that's one of the reasons why I thought the entree in small group and one on one rather than kind of hitting people over the head with a workshop. But if we can have some dates or times for upcoming workshops that these folks might attend after a five-minute conversation, we might be able to convince them that they should in fact attend some of those workshops, and the barriers would seem much less onerous at that point.

DR. McCABE: At the risk of giving her extra work in an already busy schedule, I can tell you that Pat Charache has also been very good at providing technical assistance and helping make this transition.

Yes, Joann?

DR. BOUGHMAN: I wonder, Judy, if you might spend just a moment talking about the difference as CLIA would see it between a genetic testing laboratory -- i.e., a geneticist who at this point is considering themselves a research lab in a rare disease but may want to come under CLIA compliance -- versus a laboratory that does some genetic tests that would already be in CLIA compliance, a large pathology lab, for example, but in fact they have

one section that does genetic testing. Can you talk a little bit about your approach of going in and how you would look at the genetic testing in that large, already CLIA approved laboratory versus this new kid on the block that's getting a great deal of focus on the one genetic test they're doing?

MS. YOST: Usually in a situation where there is a lot of additional clinical laboratory testing being conducted in a laboratory, the laboratory director and their technical supervisors can clearly provide guidance to the laboratory as far as how the genetic tests would come into compliance, because there are clearly a lot of existing CLIA requirements that apply to genetic tests just as they apply to any chemistry or hematology test.

So I think that that system would almost help itself. Obviously, that educational approach that we have is for all laboratories, because you may also have a situation where maybe the lab director changed and the particular supervisor or overseer of the genetic testing isn't as strong and knowledgeable about, say, quality control or something. In that case we would still, again, provide customized assistance to that laboratory to help them in that area.

With the smaller type of laboratory, it's more like a one-on-one exchange, tell me what you do, so that we can understand better and we can see by walking through the process in the laboratory what exactly they do and what things they may already be doing that they don't realize will help them to meet CLIA. So it's more an information sharing, and then it becomes a sequential process. We realize that with a brand new laboratory that isn't really familiar with regulation and oversight but at least has some inkling of what quality is, we can work with them on a sequential basis. We know that the first time we visit them, they may not be familiar with anything. When you go back the second time, you hope that they have concepts of what their responsibilities are and maybe what to do for quality control, and then you can help them with additional pieces of the requirements to help them meet them.

Even with proficiency testing, there is the ability to allow them to fail one time without any penalty. We assume that everybody has a mistake once or at some point, so we give them the opportunity. The idea is the learning experience that you get to go back and

figure out what went wrong so that you can fix the problem so that it doesn't happen again.

For example, we had, just for the simple strep A test, the rapid test, they have two reagents, A and B. We found a lab that was adding the reagents in reverse order, even though the instructions from the manufacturer said add A, then add B. They were doing B, then A, because I guess it was one of those whisper down the valley kind of situations. They never, ever had a positive test as a result of that, and never thought about the fact that maybe there was something going on. It wasn't until they did the proficiency testing that they realized what was going on, because they failed the PT. Then they went back and looked at their process.

Every piece of the program works together to ensure quality, and that's just one example.

DR. McCABE: Thank you.

I'll address this to both you, Judy, and Joe Boone, who is also very involved with this, and possibly Pat as well. Do you have any idea when the Frequently Asked Questions document might be available, and could our rare disease --

MS. YOST: (Inaudible.)

DR. McCABE: So it's in progress right now?

MS. YOST: Yes. I'll take what you saw and essentially just re-work that into questions and answers, if that helps.

DR. McCABE: That would be good, and I think we would certainly like to offer the Rare Disease Work Group, the Education Work Group, anybody that we can help you with that, and then send it out for some pilot review.

MS. YOST: We'll do that.

DR. McCABE: We'll be happy to do that.

MS. YOST: I'll draft it and we can send it out to all the CLIA agencies, as well as the work group, and they can have at it and do whatever they like.

The other thing I can offer is we can put it on the CLIA Website at CMS, as well.

DR. McCABE: Great.

Joe, any additional comments that you want to make?

Pat, I saw you had your hand up?

Joe, you want to go ahead?

DR. BOONE: Well, I'm sure that the question about the NPRM is one of those things that you would like to hear about, what progress is being made in that area. We have made behind-the-scenes considerable progress. We and CMS have reached agreement about what the content of the Notice of Proposed Rulemaking would be, taking into account the CLIAC recommendations and things that we've also heard from SACGT. We're now at the stage of trying to award a contract to do the impact analysis. That contract will run approximately six months, and during that time we'll put the final piece of the puzzle in, and then we can start putting the NPRM through the clearing process.

DR. McCABE: And is there any thought -- you mentioned CLIA light. Is there any thought with this Notice of Proposed Rulemaking of having any difference for the laboratory that may be running a single test?

DR. BOONE: I'm not sure. That's an implementation issue, and I'm not sure -- Judy, we really haven't talked about it specifically. We think actually the requirements are pretty minimal extensions of what we already have in place, and those are minimal standards to begin with. So I'm not sure we need to go any lighter than we are going, but we'll certainly take that into account.

DR. McCABE: Pat?

DR. CHARACHE: I have a question for Judy and two comments to reinforce two things that Judy has said.

One is I think there's a major perception barrier in terms of how difficult CLIA is, and when one gets all of the prepublished papers that say what the safety requirements are and all the rest of it, it's just common sense, 99 percent of it.

The second thing I would enthusiastically support is the educational

approach that's been the hallmark of Judy's leadership of this program. They really do want to help people do it right, and if there's any issue, it's sometimes that they spend a very long time and a very long effort trying to salvage people who are having difficulty. It really is a very thoughtful approach to this.

The question is, in an unnamed hospital which is CLIA approved, what we have found to be a major problem applies to genetic tests that are done in CLIA approved labs. The problems are not in the analytical component of the test. It's not in the quality control or the proficiency testing concepts and the rest of it.

It's in the pre-analytical, what you have to do for a genetic test before you run it, what you have to know, and then even more important, the post-analytical, what your report looks like. Do you tell the physician who receives it that you haven't the foggiest idea what it means? And if so, do you still charge the patient? Do you indicate whether you're doing the number of alleles that one does for the Ashkenazi Jewish population test versus what you do when you sequence and look for it? How do you communicate what you've done to the non-geneticist, and how do you assist them in using it appropriately?

That's the area in which the laboratory physician or the geneticist in the laboratory knows far more than the person who is receiving the data and needs guidance on how to use it. So I'm wondering what is being done both by CMS helping the state labs, helping those who have deemed status through CAP and Joint Commission particularly, to be able to address these two aspects, even when they're doing everything right during the testing process.

DR. McCABE: Do you want to comment, Judy?

MS. YOST: Well, again, as I mentioned, we will be providing very specific training to our surveyors in regard to that, and based on the CLIAC recommendations there are very specific recommendations from CLIAC in both those areas that will be in the new and improved CLIA requirements for genetic testing, and with that we'll certainly be focusing on both of those areas. We do focus on those now because we realize that actually the majority of

errors in the laboratory take place in that pre-analytical phase, not in the analytical part per se.

So we do focus on that now. However, with genetic testing, we've got to have specific instructions. Again, we'll work with all of you on those pieces, because they are critical pieces.

DR. McCABE: Thank you.

We're going to have Michele, and then Mike, and then we're going to wrap this up so we can move on to the next section, and I would ask maybe if staff could get the slides up for the next section so we're ready to go with that.

So, Michele?

DR. LLOYD-PURYEAR: What happens if a lab is consistently non-compliant?

MS. YOST: Oh, we will take action.

DR. LLOYD-PURYEAR: What's the action?

MS. YOST: We have a whole menu of things that we can do. That was part of what the anxiety was at the outset with CLIA, that people saw the $10,000 fines and they saw lots of Medicare payment and all those kinds of things, and forgot anything else they ever heard, because it kind of scared them away.

We actually have an armamentarium of things based on the scope of the problem, based on how long it's occurred, based on how much it impacts patient health and safety, and we will take those actions. But again, it's over a repeated series of times. We go through a sequential process, and clearly the laboratory's own motivation has a lot to do with this. If they're planting feet and just absolutely refusing to do anything after multiple times, then we've got to take some action because there are concerns that in that case they could be providing inaccurate results or risking harm to patients.

So we will do that, but that again has its own appeal process. So if we find that after multiple months and even years of educational process the laboratory is still not in compliance with requirements that impact quality, we will notify them that we intend to take an

action and give them a chance to either fix it or appeal it, or we will impose that action. It goes all the way from removing their certificate, removing their Medicare payment to maybe going on-site and giving them what we call a directed plan to correct their problems, where we actually go there and spend days or weeks or whatever it takes for them to correct their problems, because they really just don't have an idea about how they might do it.

So it varies, but we don't go for years and years and years just allowing it to occur, because obviously that's not safe either. So that's kind of like the end result. We're actually required by regulation to do a listing of laboratories that have actions imposed every year, and it's on our Website now, and you'll see that it actually runs about 120 to 150 laboratories a year, and that includes the accredited laboratories. If you think about it, that's 40,000 laboratories that get inspected very two years. So it boils down to a very small percentage of laboratories that actually have actions taken, because again, we're much more successful on the other end. But you have to use the cannot sometimes.

DR. McCABE: Mike?

DR. WATSON: This will be fast because I'm eating my own time.

I would only say that as you think more broadly about policy perspectives on genetic testing and look really at where problems occur, I think you can think more broadly than the existing programs, and I don't distinguish the CLIA program from the CAP program in that sense. I think that if you look at the hemochromatosis study at NHLBI, if you look at the Cancer Genetic Networks, if you look at the Children's Oncology Group, Cancer and Leukemia Group B, all of these clinical trials models that deal with this translational aspect which so many genetic tests, certainly rare disease tests go through for a very long time, you'll see that almost all of them now have much stronger internal quality assurance mechanisms.

We don't just accept CAP and CLIA in the Children's Oncology Group. Almost half the labs in the country were told they could not participate because they didn't meet certain standards based on comparison of results. We see in the Cancer Genetics Network that we set some much higher bars for the laboratories early on and systems whereby the

laboratories interacted, and I think that's going to be important for these translational aspects of these tests as they develop, looking not at the standard of care test, where you expect there to be a lot more stability in how the tests are done, but much more carefully in those translational trials types of situations that we're going to be in for a long time to come in genetics.

DR. McCABE: Thank you.

Thank you very much, Judy, for your leadership in developing this.

Now we're going to move on to a presentation of a very preliminary draft of a white paper on the development, translation, oversight, availability and accessibility of genetic tests for rare diseases, which is being developed by the Rare Disease Work Group. The draft report is at Tab 8 of your briefing book. Mary Davidson and Mike Watson, the work group co-chairs, will present the major findings of the report and discuss areas in which future guidance from SACGT is needed for the further development of the report and in the formulation of accompanying recommendations.

I think our plan will be to have you present the slides, then break for lunch and come back for the discussion after lunch. That would be my proposal.

Mary?

MS. DAVIDSON: Mike and I are going to do this as a team just to model the theme of collaboration that we've been talking about this morning. We want to report to the committee on our substantial progress in identifying and understanding the key issues related to genetic tests for rare diseases. We spent considerable time and energy in developing this preliminary draft of the white paper to this point, and I want to thank Sarah Carr in particular and the rest of the staff for their efforts both in having gotten us to this point, but also in advance for the work that needs to go into it before this preliminary draft is really ready to go.

Here are the members of the Rare Disease Working Group. Mike and myself are co-chairs, Judy Yost, Alan Guttmacher, Henrietta Hyatt-Knorr, Vicky Whittemore, Jeanine Lewis, Pat Charache, Kate Beardsley, Diane Doorman, and Steve Gutman.

One thing that I just want to mention at this point is that we might start to

think about the need for some representation from the Informed Consent Data Template and Access Working Groups on our committee, just to bring all the information and understanding that we'll all develop together.

The Rare Diseases Work Group was established in August of 2000, and this was to address the unique and significant challenges that we face in the development, translation, oversight, availability and accessibility of genetic tests for rare diseases. The working group's initial task was to outline criteria to classify and define rare disease genetic tests, and our new task is to develop a white paper to describe specifically the challenges that are inherent to rare disease genetic testing and to pose recommendations to address those challenges.

We put this slide together yesterday to try to really make explicit the challenges that the working group is looking at, and particularly how to safeguard rare disease genetic testing as we, the committee, and other agencies make recommendations on policies and regulations, changes which could impact significantly on the quality of and access to rare disease testing. It's key to understand that we're focusing here on issues related to low-volume rare disease tests that will be done, by definition, in small numbers and not on populations in a high-volume basis. These are low-volume rare disease tests, and in some cases difficult to access now, and we're projecting ahead subject to market disincentives as the tests move from the development stage in research, largely academic labs, to clinical availability.

At every step, we want to be sure to balance quality requirements with the potential impact on access. So in other words, our intent is to ensure that people with rare diseases receive tests at the highest possible level of quality without compromising access.

Just an overview of the activities of the Rare Diseases Work Group. To date, we had a meeting in February 2001. We began the development of a white paper outline in the fall of 2001. In November, many of you may remember, we held a rare diseases session on genetic testing for rare diseases at that meeting, and we've been working on the draft of the white paper since then.

Just also an overview of the November 2001 session, because this has really informed and directed our work on the white paper. As you can see from the panel line-up, all the perspectives of the test stakeholders along the test development spectrum were represented at that session.

The goals of the white paper are to describe issues related to the various definitions of rare diseases in different government agencies; to understand the issues related to research, development and translation of rare disease tests; the oversight of rare disease tests; and to identify and in some cases make links between resources on rare diseases and testing and laboratories. Also, we wanted to in the white paper describe some pending legislation which may bring some additional resources to these challenges.

Of course, the most important goal of the white paper is to propose recommendations to enhance the development, translation, oversight, availability and accessibility of tests for rare diseases.

This is to give you an idea of the organization of the white paper: Introduction, things to consider in defining rare diseases, the stages of rare disease test evolution, the translation of tests to clinical and public health settings, an overview of the current regulations and oversight relative to rare disease testing, and ongoing data collection efforts, resources, a summary of pending legislation which would bring additional resources to the development of rare disease testing, and our recommendations.

I'm just going to summarize very briefly, and this will be in the white paper, the recommendations on genetic testing for rare diseases that have happened thus far. In 1994, the Institute of Medicine published "Assessing Genetic Risks" and made in particular two strong recommendations with regard to rare disease genetic testing, that rare disease testing be performed in reference laboratories, and that provisional premarket approval be granted by FDA given the small numbers of tests.

In 1997, the Task Force on Genetic Testing published its final report, making the recommendation for the need for a comprehensive data collection system, in

particular for rare diseases. It also called on the Office of Rare Diseases to heighten its effort to encourage access or make available possible access to clinical and research information. There was also a call for leniency in CLIA regulations for small test volume laboratories, and we've put the SACGT down because we're expecting recommendations to come from our group.

Mike, you're on.

DR. WATSON: All right. What we're really going to try to do is just go back and review some of the highlights of the issues that arise in rare disease testing that our committee discussed in thinking about ultimately the recommendations that you're going to have to come up with to address a lot of these unique aspects of rare diseases. Obviously, inherent in rare diseases is the fact that there's not that many patients, so this longer period of clinical investigation is always going to be taking place. There are diseases for which we've tested for many, many years now from which we're still learning.

Now, inherent in not just rare diseases but also in common genetic diseases are these unique aspects about genetic conditions themselves. Allelic heterogeneity, meaning there can be multiple mutations within a gene which can lead to the same condition; locus heterogeneity, that there can be multiple different genes that can lead to the same condition, and those are all individual entities that could be unique in various ways. And then even within a condition that has the exact same mutation that causes it, there is variation in the expression of the condition that is probably related to environmental factors or other genes in the genome that have an impact on the expression of that particular gene and its mutations. Then there's another unique aspect of genetics of a particular gene actually leading to two totally independent conditions. We see that with ApoE4 being a risk factor for both Alzheimer's disease and congestive heart disease.

Now, as we began to look at some of the regulatory aspects of these conditions, it was clear that we had these aspects of incidence and prevalence that are discussed in various regulatory bodies that we had to think about. Genetics brought another issue to the

table with both incidence and prevalence, and that was that there's variation within ethnic groups in incidence of conditions and prevalence of conditions. There is even variation within the distribution of the individual mutations among ethnic groups. So in one ethnic group, a condition may have a higher incidence but a broad distribution of mutations, and another ethnic group may have a very prominent mutation but a lower incidence of disease. Balancing these off has been quite difficult, and there are issues that we've been thinking about and need to factor into any decisions that the committee makes relative to the rare diseases.

Then this issue of associated test volume which has been, I think, the bane to FDA's existence in thinking about genetic testing, which is that even with a rare disease, Tay-Sachs disease for instance, or even Canavan disease, tests that we don't do very often for disease diagnosis, truly rare diseases, but both screened for for carrier status in the Ashkenazi Jewish population, leading to a much higher volume of testing. So figuring out how do we really define the test if it's around the intended use, then as you begin to look at some of the regulatory language, I think you'll want to focus a little bit on some aspects of the language that make it difficult to address rare diseases for testing versus orphan drug development and such in the language, and we'll come to those in a bit.

Now, associated test volume is an interesting problem, because we have the rare disease, which will have a very rarely delivered test. We can have the rare disease that has the very common screening test that may be done in a focused ethnic group, a subset of the population, or as in newborn screening may be done universally. Then we may have the common disease, the more common disease for which there will be a mix of relatively common mutations which we see in cystic fibrosis. We're doing carrier screening on a subset of 25 mutations in that gene, yet 15 percent to 20 percent of patients with cystic fibrosis have one of the incredibly rare or private mutations. They may be the only person in the world's literature who has that particular mutation of the gene that led to their disease.

Those types of patients will never have the same evidence base about that mutation's relationship to disease as will the deltaF508 mutation that's so very much more

common in cystic fibrosis. So we begin to think about two tiers or levels of information that one can have for evidence about a genetic test, and those being a mix of the common things for which you can have a highly specific, directed evidence base, and then others for which there's a much more scientific and clinical base to the evidence based on knowing it's the same gene and knowing there are abnormalities within that gene that are likely to be knocking that gene out that will lead you to interpret that test in a very different way than one would do the more common mutation in that gene.

Now, the other aspect that is common to both rare diseases and common diseases is the way these tests evolve in the laboratories. There's actually a step prior to this R&D step. There's a research step where one is not talking to patients about results. That's where you're establishing the relationship between the gene and the condition in question, and that's generally done at a population level of a whole bunch of people with the same condition, establishing the fact that something wrong in a particular gene is related to that condition.

But at that point you begin to go through this R&D stage where you're trying to learn about the analytical validity of the test that identifies that change, and the clinical validity of that change in those individuals and broader groups of individuals.

But then you hit this much more difficult part of genetic testing that is common in rare diseases and in common diseases, and that's this clinical investigative stage, because it's a discontinuous process. We saw it in cystic fibrosis where the initial reports were of half a dozen mutations that were much more common in cystic fibrosis patients were shown to be clearly related to the condition, and then over the next 10 years we found the other 800 or 945 mutations that have been now described in that gene. So we have a test that's very useful for some people very early on in the development, so the test gets out there. Yet, we're also doing a much more complex test as these patients come along to complement this much more directed test that we had good evidence about. We're doing this genome scanning test to really find sequence variation that can be interpreted for that individual, because the variation in individuals is truly quite broad at a genetic level.

Then we have this point in the test development where it begins to get introduced into the standard of care environment, out of the cooperative study groups and the clinical trials that are organized, sometimes organized, sometimes actually not organized depending on how rare the condition might be. We begin to move into this clinical and public health setting where we now want to begin to make sure we're raising the bar to the kinds of data and standards that a condition should meet before it gets out into this much more broad use, and I think that's the sort of issue that arose with BRCA testing.

I think if you're a geneticist, you come from a world where we live, the ultimate bias of ascertainment. A geneticist wants the most severe presentation, the most dense family concentration to find the gene, leading you to the most warped perspective of the condition. Yet within those people that present that way, it's a very useful test. It's make that next step to broader use and bigger populations, and I think those are going to be some of the balancing acts that you have to think about with genetic testing, how do you go through that knowledge acquisition about the broader applications of the test without constraining to only be testing those people in whom you initially identified the changes.

I think one of the things that you need to look at as these evolve in parallel, you can look at some best practices models, I think, of what are the pieces that have allowed for these things to happen appropriately. One of the benefits of genetic testing is that it was heavily in an academic sector base, did not have a significant private laboratory component, so many of the clinical trials were ongoing within academic environments where they were very much differently regulated than they could have been in a much more privatized environment.

That's not the case anymore, and now we have a much more two-tiered system developing where the more common test gets moved into this either private laboratory or more generally applied laboratory, a pathology laboratory, that will pick up the common disease test because it's much more likely to be profitable. Now the rare disease tests are being left in the academic laboratories running low volume, and that's why we see them languishing often in the research laboratories without making that jump over into the clinical laboratory

setting, and that's what we're trying to think about with the CLIA modifications and some other types of processes that may control that process a little better through either organized clinical trials, consortia and such.

Then this process that is ongoing of data collection because of the inherent biases in the way we initially identified genes, the fact that there is variable expressivity almost routinely in genetic disease, and the fact that we almost never are given money to study normal populations. We learned this in cystic fibrosis. Everything we knew about cystic fibrosis was based on studying patients. When we began carrier testing in the normal population based on what we knew about patients, we learned a lot of stuff. Nobody funded that research in the normal population. We learned that one of the mutations we identified in patients was far more common there than we ever would have expected, telling us that there has to be something else going on that explains that one mutation. So we're retrenching on that as we go, because there is not funding available for studying broad populations, multiple ethnic groups of normal individuals when one is sorting some of these things out.

So we talked a lot about some of the issues that are arising as we look at clinical genetics tests that are translating. Obviously, one of them is the transfer of what during the research stage is generally a quite labor intensive test, and moving that technology into a more routine laboratory setting where it's much more controllable, high sensitivity, well described validation data about the test, and that's something that is ongoing. It's what defines this clinical investigative stage. You're working with people, you're telling them the results, yet you have to be able to fold in that what we know and don't know aspect of it very clearly so that they understand the implications of the test results at that stage of translation.

You have to deal with issues of compliance with state and federal regulation, and there are certainly legal and economic considerations that arise, patents, issues of reimbursement for testing.

I think I'm going to have to pick up the pace considerably to get there anywhere near lunchtime.

So that's one of the aspects that often comes up when people are concerned about the way a particular genetic test was moved through the clinical investigation stage or from research into practice, is that gray zone that you can see reflected in this particular slide, where the test is clearly valid in some settings for some people who were informative for that test, yet perhaps not everybody with that condition. How do you deal with that gray zone and manage it better? I think that's really one of the fundamental issues of the problems that at least drove the development of the Task Force on Genetic Testing, and likely led to this group being continued from that process, is how do we manage that gray zone in there.

The gray zone is a poorly defined thing. I'll just cursorily go over this because the data's not good as to what is a research test and what is an investigational test and what is a standard of practice test. If you go to GeneTests and look at the data for what a laboratory says is a research test, they're often clinical tests. There's no doubt that they're giving out results on the test. They call it research because they have a grant that funds them for a portion of the test delivery. So I think you would probably benefit laboratories considerably by just better defining what is meant by research, clinical investigation, and standard of care testing, because clearly at least two-thirds of the tests that were labeled research were labeled that way in June of 2000 in GeneTests and are still labeled that way, yet clearly are being used for clinical practice decisionmaking.

But the rare tests are often unique in the fact that there's often only one laboratory in the country doing them or only a couple of laboratories. So their ability to do proficiency testing, to do comparison with other laboratories is much more limited, and we begin to have to think about much more general ways of qualifying those laboratories, and that's where it gets complex with the research laboratories, is what are those more general aspects that define how well they do what they're doing independent of that individual disease test they're doing.

We focus a lot on the barriers because as we develop regulation policy for genetic testing, we want to make sure that we don't knock the rare disease tests out of the

practice community, and clearly there are a lot of barriers to their translation that we want to try to relieve and not add additional barriers as we try to regulate these more common disease tests that are coming along.

Certainly, the lack of research funding for data collection to validate tests is a significant problem. The issue of low test volume and uncertainty about test results is inherent in rare diseases and I think can only be dealt with by giving a bit more latitude to the type of clinical validity evidence that's required for those tests to be delivered to people. They clearly can't meet the same standards as a high-volume test, at least in the quantification of the performance characteristics of the test and some of the clinical validation issues.

Very often nowadays there's lack of institutional support to provide for the test as a clinical service. Clinical laboratories in an academic environment are no different than commercial laboratories nowadays. They're not going to do tests that lose money. The health care system is one that is trying to operate at a budget neutrality level, and individual laboratories now are much more forced, whether academic or not, to function as a profitable or a break-even entity, and there's little institutional support for taking those rare disease tests and moving them into their clinical laboratory environments.

Then there's also obviously limited interest from the commercial sector because of the low profitability of the test, and that occurs in both the service side and in the manufacturing community. The manufacturing community actually considers one of their greatest impediments to be the high bars for clinical validation of a test in a rare disease scenario that they know could go on for years and years and years and greatly discourages them from developing the devices and products that might be used to test for that particular entity.

We looked at some of the models that were out there for how one can better manage this process. We looked at modifying, making the CLIA regulations easier for research laboratories to comply. We looked at mechanisms of whether or not we could link research laboratories with institutional clinical laboratories and hopefully develop funding mechanisms to support both to translate tests. We're also now seeing the evolution of clinical laboratories

that are willing to establish a service to translate a research test into clinical service for a research laboratory that isn't a CLIA licensed entity. All those are models out there, and I don't know that we have evidence as to what's the best yet, but I think they're all ones to be thinking about as you look at policy development.

I'm going to briefly go through some of the oversight aspects from the regulatory side. There are a number of accommodations within regulatory rules for rare diseases, and not all apply well to genetic conditions for some of the reasons I've alluded to, but I'm going to go back over a few of them just to highlight them, because it's not uncommon that it's just the language and policy that makes things hard.

We see this in newborn screening nowadays, where some states have in their state policy or regulation the word -- you can add new conditions if they are metabolic diseases, because all of the early conditions were metabolic. Cystic fibrosis comes along and they can't even think about it because it's not a metabolic disease. So in thinking about policy development, using language that's more general is often better than getting too specific about conditions and whether they're genetic or not, whether they're metabolic or not. So to be very careful on that front I think is going to be something that's important, because we're seeing it in states and in federal regulation as we begin to apply it to genetics, which is really broadly applicable across all kinds of conditions and all specialties of medicine.

There's also the humanitarian device exemptions under FDA that came out of the SMDA of 1990. The definitions in the system are not -- this is an issue that was discussed by our committee, the fact that definitions for rare and orphan diseases vary between drugs, devices, and laboratory use, and that's not entirely inappropriate, I don't think. As we look more carefully at it, it became clear that an orphan drug was directed at the individuals with the disease. So the fact that the criteria are somewhat different there is probably not important. We're not going to be treating carriers at this stage. We're going to be treating people with disease. So we would expect some variation in some of the language of the regulatory rules.

Now, just to quickly summarize these, we've talked about them at the meeting previously. Under the Orphan Drug Act, the term "rare disease or condition" means any disease or condition which, A, affects less than 200,000 persons in the United States or, B, affects more than 200,000 persons in the U.S. but for which there is no reasonable expectation that the cost of developing drugs and making them available will actually occur.

Two hundred thousand persons for a disease -- I mean, most genetic conditions would be hard pressed to have anywhere near that many. So I suspect that the vast majority would fall under that bar.

Under that Act, the Orphan Products Development Program is administered by the Office of Orphan Products Development. Since its implementation, there have been about 224 products approved. Several economic incentives exist for developers of orphan drugs, but we don't see this on the device side. We're seeing some problems starting to develop on the drug side, but that's not really this committee's focus, as I understand it. But certainly for rare diseases, there are aspects of surrogate markers of clinical effectiveness that are going to have to be thought about as some of these therapeutics are developed and are applied, obviously very early on in the life of an individual with one of these conditions that are not the classic models we've thought about in the past for looking at the safety and effectiveness of drugs.

Similar kinds of things arise on the device side.

Is it safe to go five minutes?

DR. McCABE: If you could wrap up, we could either wrap it up now and come back, or we could end at the end of the ASHG survey, whichever you would prefer.

DR. WATSON: How far are we from there?

DR. McCABE: Why don't we take a break now.

DR. WATSON: That's for the better. We lost about 20 minutes.

DR. McCABE: Then we'll resume at 1 o'clock sharp. Thanks.

(Whereupon, at 12:08 p.m., the meeting was recessed for lunch, to

reconvene at 1:00 p.m.)

AFTERNOON SESSION (1:03 p.m.)

DR. McCABE: For those of you who are just arriving, Mike gave a wonderful talk, we've finalized the recommendations, and we're moving on.

(Laughter.)

DR. McCABE: So let's resume. We have a total of now until about 1:45 allocated for this. If we finished a little bit early, I don't think people would be upset. But as much as you can, try to wrap it up so we have time for discussion. Thanks.

DR. WATSON: We want discussion because that's the point of presenting this document at this stage in its development, because we want to move it pretty quickly and get it back through the work group itself, but we want to be able to factor in some of your suggestions as well when we're having that next level of discussions.

I think we talked about the orphan drug stuff. The flip side is the devices side where the manufacturers get involved in developing test products. On that side, another set of regulations exist, and there are some language problems in the way these rules are written that I think have led at least the Office of Rare Diseases -- is it the Office of Rare Diseases at FDA?

PARTICIPANT: (Inaudible.)

DR. WATSON: But there's a rare disease group at FDA that suggested these regulations would not work well for genetics because of the way they're written.

They talk about a medical device that's intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. So they're approaching sort of an incidence and prevalence kind of blend on this particular issue. It talks about being affected there. As you begin to get into some of the other regulations, you see that the humanitarian device exemption application authorizes marketing of humanitarian use devices. Sponsors come before FDA with an HDE application, and the Office of Orphan Product Devices may file an IDE

application, and it gets reviewed within CDRH. There have been about 84 requests, 67 of which have been approved.

I'm going to move quickly through these to get to the part that really applies to genetics issues.

As they sit at the meeting, they encourage the submission of HDE applications for qualifying medical diseases or conditions. Genetic tests for rare diseases are probably not a good fit, was the recommendation from FDA, and that was inherent in this preamble to the final rule, which even though it says the rare disease or condition affects or is manifested in fewer than 4,000 people, for diagnostic devices the documentation should demonstrate that fewer than 4,000 patients per year would be subjected to diagnosis with the device, and that extended from the affected individuals over perhaps to the carriers. Even though you don't think of them as having a disease, they have a genetic condition of a carrier status, and the suggestion was that that language complicated the application of this particular rule to the rare diseases device manufacturers.

Therefore, if significantly more than 4,000 patients need to be tested to identify those with rare diseases or conditions, and this applies to now going out and screening in newborn screening programs, where you have many, many, many more people being tested for the condition, most of whom won't have it, but the test volume vastly increases now and can be done in a subpopulation or universally within a much larger population, and for that reason they also felt that this was a poor fit.

Now, I'm going to skip most of the CLIA stuff because I think Judy covered it all pretty well in her talk, which saves us at least two slides, and I would only expand a little bit on them to try to broaden the perspective on genetic testing because so commonly we get focused on what's happening right now, which is molecular-based diagnostics, and bringing it back to remembering that there are genetic tests that are very direct, that are highly quantitative, and there are highly subjective genetic tests, and they may not necessarily be thought of similarly in regulatory schemes.

Cytogenetics is highly subjective. Genome scanning for unknown mutations is also highly subjective and not well standardized. I think these are important kinds of genetic tests to be thinking about as you're crafting policy.

Now we're going to go back over the ASHG/ACMG survey that was done. As Joann said, we're looking at mechanisms to target really a population different than the American College of Medical Genetics. Our membership, by definition, are board certified, trained genetics laboratory directors and clinicians, and therefore tend to be the CLIA certified laboratories and not the non-CLIA labs, although there are some physicians who operate in a non-CLIA environment. For the most part, we were able to identify -- most of the participants in our survey were out of the research organizations, and clearly many of them were involved in rare disease testing as was reflected in the survey, though there wasn't a one-to-one correlation. We weren't able to say this person was non-CLIA certified and was doing the rare disease because we didn't have that linkage within the survey since they were anonymized to a large extent.

So the survey itself told us a number of things. There still are a fair number of research laboratories involved. I think the things of interest – I'm going to, again, skip over some of this. I think the goals were obvious, to identify them and try to deliver better education and training about what's important in genetic testing.

We had 99 surveys returned to us, 35 of which were non-CLIA certified laboratories, and the reasons that they did not get CLIA licenses yet felt that they should still be delivering whatever service it was that they were delivering was that they thought if they didn't do the test, it would no longer be available to patients. Many of them were for rare diseases, and these were people who were, by and large, not trained as clinical laboratory directors and were concerned, for all the reasons Judy presented, about what they perceived as a very onerous system into which they would have to try to fit their laboratory, and with no training really in quality assurance and quality control and tracking.

That's an educational process that will be ongoing as to how to balance out

ensuring high-quality testing in laboratories that are well trained to do testing and have experience with the conditions that have come out of those research laboratories, which is a tough balance at times.

Surprisingly, half of those labs didn't know there were CLIA regulations.

Several types of assistance were identified that these laboratories felt they needed. Clearly, they needed help developing protocol books to understand the pathway that a laboratory test works its way through in a lab. They needed a lot more assistance with quality assurance program development for a clinical laboratory setting. They also wanted resources that helped them identify laboratories out in the private sector that were willing to work with them to translate their research laboratory into a clinical environment, with all of the quality assurance and quality control already built into that lab that offers that as a service. The development of workshops on CLIA regulations so that they would better understand some of the ins and outs and idiosyncracies of those regulations.

Mary is going to pick back up on the resources, and then I'll come back with some of the suggestions that we've tried to pull together.

MS. DAVIDSON: In this last section of the white paper, we focus on resources for laboratory testing labs. We've identified these major organizations, agencies and groups as key resources to facilitate the translation of rare disease tests into clinical settings. I think these are pretty familiar to people in this room, at the Office of Rare Diseases, the new Genetic and Rare Disease Information Center that was established by NHGRI and the Office of Rare Diseases, the Genetic Alliance and the National Organization for Rare Diseases, as well as numerous patient disease advocacy groups, GeneTests, GeneReviews, the National Laboratory Network for Rare Disease Testing, and of course trained geneticists.

I wanted to bring your attention also to a new possible resource. This is dependent on successful passage of the Rare Disease Act of 2001. We're very encouraged by this, and this effort is really led by the National Organization of Rare Diseases, in collaboration with the Genetic Alliance and many patient advocacy groups. Already this year, there was a

very significant increase in appropriations for the Office of Rare Diseases. This will most importantly provide statutory authority for the Office of Rare Diseases, it will increase national investment in the development of diagnostic and treatments for patients with rare diseases, and it will establish Rare Disease Regional Centers of Excellence.

So the last but certainly not least, in fact the most important part of the white paper, of course, is going to be the recommendations. On this slide you see the issues that were raised and highlighted at the close of the November 2001 Rare Disease Panel session, and it could lead to represent some of the committee's recommendations.

These include reimbursement for clinical interface with a testing laboratory; increasing funding for translational phase of research; to facilitate the transition of testing from research laboratories to a CLIA-approved laboratory.

So I wanted to thank you in advance for your comments on this presentation and on this draft, preliminary draft of the white paper. I also want to take this opportunity, because apparently I misspoke, and I want to thank Susanne for all of her efforts in getting the white paper to this point, and thank you also in advance, Susanne, for helping us get it to its final version.

So what we're asking from the committee is are we on track? What are we missing, if anything? We really would like your feedback on this preliminary draft, as well as any thoughts that you might have about the recommendations that need to accompany this white paper.

Thank you.

DR. McCABE: Any comments?

Wylie?

DR. BURKE: I want to note that there's just a lot of overlap of issues being identified, and that's pleasing. The increased funding for translational research, it sounds to me as though every single work group that we have working on topics is coming to that conclusion, and I want to sort of note now that we may at some point want to bring together a single

statement that identifies the different kinds of translational research that are a part of the process.

DR. WATSON: I completely agree, and I think that we can actually stratify them. There are best models out there. In the common diseases things like hemochromatosis is going through a very well organized clinical trial environment at NHLBI that can be done in a short interval of time and can be sort of a point-of-time analysis because it's so common, versus the rare diseases where there are much longer processes.

The success of all the oncology groups, and the reason they were developed, is because all of those acquired conditions were individually incredibly rare conditions and have provided the mechanism to collect all these patients nationally that allowed for the information to be developed much more rapidly, in a much more controlled environment, with continuity between the federal government, all the way down to the level of the patient, with iterative development of the tests, iterative introduction of interventions, and much more rapid acquisition of knowledge about natural history of the conditions all are things that came out of those models, and the ability to find problems much more early in the process because they were much more organized in those sorts of ways. I think things like that could be useful here.

DR. BURKE: And I actually think you've just identified an area for further explanation, because it seems to me that you're describing a mechanism that has worked for relatively rare conditions and may actually work well for not so rare conditions because the same principles applied if the disease is less rare simply get us to the answer quicker. So it's worth our really thinking through exactly what the best models are.

DR. McCABE: You know, I think that if we really do want to make progress, we're going to have to have some organized, concerted effort. In addition, if one looks at common diseases and we think, let's say, that there are 20 genes that ultimately are responsible for a common disease, but in any individual patient it may be only three of those genes or four of those genes, so the combination, the subgroups of genotypes actually becomes relatively rare even for a common disease, and if you want to track genotype/phenotype and

think that those groups may respond differently to interventions, then you need to take even common diseases and develop relatively rare and relatively small numbers of patients to really track and determine the effectiveness of the intervention.

So I think it's a model that we definitely need to explore. I don't know if it would be worthwhile. We've brought this up a few times before about the pediatric or oncology group and the lessons learned from there. I don't know if this is something we should bring before the committee at some point rather than us trying to guess what they're doing and reinvent what they have accomplished.

Joann?

DR. BOUGHMAN: I might suggest that we not only have the pediatric oncology group but we ask Dr. Collins to inform us of the results of the planning workshops that are happening this year, because I know that there are one or more of those coming out of NHGRI that we're going to focus, if you will, on some of the consortia kinds of models.

DR. BURKE: Well, yes. Depending upon whether you're talking about basic research, but I think there are consortia addressing basic research questions that may be not as relevant, but there is a workshop called Genomics to Health, which is focusing, in fact, precisely on the translational questions. So a report of that might be useful.

DR. WATSON: I should lay my cards on the table and say that I've been in discussions with some NIH institutes about developing a cooperative group system, with the intent of developing it through the college but not having a controlling interest in it over any length of time, to develop it around the kinds of things we've had in these discussions, but then to move it just like all the other cooperative groups, into that private sector, academic setting to be competed for, just like all of those have routinely been competed for. I mean, there have been tremendous benefits, and the system is really primed for these things because CMS has an approach to reimbursing the clinical services that are associated with these programs so patients with rare diseases actually don't end up burdened by the cost of participation.

The system is really very well developed. I've been a member of the

Children's Oncology Group and Cancer and Leukemia Group B for 25 years, and on various committees within those, and have a reasonable understanding of how they developed. They all have very strong ELSI components, what would be similar to an ELSI component within those cooperative groups, and a lot of the things I think that would be attractive. If I get the grant done by June 1st, I can share with you the information in it, because it does summarize a lot of the pros and cons of those sorts of systems for these kinds of rare disease research and investigation.

DR. McCABE: Sarah was actually saying that perhaps that would be better than hearing about the pediatric oncology group but really try have you make a presentation about how you saw this applying to genetics. So we might ask you to do that in the future.

Pat?

DR. CHARACHE: I think also on that trail it might be very helpful to see how some of the real problems that have been brought to the surface have been addressed by that group, particularly issues of patient confidentiality, patient participation, the issues of maintaining privacy, of documentation during follow-up, the role of the clinician versus the laboratory versus the patient. So I think some of those things would be very helpful to hear outlined.

MS. CARR: I think hearing from them would be a good thing, but whatever we produced as a result of that we would want to have tailored to a particular genomic --

DR. CHARACHE: I think it might be a very good idea, though, of getting us further down the road efficiently.

DR. McCABE: Michele, and then Joann.

DR. LLOYD-PURYEAR: Actually, I would like to hear about it before NIH does it, and I hope you're going to tell Francis and Alan to look at the case studies, because I think what they illustrate is that it is never just basic research. It really requires very much a collaborative effort with other federal agencies, with academic centers, with health care providers, with the community, and if you don't have that, you have research that's very

isolated. It's not truly a translation if you're really going to try to implement something. Sickle cell is a good example of what was good and what was bad.

DR. WATSON: Well, specific to the grant I'm writing, it is not to set up a group.

DR. LLOYD-PURYEAR: No, I want to know what NIH is doing.

DR. WATSON: Yes. I mean, it is a developmental process of what goes into developing a group for genetics. I've talked to FDA about whether it is of interest to them, and they expressed interest in how it might relieve them of certain burdens that they have in genetic testing that are difficult to manage.

DR. LLOYD-PURYEAR: Ed, can I ask a question of Mike too on your presentation? Can I ask that?

I was trying to figure out something you were talking about. You talked about some tests being highly subjective and other tests being highly quantitative, but you sort of didn't say what that meant for sure, very clearly to me. Are you saying that some of these might not lend themselves to the CLIA process? And if so, why?

DR. WATSON: Everything has to lend itself to the CLIA process. Some are less amenable to --

DR. LLOYD-PURYEAR: Why? Because you can't do proficiency testing, or what?

DR. WATSON: Well, proficiency testing isn't required specifically in genetic testing. Lab comparison types of things are required. We won't know until the new regulations come out if PT is going to be required for anything.

DR. LLOYD-PURYEAR: It's just that everybody has to understand what the problem is, at the table here. That's what I'm trying to say.

DR. WATSON: Well, it's based on experience, and I'm not saying that CLIA is necessarily better. There are aspects of laboratory genetics that are very expert based. Clinical cytogenetics. We didn't expect certain kinds of problems to be evident there until we

did direct comparisons, head-to-head comparisons of laboratories involved in the oncology groups to qualify them to participate in the clinical trials, because we wanted to spend that money the most effective way possible to get the most accurate information possible, and we had these competing models of a central reference lab that did all testing and became highly proficient at it, versus a mandate to distribute testing to all institutional participants in these studies.

What we found when we tried to distribute was that not all labs were equally proficient. They could meet a certain level of competence but were not all equally proficient in the test itself. We felt that in order to get the best data while we were in this translational phase to better understand the tests, that there were mechanisms that we could put in place to set a higher bar for the labs. The bar may be effective for standard-of-care tests that are well understood, for which there's a strong and stable knowledge base so that labs have an expectation of the result upon which they can evaluate their own performance.

But in a translational phase of test development, you often don't have that kind of information. Most labs in the country didn't know that if they were doing an acute lymphoblastic leukemia case, 70 percent of their cases should be abnormal. These patients are so well defined and qualified to get into a cooperative study that you actually have expectations, but nobody ever applied those clinical parameters to the way they operated their labs. So most of the groups, we do it in the NHLBI hemochromatosis study. I'm on the observational study monitoring board for the laboratory practices. We organize central laboratory committees within that group and have a higher level of oversight.

All the labs are CLIA qualified, but during these translational phases where you want to get the most accurate information as rapidly as possible, because you're doing things to people that you aren't completely certain of and comfortable with, and you're developing the data on which you're going to base practice, we thought it was necessary to have a slightly higher bar than CLIA. I would predict that genetics testing labs, I would guess 90 percent probably go through the CAP programs and probably are not inspected by a state med

tech type of environment.

So I think that maybe there are benefits to both programs, and I think there may be a higher standard for one that has a well educated inspector when the laboratory is doing a much more highly subjective type of testing. Not everything can be treated the same way. We talk about acquired diseases being included in genetic testing. Well, they don't have the same issues of clinical validation because of the existence of the cooperative groups. On the pediatric side, 95 percent of those patients are going through a well organized process of development of knowledge about the disease and the implications right from natural history to testing.

Adults are not. They're unmanageable, by and large, because they can fly anywhere to get anything done that they think is right, whether it actually has validity or not.

DR. McCABE: Joann?

DR. BOUGHMAN: I'd actually like to pick up on the last comment that Mike made. If we have the pediatric oncology group come and talk to us, one of the questions that I would like to ask them is why has the pediatric oncology set-up been so successful, with 95 percent-plus of those patients in organized studies, and the flip side seems to be true of even the rare cancers in the adult population? What do they see those barriers being? Because I think that could be very informative for genetics on childhood or newborn screening kinds of things versus predictive testing in adult onset diseases, if we could understand some of the reasons that it seems not to be translatable to adult disease.

DR. McCABE: I've asked our oncologists that, and they tell me that it's cultural. It just becomes an expectation of the pediatric culture that they will be enrolled. In addition, they say that if you look at those who are in prospective interventional studies, it's actually quite a bit lower than the number we always hear of 95 percent-plus. But what they've done is they've captured that additional significant percentage by simply observational studies without intervention. So it's a combination of culture and expectation, and then having various levels of intensity of involvement within the system.

DR. BOUGHMAN: The culture of the docs, or the culture of the --

DR. McCABE: The culture of the docs.

DR. BOUGHMAN: Not the patients.

DR. McCABE: Well, the culture of the docs, because it's considered sort of standard of care to have your patients enrolled in these studies. It's also, then, once you get to a certain level, it's the expectation of the patients that they know sort of by word of mouth that this is what is done in pediatrics, and if their physician isn't enrolling them in one of these multi-center trials, they're concerned that they're not getting the same standard of care.

DR. BOUGHMAN: So, in fact, we may have a leg up, because geneticists may tend to take care of a full range of ages of patients in their practices, and we have a different patient cultural environment as well. They aren't quite as separate.

DR. McCABE: Right. The only problem is that we've tended to do things in a very individualistic way. What it takes is an understanding that you lose control of your patients by enrolling in these studies. You can't do things quite the way you want to do them. You have to follow the protocols. So that's apparently the energy barrier that needs to be overcome early on, to get people to understand that, in fact, they will learn more and do better for their patients over the next 10 years by actually involving them in this bureaucratic protocol-driven study where they lose the rugged individualism that's typical in American medicine.

Pat?

DR. CHARACHE: Just getting back to questions of some of the issues that we're going to want to look at, this I think emphasizes one that's not on this first group of three slides, which is, for rare diseases, how to capture enough patient information or the data from enough patients to be able to get the interpretive information that's required. That's much more difficult than in a common disease.

Another feature that I think we have to wonder about also from the testing perspective, but I don't know how much of this gets into education, is the fact that for many rare

diseases, up to 90 percent of the patients are never diagnosed, and these are particularly those in which the damage is done before the disease becomes expressed, because the physicians who care for these patients don't recognize the presentations for those that are symptomatic, or for other reasons. So another question would be how to improve the detection of patients who are prone for this disease or actually have it expressed that's not recognized.

So I think that we have to highlight those issues that pertain particularly to this group. Then I think maybe we could also be looking at why some of the fixes that have come through the FDA and other groups don't work for rare diseases. I mean, is the bar set up for too many patients, or to what degree do they not apply, and can we come up with strategies that address the things that make them not work?

One of the problems came forward when Joe Boone showed us that our initial gut choice of gene frequency that would make a disease rare in fact covered 90 percent of genetic disorders. So I think this is something, as was pointed out by Mary and Mike in this draft -- what is the definition of a rare disease? Is it the number who are detected? Is it the number that should have been detected? Or is it the test volume? I think these are all things that maybe need to be addressed.

DR. McCABE: Good.

Other points, Mike?

DR. WATSON: I have one other question for you, actually. As we went back and looked through the history of the IOM and the task force and whatever recommendations come out here, I know one of the things I didn't like about the task force is that we never said there should be a mechanism to evaluate the impact of the recommendations we made.

Do you think it would be useful in this report to reflect back on those prior recommendations? Because one of the suggestions was that there be a centralized reference lab for all rare diseases. Obviously, it never happened, and I think there are real obvious reasons why it didn't and probably couldn't happen, and try to reflect on really what were prior

recommendations, did they work, what were the pros and cons of them, as we work through the development of this paper.

DR. McCABE: It's always good to learn from history. So if we've learned some things in the area of rare diseases, we should highlight the lessons learned. If expectations were established in prior recommendations and not realized, we should try to assess why that may not have occurred. Was it that it was a bad idea? Was it a physical reality? So I would certainly look back at some of the recommendations, at least from the task force. That was an immediate antecedent to the Secretary's Advisory Committee on Genetic Testing.

Joann?

DR. BOUGHMAN: In commenting on the status of the report now, it seems to me that with that addition, that in fact this draft is moving much closer to where we can crystallize some specific recommendations. I wonder if it might not be useful to potentially include some of the materials that Judy Yost presented on the status within this, so that we would have everything within one framework that we could then bring together to make our recommendations more clear. If I remember correctly, those were actually in another document. It might make it easier for us if they came into this document.

DR. WATSON: It's one of the problems of having five competing work groups, I think, that our document is probably longer than it should be. I think it talks about a lot of general issues of CLIA and things, and there might be some larger overview that gave a lot of background on all these kinds of things, and then the various work groups came in under that, because we could narrow ours down in rare diseases a lot and probably trim the paper back a good bit if we consolidated a lot of the general overview information into a broader document of some sort.

DR. McCABE: Well, I think one of the things we've begun to realize is that there's a lot of overlap and synergy between the work groups. One of the things we need to evaluate in August is how we can focus on the topics that are common and maybe redefine

some of our work effort so that we're not having parallel courses run by different bodies. So that will certainly be a significant part of the August meeting.

Joe?

DR. BOONE: I'd like to speak to the issue of assistance to these laboratories in particular. I think one of the things we did in CLIA was develop a guidance document for physicians' office laboratories that would be coming under compliance. So we need to simplify CLIA as much as we can, and with the assistance of ACMG and other groups. I think we can develop a document that will make it quite clear what is necessary to become a CLIA compliant laboratory, make it a lot less onerous than having to read through all the material.

I did like the concept that you were talking about of what I would call matchmaking between a CLIA laboratory that's already certified and one that's not, to allow them to more clearly understand what needs to be done. We did this same sort of thing on the global scene that I think is working quite well, trying to pair up a laboratory that's experienced in quality assurance with those that are not experienced with quality assurance. That seems to work quite well.

The third thing I'd like to raise is this issue of needing materials for quality assurance proficiency testing and for research purposes. I had some exploratory conversations with Mary about the fact that we now have a fairly mature research project at Duke that has developed a process to do cell transformation, grow up cultures which could then be placed in cell banks which could be used, then, for research, quality assurance, quality control, those kinds of purposes.

What is missing is the stable process at the end for these materials to be stored and made available, and that's going to take some funding to have a sustainable process. So that's something that NIH or someone else is probably going to have to help look at.

DR. McCABE:

Joann, this is the last comment on this, and then we're going to move on.

DR. BOUGHMAN: Actually, maybe I should wait until the final commentary. But I was thinking here that in this concept of the overlap and synergy among the groups, that possibly the work groups could be working on their individual documents but some sort of executive or oversight group made up of the chair of the committee and maybe chairs of one or two or all or whatever of the work groups could then make a concerted effort to look at those documents as they are coming forward and see if there isn't some areas that could be pulled out and used as combining material. But we might want to use that layered approach to this, because I think there are certain pieces of these two documents that would come out very nicely.

DR. McCABE: Good idea. We may need to bring it up again at the end and may even need to talk about it offline to get organized for August, because I think that would be an interesting exercise as we plan for the August meeting, to look at where, in fact, there are direct overlaps that could be usefully identified.

Okay. We're going to move on now. Thank you very much, Mike and Mary, others who worked on that.

Yesterday we reviewed the report of the Access Work Group addressing issues in the reimbursement of genetic education and counseling services. Today Dr. Lewis will discuss a second report of the work group on more global coverage and reimbursement for genetic testing services. An outline of this paper is at Tab 4 of your briefing book. Judy wants to be sure we agree that the work group is moving in the right direction with the paper, and she's seeking our guidance on the paper's thesis, goals, and further development, including a proposal to convene an expert roundtable to gather additional input on the issues. So please be thinking about that as Judy is making her presentation.

DR. LEWIS: Thank you, Ed. I just wish we were having about as much fun as the group in the next room. They certainly seem to be having a good time.

DR. McCABE: We could start cheering and laughing for you if you would like us to.

(Laughter and applause.)

DR. LEWIS: Throw candy. What can I say?

(Laughter.)

DR. LEWIS: Anyway, thank you very much. For those of you who have been on the committee longer than two days, you may remember that several meetings ago we brought a draft of a white paper to you looking at some guiding principles on reimbursement issues. One of the things that happened in a subsequent phone conference call was that the group just sort of had this "a-ha!" experience and started to think about the fact that maybe these were issues that were unachievable. So for those of you who have that previous white paper somewhere in your files, that no longer exists and this is its next iteration. Again, thanks to Suzanne and thanks to the members of the work group, who are the same members of the work group that I talked about yesterday, for their thoughts in terms of moving this forward, and that's Suzanne Goodwin, just to make sure people know which is the right Suzanne this time.

So what we're looking at now is a paper that will take a broad look at coverage and reimbursement for genetic testing. As we describe genetic testing services, we're talking about a broad product, not just the test per se, but the genetic evaluation, the pre- and post-test education and counseling, the testing itself, and then that leading to the management and treatment of the individual or family.

What we're trying to do is identify some of the issues and problems in terms of access of this broad scope of services, and then our goal is to develop some recommendations to deal with what we perceive as a problem in access, presuming that everybody else agrees there's a problem in access, which I don't think is an issue from what I'm hearing. I will say in regards to what Ed said earlier, I'm getting a tremendous sense of convergence among our issues, so obviously we've been approaching it from a variety of perspectives but I think we're coming to conclusions independently that it's the same key issues.

Our approach to this white paper was looking at a consideration of coverage

and reimbursement for genetic testing services in the context of the current state of health care financing and delivery and a discussion of the roles of the various players in coverage and reimbursement. By the various players, this is something it took me a while to get a real good understanding of in terms of reimbursement seekers and reimbursement providers. In this particular language, the seekers are people like test developers, laboratorians, patients, providers, and clinicians, people who are looking for payment from the reimbursement providers, who are insurance companies, employers who pay for health care insurance, the federal government who administers several of the large insurance programs such as Medicare and Medicaid, and other people who are reimbursement providers.

Some of the issues that exist right now are things like rising health care costs, the fact that there are an increased number of uninsured, the fact that even for those of us who do have insurance, our insurance premiums continue to increase on a regular basis, and the fact that even though we all consider genetic testing a top priority, there are lots of competing priorities for those health care dollars.

So that's sort of the background in which we started looking at this, along with things like the current and projected future landscape of genetic testing and the coverage of genetic testing services, and suggestions on how health care payers can begin addressing genetic services.

For example, what tests are currently available, and what tests are in development? How are health care payers addressing genetic services? And if they're not addressing genetic services, what are some of their reasons for not doing so? One of the things we want to do is convince health care insurers as to why they should be considering addressing genetic testing services. By that, we're talking about things like coverage decisions, reimbursement decisions, education for planholders and providers, consideration of some of the different purposes of genetic tests, and then the whole issue of access to providers of these services.

Some of the challenges that are out there are the fact that the FDA review of

new genetic tests is not yet implemented; the fact that we still have unknowns in the area of clinical validity for some of the various tests; the issues of privacy and genetic discrimination may be limiting the demand for tests, so that we may just be looking at the tip of the iceberg and the fact that once the privacy and discrimination issues become less of issues, hopefully, that we will see a huge increase in demand for tests; and the fact that the traditional medical necessity criteria aren't easily applied to the testing of healthy individuals and testing for social informational purposes.

Some of the challenges. There's a real blurry line between research and clinical testing, and some of the stuff that Mike and Mary just shared with us I think makes that eminently evident. In rare disease testing, it's really sometimes unclear where research testing ends and where clinical practice testing begins. The issue that coverage may not be economically sensible for health care payers, and I think we've heard that from some of the health care payers who have provided testimony; the issue of coverage for genetic testing of non-covered family members, and some of the other considerations, such as how should coverage for genetic testing services be weighed against competing costs and priorities, especially when those costs are additive.

Are consumers willing to pay more to have these benefits added? And if so, what are the appropriate costs to consider? How should costs and benefits of genetic testing be measured and compared to one another? How can the use of genetic tests and services be responsibly promoted through health insurance coverage in light of the unresolved challenges that surround genetic testing? How should decisions be made about which tests are acceptable to cover, and what information would health care payers find useful to assure rational decisions are made and limited resources are used prudently? How can test developers, health professionals, professional associations, patients, consumer advocacy groups, and so forth provide such information to health care payers?

So what we're proposing is a roundtable, and the purpose of the roundtable is to consult with the players who are involved and affected by coverage and reimbursement

decisions on genetic testing services so that the various players can share their perspectives with us and we can gain an understanding, each to the other, of some of the difficulties of obtaining and providing coverage for and reimbursement of genetic testing services, and to seek input on issues to consider as we develop our white paper.

We're proposing, and you've got an outline of this in your notebooks, a two-day conference, and on the first day we want to have two concurrent roundtables, one to help us understand the barriers to obtaining reimbursement, and the second to the challenges to making coverage decisions for genetic testing decisions.

We see the second day as sharing perspectives on these two and having the participants give some guidance to the Access Work Group, and then after that adjourns to have an Access Work Group meeting so that we can then be prepared to bring something back to this group in August. What we'd like today is guidance on the direction of this paper and your approval to convene this roundtable.

Ed, were you asking about the timetable?

DR. McCABE: No, I was asking how many people, how big a meeting this was going to be, and I was told it's 15 to 20 per group, or 30 to 40 for the meeting.

DR. LEWIS: Yes, and we're looking at hopefully maybe the second week in July or somewhere around there so that we have an opportunity to refine this material and be able to bring it back in August. So I think we've got a lot of expertise on the work group, but we need to get even broader perspectives because it's really hard for one or two individuals to speak for a whole sector.

That's what I have to say.

DR. McCABE: Okay. Thoughts on the proposal that this work group convene a roundtable to address these issues, the time frame being July, the numbers being in the 30 to 40 range, the goal being to develop some materials to bring back to the SACGT for our August meeting? It seems fairly ambitious to do that given that we're already well into May, but it would be great if it was doable.

Victor?

DR. PENCHASZADEH: Well, certainly you outlined most of the essential issues that have to be taken into account, the coverage and reimbursement for genetic services. I think the document is very well outlined.

My concern is the time frame, and my question then is do you have already an idea of logistics? Do you have more or less identified people for this meeting, and location and so on?

But before that, actually, I have another problem. I realize the centrality of genetic testing in all what we do. After all this is a committee on genetic testing. However, it strikes me that throughout the presentation and the document, we talk about genetic testing services, as if genetic services really are centered inevitably on a particular genetic testing.

I have the concern that we may be focusing too much -- actually, when you outline what genetic testing services are, you start with genetic evaluation, with counseling, with treatment and management, and testing is only one part of the whole spectrum. So I'm concerned that we are focusing almost exclusively, or at least in the minds of people, on testing. So I want to preempt paralleling the fact of physicians who don't write a prescription. When you go to a physician, it's as if you haven't gone.

I'm concerned that if we focus exclusively on testing as the centrality of a genetic service, we may be taking all the nuances of what genetic services are all about.

DR. LEWIS: And I think what we tried to do, Victor, is frame this in terms of access to services, as opposed to something that was very narrow in scope. I do think the issue is broader than just the test itself, and I think the test is a piece of it, because sometimes the decision is made not to have the test. But if you don't have access and have information, you can't even make that informed decision.

If somebody goes through this whole, long work-up and then doesn't have the product, what does that do in terms of reimbursement? Some of the other issues are that many times the issue goes far beyond the patient. So I think it's an access issue, but I think we

also have to frame it within the scope of our mandate. So that's the tension that I see. I think the issue is way broader than genetic testing and genetic services, but that's not this committee's charter.

DR. McCABE: Michele, then Joann.

DR. LLOYD-PURYEAR: I had some of the same concerns Victor did, but I'd also like to ask a question. What information that we don't already know are we trying to find out at this meeting? Because we've had many presentations from health insurance on the issue of paying for genetic tests, and we certainly have had wide input on conference calls to the documents.

DR. LEWIS: I think we're looking to get to a broader group of individuals and to be able to have some dialogue at the table so that we can go ahead and then maybe move this forward, and maybe reach some consensus in ways that we haven't been able to. I mean, we have had representation from the various sectors, but it's been one or two representatives from the various sectors, and we haven't had, for example, as much consumer representation as I'd like to see, bringing in some people who represent the advocacy piece too. So I think it's going to be a broader representation and a limited time frame where we're going to leave at the end of the day with a product, and I hope I can do as good a job as Joann did in terms of bringing that education group to the table, where again we had had lots of input, but be able to leave with some consensus and an ability to move it forward. I think sometimes you need that face-to-face meeting to be able to come to the table, say your piece and then let's look at where we're going from this. So that's our hope, I believe.

DR. LLOYD-PURYEAR: You wouldn't want them to react to a white paper first, to have that as part of the structure?

DR. LEWIS: What we're trying to do is get them to help us develop this.

Suzanne, did you want to add to that?

MS. GOODWIN: I think, in preparation for the roundtable meeting, that we would have part of this white paper developed as more of an issue brief than anything, to get a

meeting of the minds beforehand. So some of the issues would be teased out of it more beforehand.

DR. LLOYD-PURYEAR: So they'd be framed and narrowed.

DR. McCABE: Joann?

DR. BOUGHMAN: I was just going to say if you think you can get some of the right people in the room, if you are lucky enough to have any of the "a-ha!" moments that we had at our roundtable in November, then I think it would be worth that discussion.

The other point that I wanted to make, though, was I think it is going to be absolutely critical in framing these issues for this group, because you are the access group, to make it very clear what about underserved, uninsured populations is on the table, or whether those issues are off the table and the focus is on a subset of individuals, or it will get very fuzzy very quickly. It doesn't matter to me right now. It seems like you have taken those off the table for the focus of this roundtable, which I think is probably good, just as we took public education off the table for the education roundtable, because there are still plenty of issues. But I think that needs to be made very clear before we bring people to the table to discuss the issues.

DR. McCABE: Did you want to follow up, Judy?

DR. LEWIS: No, I think you're very right, because I think that this is a huge issue, and it's an issue that's got debate throughout society right now, but there are huge pieces of it that are very important but are not part of our mandate.

DR. McCABE: I still think it's fairly ambitious, especially because some of the people you may want to come to the roundtable may have their schedules already booked for July. If we're going to occupy ourselves in August with significant reflection, I don't know that it would be too horrible if this was postponed. So if you can do it, fine, but I think it's better to do it right than to do it quickly.

DR. LEWIS: So what I'm hearing, at least from Ed, is that people are in agreement with the idea to move forward but that the timetable may -- it's okay if we re-think

the timetable.

DR. McCABE: Yes.

The other thing that I think needs to be thought about is how this piece would fit in with our letter to the Secretary regarding the IOM. They might appear to be different issues, but they really do have some convergence also. So I think that perhaps we should talk a little bit about that. I'd like to move forward. We decided yesterday that we would move forward with that letter to the Secretary through the Assistant Secretary for Health, but does anyone see this as competing or interfering with what we would be proposing for the IOM study?

DR. LLOYD-PURYEAR: No, but I do think they are really very similar, and you probably need to include -- you can't exclude this, I don't think, from the IOM letter.

DR. LEWIS: We may be able to mention it as an issue but not one that we have a lot of data on yet.

DR. McCABE: Well, which is the whole purpose of the IOM, that there's considerable absence of data around all of the issues here.

Pat?

DR. CHARACHE: I wonder, though, if this might not be helpful in helping us sharpen our ideas and what we want the IOM to be looking at if we brought together these groups. Just from a logistical perspective, if you want 15 or so from this work group, I'm wondering about tieing it to the August meeting, either the day before or something like that, if you could get it together by then.

DR. McCABE: We'll just have to see what is doable.

DR. LEWIS: Yes. We'll work with staff in terms of logistics and looking at key people's schedules, because I agree that having a meeting and not having the people you want at the meeting there doesn't really serve our goals very well.

DR. McCABE: Joann?

DR. BOUGHMAN: If I remember correctly, we had talked about putting

some background around the request to the Secretary to seek an IOM study, and it seems to me that some of that background information could include the fact that we are moving forward in looking at and clarifying these issues, but timing is everything and we have to start the request process, but we would be able to inform or clarify the request to the IOM by our continued work in the interim. I think that can be worded in a letter fairly well. So I think we acknowledge the convergence of these, but make sure that the Secretary knows that we're still plugging right along.

DR. McCABE: Okay, and that's important because the time frame is such that it will take a couple of years, even if we're successful in getting an IOM study.

Any further discussion on these points?

(No response.)

DR. McCABE: Thank you very much.

DR. LEWIS: Thank you, and thanks to everybody for their input.

DR. McCABE: Let's move on, then. Before we look at the list of possible topics for August, I want to discuss another possible agenda item, and that would be, as we've talked about, using a considerable portion of the August meeting for self-reflection and analysis to assess what we've accomplished and the committee's future directions.

At our inaugural meeting in June of 1999, we made a commitment to evaluate our role, effectiveness and accomplishments at the end of two years of operation. We've actually been in operation for three years, and though we may be a little bit late in carrying through on our commitment, I think it's extremely important, and August will be a very good time for us to take stock, review our accomplishments, assess their impact, and determine our future direction. It's an especially good time as well because it will allow us to incorporate the issues and concerns of our new members, and I think it's very important that we get input from our new members and not just maintain the momentum that was established by the inaugural group.

We need to be mindful of five key criteria when deciding which issues and

projects we commit ourselves to addressing. One, the issues fit within our charter, and we've come back to that a number of times over the last two days. The issues are in need of policy remedies. No other body is working on them. We are uniquely positioned to make a contribution, and the contribution will have an important impact. These criteria were first articulated by Francis Collins at our August 2000 meeting during our first priority-setting session, at which we identified our current portfolio of issues and projects.

With the distance of two years, we should be well positioned to review our work group mandates and projects, and be sure that everything we have undertaken meets those guiding criteria. I think it's important to look at what we have accomplished and how they fit into the criteria, because some of them may have been developed and got up a head of steam before we really began to apply these criteria.

So at this time, I'd like to ask the members of the committee for your thoughts and comments on the proposal, and then depending on what we decide, we can take a look at other possible meeting topics for August. So what do you think?

Yes, Judy?

DR. LEWIS: You know, this I think makes eminent sense. As I've been sitting and thinking about the issues over the last couple of days and how they've converged, I see maybe a couple of different ways to slice the issues, not that the issues are going away but that there may be ways to slice them differently so that we end up with some economy and some efficiency of effort. So I think that not only rethinking the issues that we're dealing with but looking at them in different frameworks might be real helpful in terms of helping us move things forward. So I think this is a really good idea, and summertime is usually, at least for me, a time of reflection and planning for the next year because I don't think from January to January, I think from September to August. So the timing is really good for me.

DR. McCABE: Other thoughts?

Joann?

DR. BOUGHMAN: One thought on the priority-setting criteria, and I don't

know whether we want to actually talk about those now or whether that might be incorporated in our self-reflection. I would suggest that we are combining 3 and 4 in a slightly different way. Rather than no other body working on the issue at all, that in fact we are cognizant of and capitalizing on what work is being done and filling in some gaps and pulling some things together. There might be a better way to word that, but I think we have been aware of not duplicating efforts rather than being absolutely unique in the approach, because I think that's one of the things that we have with all of the players around the table.

I would just come back to the comment that I made before on the reports that are now coming together and the convergence of some of these issues that, in fact, if we had a subgroup that was willing to look at all of these papers carefully and pull out some of the overarching issues, that that might give us a way to organize some of this reflection and allow us a way of acknowledging separate work products but also the convergence of ideas in a way that separate issues or approaches have complemented each other.

DR. McCABE: Michele?

DR. LLOYD-PURYEAR: Well, I agree with the rewording of 3 and 4. But I think, in terms of looking at the issues within our charter, I was always comfortable going off and looking at issues around informed consent and access and education when I thought we had solved the problem of the template and the oversight and the regulation. It's very hard to talk about education, access and informed consent, and the data, without having solved the central problem.

Do you think FDA will have a decision by then? Because everything sort of flows from what that framework is. If you don't have that oversight or regulatory framework, you can't be concrete the way I think we need to be concrete with some of our recommendations.

MS. CARR: I just want to speak to whether FDA will have a decision. I guess I should refer back to what Sherrie Hans said yesterday, that her expectation or her hope was that Dr. McCabe would have participated in a briefing of the Secretary by that meeting and

would be able to report back to the committee what the outcome was. I think you're absolutely right, that if the answer is no, we don't have the authority. That is, in a way, what makes August even more timely.

DR. LLOYD-PURYEAR: (Inaudible.)

MS. CARR: Well, it does, and then everything else has to, I suppose, be adjusted accordingly. Then the committee's focus I think would have to be on what are the alternatives to FDA review or should the committee be recommending to the Secretary that the Department seek the legislative authority they don't currently have, if that's the answer.

DR. McCABE: I would suggest that if we don't have an answer by August, that we assume we have an answer, that we've been sitting in limbo now for some period of time and that the absence of an answer should not paralyze us. The absence of an answer tells us that we need to be creative and begin to look at other options. If, then, in the next month there was a reversal of that perception, that would be wonderful. But in the absence of any movement, I think we should move. So I think that we need to be, and I think we've already begun to think about some alternatives.

Labeling has become extremely important. Labeling that's mandated by the FDA or some other organization is certainly stronger than voluntary. But if we can create expectations among patients that they have accurate information on tests, and they demand that information, then that will work. It will be a somewhat larger job to educate people. But I think that we should begin to think and really approach how we're going to address these issues in the absence of a decision.

DR. PENCHASZADEH: Yes, but that will essentially define the content of our agenda for August, I think. I agree with Michele that at this stage, we are in a limbo waiting for an answer or not an answer. But that essentially will define largely what our priority will be in August, because I think that it's obvious. If there is no answer or an answer that is not the one according to what our recommendations have been, we'll have to devote a large part of our meeting in August to come up with alternatives.

DR. McCABE: Judy?

DR. LEWIS: I also find these meetings especially exciting and gratifying when we not only come together to discuss issues and make decisions but when we go ahead and continue our group learning. From that perspective, I don't know how you're planning the agenda for August, but I for one would love to see that piece on the follow-up in a more expanded session on the issues around racial disparities. So if there were time to have a piece of us being educated by an outside group, I would love to see us consider the possibility of maybe fitting that into some of the agenda, because that session last time was very good but it was way too brief and I could see us spending really a big chunk of time doing that, and that might help us frame how we move the issues forward. At least from my perspective, that's an issue that I think is critical.

DR. McCABE: Pat?

DR. CHARACHE: Following along on your thought that if we don't have an answer, we should be prepared to consider what options we would have to meet the goal of ensuring this information and quality in labeling, would it be reasonable to ask the CDC, FDA and CMS ad-hoc members if they could be prepared to tell us any thoughts they might have should that event occur?

DR. McCABE: We can ask them, and there may be other agencies as well that might jump into the breach.

Any thoughts from agency representatives?

DR. CHARACHE: I was thinking of giving them until August to think about it. I don't know.

DR. McCABE: Well, is this something that the agencies would want to take on? Certainly, I think it will be all of us trying to figure out how we can be creative.

Steve?

DR. GUTMAN: Well, I would hope that the answer would be yes. I'm not sure that anybody sitting at the table has the authority to, for example, reconvene the ad hoc

group or to formalize it. We work together informally quite well, and I certainly stand committed to using whatever ideas have been generated to try to work with my colleagues at CDC or CMS. They are both creative agencies. It's awkward since there really isn't a decisionmaker at the table, but certainly at the working level we're prepared to try to brainstorm and offer suggestions. That might be a recommendation this group might formally make to HHS, and then HHS ought to start thinking about alternatives. Informally, we could do it. If you want it done formally, you probably ought to make that suggestion.

DR. McCABE: Well, the ad-hoc group hasn't met for some period of time. It would certainly be good to have all of you meet formally offline outside of these meetings and in preparation. Let's hear from some of the other members of the committee, but that seems like a very reasonable perspective.

Judy, Joe, and then Cindy.

DR. LEWIS: I guess I think that what I'm trying to sort out is what that would do that's not already happening, because it's not like the agency folks aren't able to share with us what they're doing and what their perspective is. It seems to me that it's maybe a level higher up the food chain that needs to make some of this happen, because what I don't want to end up doing is killing the messenger. It may well be that it's more important for us to make this point, because I'm not sure how well the agency folks can if the issues are agency constraints.

DR. McCABE: Well, I think what we would do is give a task, and we would task them with coming up with some creative approaches should FDA decide that they did not have authority over home-brews.

DR. LEWIS: And that makes sense.

DR. McCABE: Joann?

DR. BOUGHMAN: I was actually going to change topics a little bit.

DR. McCABE: Well, let's hold that, then, and finish this up.

Cindy?

MS. BERRY: Well, when I talked to Sherrie yesterday – this is just sort of FYI -- I asked her the very question was HHS General Counsel's Office involved, and when the FDA attorneys and HHS overall agency folks get together and make a determination, will it just be FDA does or does not have authority, or will it also include if FDA doesn't have authority, what might the alternatives be, and she thought the latter would actually be what they would hope to achieve. So it sounds like they're already thinking along those lines and that we'll get a little bit more guidance than just yes or no.

DR. McCABE: And it sounds like that may be more effective, really, at that level, rather than us come up with another plan which took six months for the Council to decide wasn't viable. So thank you for gathering that information.

Michele?

DR. LLOYD-PURYEAR: Well, that leads into that I don't think you should suggest the small group meet and come up with a plan, because it might be a waste of time, but it also creates an out and more deliberation. I know when we first deliberated whether or not FDA had the authority, everybody was at the table. That was at the Department level. So I think that would happen again.

DR. McCABE: But I think that's very good and this is something, Sarah, that we need to stay on top of to be sure that Cindy's discussion with Sherrie is the way things move forward.

PARTICIPANT: Carol is here.

DR. McCABE: Carol has a slightly different spot in the organization, but similar issues could be raised.

Carol, do you want to use a microphone, please?

Dr. Carol Greene, who was not here yesterday, but apparently there was some exchange of information.

DR. GREENE: There will be some exchange of information is probably a little bit more fair way to say it, but thank you. So I want to be very careful to make clear that

I'm speaking very, very generally. But I think it's probably very fair to say that what Sherrie Hans had said yesterday matches my understanding of the process, that this is something that HHS is already concerned about, it's an issue that is receiving attention certainly from the Assistant Secretary for Health. At the moment, as far as I understand, this is an issue being considered by FDA, but there's already concern raised by the agencies about what would happen to the plan that had been developed if, in fact, FDA does not have that authority. I can already tell you that that's been a subject for discussion.

I think it's highly likely that whatever choice FDA makes would be subject to further thought, that if FDA makes a decision that will not permit HHS to move forward with the originally outlined plan, that there would be some formal consideration, whether that requires another look by some other legal office or whether that decision would stand and then it requires a look at other alternatives. I can't say whether somebody would review and overturn. That's a decision that will be made by people far above my level. But I can say for certain that there's already consideration going on among the agencies, and there will continue to be consideration whatever FDA's plan is.

I don't think it's necessary for the SACGT to tell HHS to do that. I believe that that process is already starting.

DR. McCABE: Thank you.

Joann?

DR. BOUGHMAN: Because we will be between Congressional sessions at the time of the August meeting, it seems to me that it would be good to get an update on those pieces of legislation that this committee has specifically made reference to, including genetic non-discrimination, the Rare Diseases Act, the Privacy Act issues that are still on the Hill, so that we could first take stock and, second, have the committee determine whether there are any specific actions that we would once again want to take in any of those venues.

DR. McCABE: It's already been added. I saw Sarah was typing as you were talking.

Other issues that one sees on the screen there as agenda items? It looks like a fairly full agenda, but it's important that we recognize that our November agenda will be somewhat abbreviated because of the meeting that it will be in association with.

Mary?

MS. DAVIDSON: Just to add, Joann, to your suggestion, I think it would be good to have an update on the proposed modifications of the HHS privacy regulations.

DR. McCABE: Okay. So legislation as well as regulation.

Yes, Cindy, did you --

MS. BERRY: (Inaudible.)

DR. McCABE: Judy?

DR. LEWIS: Given the fact that we aren't going to be meeting in the D.C. area in November, it might be important to, as we start to look at issues and decide what goes to August and what goes to November, to look at who we need to have joining us, because I think the Hill issues are important and those might be more appropriate at a time when the folks are local.

DR. McCABE: So is there concern that we will be away from Washington in November?

DR. LEWIS: No. My concern was that as we start to turf issues to either August or November, that we focus the ones in August on the ones that are going to require short visits from people who are in the D.C. area, versus issues where we don't need as much outside visiting.

DR. McCABE: Okay. Thank you.

Other items for August? Everyone on the list acceptable to everyone?

MS. CARR: Can I ask what about the last one?

DR. McCABE: So the last session is an organizing session on the history of the development and implementation of CF population screening guidelines, laboratory and education, counseling components. Is that the ACOG?

MS. CARR: Yes, and I don't know that this has been discussed in any detail in the committee, but it seemed like an example of important guidelines that had been developed through a collaboration, and they've been put in place. It seemed like it would be very illustrative and valuable for the committee to hear about the process of the development for one thing, and then how it's all playing out. But I would say it probably belongs on the last place on that list, and I suspect given how long the list has gotten now, that maybe there won't be time for that. But I wanted to make sure that was the group's feeling as well.

I just want to make sure that we got all the work group output listed. Do we have it, the three things?

DR. LLOYD-PURYEAR: What about data?

MS. CARR: The what?

DR. LLOYD-PURYEAR: The data group.

DR. McCABE: I think the important thing is that we have plenty of time in August to discuss and make sure --

MS. CARR: So this would be first.

DR. McCABE: -- make sure we have the time for self-reflection.

MS. CARR: Actually, maybe that's second. Is it? Which is first? FDA is first.

DR. McCABE: Well, FDA is first because it was our original charge, but we still need to make sure we have plenty of time for the self-reflection.

Other items? Further discussion?

(No response.)

DR. McCABE: If not, thank you all very much for a busy three days. Special thanks to Sarah Carr, Susanne Haga, and Suzanne Goodwin for helping get everything done for this meeting.

Again, thank you to our new members, and thank you for jumping right in and getting involved.

Have a safe trip home, everyone.

(Whereupon, at 2:26 p.m., the meeting was adjourned.)