SECRETARY'S ADVISORY COMMITTEE ON GENETIC TESTING

Twelfth Meeting

Wednesday,
February 13, 2002

Maryland Suites
Bethesda Marriott Hotel
5151 Pooks Hill Road
Bethesda, Maryland

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PROCEEDINGS (9:05 a.m.)

DR. McCABE: Good morning, everyone. I want to welcome everyone to the 12th meeting of the Secretary's Advisory Committee on Genetic Testing. The public was notified about this meeting through an announcement in the Federal Register on January 24th, and a posting on the SACGT's Website. We appreciate the public's interest in our work and, as is our custom, we have provided an opportunity to hear from members of the public during this meeting. If you would like to make public comment and have not yet signed up, please do so at the meeting registration desk out in the hallway.

Among the issues we will address over the next two days are Health and Human Services' activities related to increasing knowledge of the validity and utility of genetic tests, the economic impact of the genetic testing market, informed consent in clinical and public health settings, third parties and human subjects research, and the use, collection and analysis of population data by race and ethnicity in genetic testing. Later this morning I am very pleased to report that Dr. Eve Slater, the Assistant Secretary of Health, will join us and make a few brief remarks.

Before we get started on our very full agenda, I want to take note of the hearing on genetic discrimination that is scheduled to take place this afternoon before the Senate Committee on Health, Education, Labor and Pensions. There is a sheet in your table briefing folder, the red folder, describing the agenda for that meeting. The Senate committee will be reviewing the limits of existing laws for protecting against genetic discrimination. If we have time at the end of the meeting tomorrow, we'll get a brief report of their proceedings.

Sarah will now review our rules of conduct.

MS. CARR: Thank you, Ed. Being a member of this Committee makes you a special government employee and thereby subject to rules of conduct that apply to government employees. The rules and regulations are explained in a document called "Standards of Ethical Conduct for Employees of the Executive Branch," which each of you got when you were appointed to the Committee. At every meeting, in addition to reminding you about the importance of following ethics rules, we always like to review the steps we take and ask you to take to ensure that any conflicts of interest are addressed.

As you know, before every meeting you provide us with information about your personal, professional and financial interests. We use this information as the basis for assessing whether you have any real, potential or apparent conflicts that could compromise your ability to be objective in giving advice during Committee meetings. While we waive conflicts of interest for general matters, because we believe your ability to be objective will not be affected by your interest in such matters, we also rely to a great degree on you to be attentive during our meetings to the possibility that an issue will arise that could affect or appear to affect your interests in a specific way. If this happens, we ask you to recuse yourself from the discussion and leave the room.

If you have a question about these rules or any others, please let me know or our ethics counsel and we'll be happy to address them. Thanks.

DR. McCABE: Thank you, Sarah. Over the last two years, the Committee has had extensive discussions about the critical importance of supporting ongoing data collection and analysis of genetic tests in both premarket and postmarket phases. We included recommendations about the need for coordinated efforts in data collection in the July 2000 oversight report. Since then we have been working largely through the efforts of Dr. Burke and the Data Work Group to understand in greater detail the depth and breadth of the challenge of achieving this goal.

At our meeting last August, we decided that we needed to find out in more specific detail what the HHS agencies represented at this table are doing to support the advancement of knowledge of the clinical validity and utility of genetic tests. At Tab 2, you will find a copy of the letter we sent to each of the agencies in September, and the agencies' responses. NIH's response was too voluminous that only a part of it could be included in your briefing materials. We have one set on hand of the project abstracts that were submitted in case we need more information about a specific project.

Our goals today are to understand the scope and level of individual agency efforts to advance the generation, collection, analysis and dissemination of data on the validity and utility of genetic tests, see what the totality of effort looks like, and get a sense of how well the agencies are working synergistically in this area. If we see gaps, unnecessary overlaps, or the need for additional efforts, we will need to decide what recommendations we should make to the Secretary.

This morning each of the agencies will be presenting a summary of their activities. Also participating is Dr. Carol Greene, who works on genetics policy issues for the Office of Science Policy and the HHS Office of the Assistant Secretary for Planning and Evaluation. Dr. Greene is also professor of pediatrics at the University of Colorado Health Sciences Center, where for 12 years she directed the Inherited Metabolic Diseases Clinic at the Children's Hospital of Denver, and for seven years chaired the Colorado Newborn Screening Advisory Committee. Carol came to Washington in 1999 as AAAS Congressional Fellow sponsored by the American Society of Human Genetics and worked for the Public Health Subcommittee of the Senate Health, Education, Labor and Pensions Committee. She now divides her time between policy analysis at HHS and clinical work as a member of the metabolism and genetics staff of the Children's National Medical Center in Washington, D.C.

Dr. Greene will set the stage for the agency reports and following these reports will provide an overarching analysis of the information. Dr. Greene.

DR. GREENE: Thank you, Dr. McCabe. Also, I want to express enormous appreciation for the hours and hours and hours of hard work from the agencies that went into responding to the request, and from Sarah's staff in really assisting me with the analysis and presentation. Anybody who knows me knows I don't make slides like this.

I should also say that our goal is to go through all of the reports, I'll set the stage, and then I'll provide some summary, and we hope to have the questions come in the period of discussion after all the presentations have been made.

SACGT made a request to the agencies, and specifically requesting information on supportive activities that increased knowledge of the validity and utility of genetic tests. That's a very straightforward request. It turns out, although it seems very simple, to lead to a rather broad and complex answer, as you will be seeing, from the agencies. FDA received a separate request, and they will deal with that question in their presentation.

Dr. McCabe mentioned a voluminous response from NIH. I want to say that the list of abstracts is about this high, and that represents months of work on NIH's part, and they'll be telling you exactly how they arrived at selecting those abstracts.

Specifically, SACGT has requested from each agency information about the agency's mission statement, and you can read this as well as I can, the specific role of increasing knowledge in this area, and project summaries. Remember, this is a focus on projects, and that's allowed us to actually provide information about funding. Examples of coordination and examples of involvement of groups outside the agencies, and future plans.

SACGT has asked us to provide this information in two stages, addressing what kind of core activity, whether it's primary or secondary research or information development and dissemination. I need to point out here that both HRSA and FDA - although everybody did try to identify a single core activity - selected multiple core activities. We recognize that it's very difficult to pick a single core activity, but you should be aware that in our analysis, we had to assign each project to a single core activity. For knowledge addressed, it was in the request permitted to assign more than one category to each project. But really, we have to emphasize the difficulty of assigning any one project to any one category here.

I have two more slides that will help us to set this up, and then I'll turn it over to the agencies. You'll see in the response that the agencies' work will be showing a range of activity from the very beginning, identification of a genetic component that contributes to disease or health, all the way through the education of health professionals. That led to what some people might consider, but we don't consider, under- or over-reporting, and I want to tell you what we mean by that and give you some examples. That should prepare you to hear what the agencies are going to present.

I'm not convinced personally that there is really such a thing as over-reporting when we're talking about trying to figure out what is, especially when you get to clinical utility of a genetic test in understanding health and disease. In order to address that point I'm going to use as an example something that I noticed as I was rifling through the NIH box, a study that I recognized from Colorado called the StrongHeart Study. Now, I should say specifically that what was included in NIH's submission was something called StrongHeart IV, which is actually an add-on study to a larger study, but it still makes an important example.

StrongHeart is an extensive study. In some ways it's almost like a Framingham in the Southwest. It's looking at the natural history and factors contributing to cardiovascular disease

in Native American populations. It's a large study recruiting a great many individuals, and without the basis of that large study, it wouldn't be possible to elucidate the contribution of a gene -- for example, ApoE4 -- to the possibility that you might or might not develop cardiovascular disease. Looking at it from the other direction, if you were to design a study to say what is the contribution of ApoE4 to heart disease in the Native American population, you wouldn't be able to answer that question unless you knew things over a long period of time about exercise, diet, cholesterol levels, EKGs, anything to do with weight, everything that you need to know to put that one bit of genetic information in perspective and ask how useful would a test for ApoE4 be in this population compared with another population if I want to predict who might get heart disease and who therefore needs some other intervention.

So the StrongHeart study actually included in this analysis, again it's StrongHeart IV. It's an add-on study. It's a family study. But there are other studies that are included in this analysis that are single studies taking a broad approach to look at a complex disease, and genetics is one part of it. Yet, if you don't look at that broad approach, you cannot answer the question about clinical utility.

In terms of genetic education, it depends on how we define your question. If SACGT is interested in the analytical and clinical validity and utility of a single genetic test for a specific disease, then a project that educates physicians, primary care providers about how to understand and use genetic tests is not directed specifically at the question that you've asked us. On the other hand, without that education, all of the wonderful information about exactly what is the meaning of a test for hemochromatosis is not properly applied.

Similarly, you'll see in CDC's submission a number of very, very important quality controls or quality assurances. Again, that may not be designed to research to find out whether the test for hemochromatosis predicts liver disease, but unless you can also tell whether the test for

hemochromatosis in Lab X in the State of Y is actually accurate, then you don't know whether that test provided by that laboratory has clinical validity and utility, and that's an important project carried out by CDC.

Under-reporting is a little bit harder to get at because it would be hard to know which ones we've missed. This was a massive undertaking and one that we realized after the fact fortunately doesn't change the budgets very much. But if you look at HRSA's submission, I think we all know how important GeneClinics is, and that's supported in part by HRSA, and somehow it didn't make it onto their list. It doesn't change the budget numbers very much, but it's an example of under-reporting. Another example of under-reporting is that using different definitions, NIH really didn't focus on work that they're doing on pharmacogenetics. Not to forget that much of this work, especially work on pharmacogenetics, is done in the private sector anyway. With that, I'll turn it over to the agencies.

DR. McCABE: Thank you very much. Dr. Lanier, AHRQ's report.

DR. LANIER: Good morning. I thought I would take just a minute to tell you a little bit about the agency before getting into the actual report. I think while most of the audience and certainly all the members of the Committee are familiar with AHRQ, there may be some here who actually don't know what the letters stand for, us being one of the newer agencies in the Department of Health and Human Services. AHRQ stands for the Agency for Healthcare Research and Quality, healthcare being spelled as one word. Some of you may be more familiar with us in our former incarnation when we were AHCPR, the Agency for Health Care Policy and Research. At that time we were responsible for developing clinical practice guidelines. We stopped that activity in about 1997, and in December of 1999 we were reauthorized and renamed the Agency for Healthcare Research and Quality, dropping the policy and adding quality, quality measurement and improvement being one of the major important

missions of the agency.

So in the materials that were provided for you, there is actually a printed mission statement from the agency, but I think this is a little bit easier for you to understand exactly what AHRQ does. Our overall mission is to improve the outcomes and quality of healthcare services, to reduce its cost, to address patient safety – and that's become a much more important element of the agency's work over the last year or two -- and finally, to broaden effective services through establishment of a broad base of scientific research and through promotion of improvements in clinical and health systems practices. In more specific terms, what we are trying to do is to provide quality information for improved patient choices within the personal healthcare system. So this distinguishes from a similar goal that you'll see from CDC, but we're focusing mainly on the personal healthcare system. We're very interested in shared clinical decision making in primary care, in research on effectiveness and cost effectiveness of interventions. Since we stopped the support of the development of clinical practice guidelines, we have established evidence-based practice centers, which are 12 centers around the country that are under contract to review all the evidence that's currently available on current topics and summarize that. That could then be the front part of developing a clinical practice guideline should a professional organization or other group want to do that. Finally, translating research into practice.

The reason I've put this up in this way is to help you understand that I think the mission of the agency is very much in sync with the interests of this Committee. I think the relevance of what we do to the potential relevance of this Committee should be pretty obvious, from our sense of wanting to provide information, wanting to help with shared decision making, looking at the outcomes, looking at the quality of care.

However, there are a number of challenges that face the agency. One of those is that there is no

specific authorization or mandate for AHRQ to focus on genetics-related research. If you look in the authorization for AHCPR and then the reauthorization for AHRQ, there is no mention of the word "genetics" and certainly no mention of the word "genetic testing." Consequently, the funding has not been there to do this type of work specifically.

Also, we've had some fairly significant budgetary limitations in our ability to do this work. One of those is that our budget, which began in 1990, was at $98 million. Up until 1995, there was a steady increase in the funding amount, up to about $160 million. That's when we went through what is commonly known as our near-death experience and dropped to $125 million. Since that time, particularly we've taken on the role of quality measurement improvement. Our budget has steadily increased up to the current level of about $300 million. Now, we're very happy to have $300 million, but I would just compare that to some of the other agencies that have anywhere from $4 to $5 billion to, in the case of NIH, over $23 billion to work with. We're thrilled that these agencies have these amounts of money, but we're pretty limited in what we're able to do. Added to that is a concern that we have that the President's fiscal year 2003 request for AHRQ will have a decrease of about $50 million, to $251 million. So it will limit our ability to do research in this area in particular.

Now, one of the things that I want to make clear is that most of the money that comes to AHRQ is directed funds. We're given money for a very specific purpose, and sometimes in great detail told how to spend this money, which is fine and we're happy to do that, but it limits our ability to fund what is known as investigator-initiated research. I'm going to present two projects here very briefly in this last minute or two that we have supported.

But before I do that, I wanted to show you that these were funded here in about 1995, where there was an increase, and the second one was funded in the year 2000, when there was another increase in the budget. Those are the times that we had money for investigator-initiated work,

and these two projects, which are not examples -- this is the totality of what AHRQ has been able to fund in terms of genetics-related research -- the funding occurred during the times of increased funding and when we had more money to spend for investigator-initiated work.

The first of these was an R01 project that we spent a total of about $1.16 million on, to look at the cost effectiveness of screening for hemochromatosis in primary care settings. The objectives were to establish prevalence rates for different age groups, females, and other racial groups, and determine the optimal age for screening and the screening strategy. These were some of the findings of that group. I'd like to point out that the majority of the findings were summarized in a single journal, the Annals of Internal Medicine, December 1st, 1998 edition, which included all of these articles that relate to hemochromatosis. As a result of that, there's been a lot of discussion between CDC. Several of the papers that were in this particular journal came from CDC, and there's been a working group on hemochromatosis that Wylie and Muin may be able to tell you more about.

Finally, this is a project that's just been started. It's an R18, which is a demonstration project at the University of California at San Francisco. The purpose is to develop a computerized tool for assisting pregnant women and their partners in making choices about prenatal diagnostic testing. We have so far spent about $1.18 million but have recently given an administrative supplement to this to expand the scope of the work. Let me stop there.

DR. McCABE: Thank you. Our next report will be from CMS by Ms. Yost.

MS. YOST: Good morning, everyone. In response to the inquiries, I can just give you a very brief summary of CMS' activities. Primarily, CMS' mission and goals are to provide appropriate Medicare and Medicaid payment for its beneficiaries. So in re-reading the revised mission statement that we have, we don't even see the word "quality" at this point in time.

As far as genetic testing research, there is none taking place currently at CMS. There's a question regarding agreements for information sharing. At this point there are no such specific agreements among the agencies responsible for the CLIA program. By the way, my answers will basically reflect CLIA program activities. But there are currently interagency agreements between CDC and CMS and between CMS and FDA for the administration of the CLIA program. So it's a more broad type of arrangement.

As far as the CLIA database, the information is already currently shared with the DLS folks, the CLIA folks at CDC for the purpose of CLIA studies and to work in conjunction with CMS and FDA regarding the oversight of laboratory quality. Information currently collected includes enrollment of the laboratories, CLIA accounting information for user fees, proficiency testing, performance, survey or inspection findings, and certificate information. So it's not specifically for the purposes of clinical validity or utility. However, if future changes in CLIA requirements warrant that additional information sharing be done, we certainly will coordinate with all the relevant agencies.

As far as plans to increase the knowledge of clinical validity, at this point, CLIA, as you know, as I've stated in the past, doesn't really deal directly with clinical validity. However, we felt that it was important that we had more information about the process of analytical validity, and several of our staff and CMS regional office staff attended a recent ASCP workshop regarding analytical validity. We have acquired additional current laboratory literature on that topic. Our plan is to train our entire cadre of surveyors in that area this fiscal year if we do not publish our final QC regulation. That, at this point, is the main priority for our agency for the program. We hope that by training the surveyors, we get two things. We are able to improve our consistency in application of the requirements, as well as then the surveyors in turn can assist the laboratories on a one-on-one basis in improving their ability to demonstrate analytical validity.

CMS routinely works with accrediting organizations, professional organizations and subject experts. Currently we have not had any formal discussions with any of these in regard to genetic testing, but we have had informal discussions with several about possible mechanisms to oversee genetic testing and again provide additional education. There are no formal plans at this date, and really this will depend on what the final CLIA standards for genetic testing are.

On an ongoing basis, CMS and CDC and FDA work on the CLIA administration, and as part of the proposed rule for genetic testing standards, we will review the extent of CLIA's current authority for clinical validity with our general counsel.

We have had preliminary discussions over the years, really since the inception of SACGT, with all three agencies to ensure that the roles of each of the agencies are coordinated, since they do somewhat overlap.

Additionally, on the topic of providing technical assistance, which was a request of this Committee, we have drafted plans to provide technical assistance regarding CLIA compliance, and specifically analytical validity if necessary, for newly enrolled genetic testing laboratories. Many times these laboratories can use existing procedures and mechanisms that they already have in place for their research to be able to meet CLIA requirements, particularly in the area of quality control and quality assurance. Part of any and all implementation process for any new CLIA genetic testing standards will include public and laboratory education about the standards and how to meet them. Pretty straightforward.

DR. McCABE: Thank you. Our next report is from Dr. Gutman on FDA.

DR. GUTMAN: Good morning. FDA, as you all know, is primarily a regulatory agency and is not viewed appropriately as a research-focused interest, although we do have research going on

to support our regulatory programs. We certainly have standard development going on to support our regulatory programs, and we have educational efforts to support our regulatory programs.

The regulatory program that I've outlined for you, that Dr. Feigal has outlined for you on two or more occasions, is currently the subject of lively discussion within the agency at relatively high levels, and I'm not able to share with you exactly the direction it is going or will go, but I certainly can provide a little bit of information about what I would view as a small amount of background activity in support of genetics work.

In terms of standard setting, Dr. Hackett, who is in the audience, has been the star of the show, and actually I'm disappointed that it didn't pop up, probably because we don't actually officially fund our pharmacogenomics activity. But Joe has led our pharmacogenomics initiative with the notion that microarray technology and chip technology particularly in this area, with or without home brews, will be knocking at our door. In light of that, he has taken what is a standing institution, the Center for Devices College for educating reviewers on how to handle cutting-edge technology, and he has extrapolated that program to a DCLD, a division-specific educational effort, and at no cost to the agency he has invited two or three dozen outside scientists to come in and talk to us about ideas, plans, problems, and even manufacturing concerns in genetic technology particularly related to microarrays and pharmacogenomics. He has crafted a pharmacogenomics working roundtable. So we meet with external players. We met a couple of times in part in educational pursuits, and in part to develop a draft guidance on the use of clinical literature in support of genetic testing. I do know that we've learned from that enterprise. I don't know that it will actually officially become guidance or that we might not merge that guidance into the instructions for use of our template. But it's been a lively and interesting process. Although Joe spends a lot of time on staff support time, there are a lot of outside drug and device companies that are involved in this enterprise, and I don't have cost

figures to associate with it.

We do have a small amount of background activity in the center in the Office of Science and Technology, which is unique among research endeavors for a government agency in that there is no aim – well, there is some, but no real aim for fame and glory, but the notion that there might be some pedestrian research that needs to be done specifically to support review processes that nobody else is going to want to do, that academics aren't going to want to do and that perhaps industry might, for various reasons, not want to do. So there is a research arm. Right now there is relatively little project activity there. There are two microarray projects, one related to TB -- that might not be of interest to you who are interested in human genetic testing; it's very interesting to us, since we expect to see genetic tests to detect TB – and one related to latex sensitivity. Both have the potential for standards, the potential for review support, and the potential for looking at things like manufacturing issues that perhaps nobody else will look at. The total funding for that is in the neighborhood of a half a million dollars. It happens at this point to, oddly enough, be external funding, representing the liberalization in our funding capacities.

There is also a small amount of corollary research being done at the National Center for Toxicological Research in Arkansas, and I won't go into that, but it is of interest. It's pharmacogenomics and toxicology linked, and there's a demonstration project being carried out by our statisticians to at least approach data analysis as products come in. Thank you.

DR. McCABE: Thank you. Next we'll hear from Dr. Khoury with the CDC report. I'd ask each of the remaining speakers to try to be as concise as possible, because we're beginning to fall behind on what is an incredibly full schedule for these two days.

DR. KHOURY: Good morning. I'd like to give you a brief overview of what CDC does. We

are known as the nation's prevention agency, and as the name implies, we try to put scientific discoveries into action in the real world. This is sort of where the rubber meets the road for scientific discoveries. As we do this, we're a mixture of service and science. So we apply the population sciences that come to bear on health policy and practice, including epidemiology and surveillance, which is a fundamental tool of public health, but in addition to many other disciplines like lab and economics, et cetera. We are intimately involved with the public health infrastructure and preparedness, not only to deal with anthrax and bioterrorism but also to deal with preventive health services and healthcare in general, and we are also about information that improves health and prevents disease. So we translate a lot of information.

As we do this, as you can see from the presentations of the other speakers, we are about partnerships, because every single thing we do at CDC involves partnerships with other Federal agencies and other groups.

So when it comes to genetics, really the mission is rather simple. The agency developed a strategic plan a few years ago, and what we're trying to do is put gene discoveries in science into action in the real world. So it's not enough to find a gene that is associated with Disease X, but what do you do with it in a certain community.

Again, the same run-down on the mixture of science and service, the population sciences that assess the impact of genetic variation on health, and the use of genetic information in improving health. We spend quite a bit of time and energy on the quality of testing, and I like what Carol said before about that, and I'll come to that in just a minute. As we do this, we spend quite a bit of time integrating genetics into public health capacity, like we do in other areas, including training of the public health workforce. We do the same in communications and information dissemination.

I want to give you a flavor of what the agency has done over the last few years. We do both intramural and extramural research. We've given you what is done mostly on the extramural side in terms of the money that goes out the door, but we have a cadre of well-trained people that provide technical assistance to a large number of organizations and groups. We do both primary and secondary research, and we also do information synthesis or meta-analyses, things of that sort. We cover the spectrum of disease, from single-gene disorders to complex diseases.

Just to put the collaborations in perspective, and since we are here about HHS, I'd like to highlight some of those. But really our primary consumers are state and local public health, because this is where the action is in terms of the delivery of health services and prevention. We also work with academia, consumers and industry. Just to give you a flavor of the kinds of things we've done with our sister agencies over the last few years, we co-sponsored national conferences on genetics and public health, about three of them with HRSA and NIH. We worked with HRSA and NIH on disease-specific workshops. You heard a bit about hemochromatosis earlier. We also do a lot of methods development, and also lab quality workshops.

Just to give you a couple of examples of projects and their scope, let's take cystic fibrosis. In order to evaluate the clinical utility of newborn screening for cystic fibrosis, we wanted to evaluate the impact of early diagnosis in the newborn on pulmonary function and infection in the long run. So we collaborated in this case with the Cystic Fibrosis Foundation, which has a national registry, with secondary analysis that led to a couple of important papers that do not show that early diagnosis makes a difference as far as pulmonary function or rate of pseudomonas acquisition at age 10.

Another project which was recently finished is the maternal PKU project, which was done in technical assistance with three states -- Massachusetts, North Carolina, and Georgia -- and the

idea there was to identify barriers to successful control of blood phenylalanine level among childbearing women and suggest methods to overcome such barriers.

So this is the form of some of our investigations. We work with states and provide technical assistance. We did the same with sickle cell disease. We funded, through cooperative agreements, three states – California, Illinois, and New York -- to evaluate the real-world effectiveness and outcomes of infants with sickle cell disease ascertained through newborn screening.

I just wanted to give you a flavor, and I don't consider this to be an over-reporting because we have two lab entities that deal with lab quality assurance, the Newborn Screening Quality Assurance Program that many of you are familiar with that has been in existence for the last 20-plus years that provides proficiency testing, training, consultation, et cetera, to many labs around the world, especially our own labs at the state level.

The PHPPO group, a division of laboratory systems, which is otherwise known for their CLIA efforts, is also doing other things to assure the quality of genetic testing, training, quality assurance, materials standards, and then looking at medical genetic test reports.

Just a couple of words about complex diseases. You heard a bit about hemochromatosis. I just wanted to give you a feel for the kind of work we do there, the population-based research, the prevalence of the mutations in the U.S. population. There was a national sample that was recently published. The assessment of the burden of disease, which we did through mortality analysis, through death certificates and hospitalization data; the penetrance of the genotype initially through meta-analyses of existing literature; and we were the initial funders of the Kaiser study that was further funded by NIH. Then the validity and utility of tests through expert panels. We're also funding Type I diabetes projects through a grant to look at the utility of the use of newborn blood spots in Washington State, to look at the validity of testing for

Type I diabetes susceptibility.

Last but not least, we have funded a model approach for evaluating data on genetic tests, the so-called ACCE project that you heard about from Jim Haddow from the Foundation for Blood Research earlier, I guess last time, so I won't tell you too much about that.

Our recent endeavor is the beginning of funding of centers for genomics and public health, which are three schools of public health – the University of Michigan, the University of Washington, and the University of North Carolina -- to conduct three things: knowledge-based development, which is pertinent to what we're doing here; training and technical assistance with a major focus on chronic disease -- cancer, cardiovascular, asthma, and diabetes. What these centers will be doing -- they just started their work -- is a synthesis and dissemination of information on genetic variation and genetic tests for use in health policy and practice for these chronic diseases; and, of course, the identification of gaps for further research.

In terms of information dissemination, we do a lot. This is the homepage for our Website. I don't have time to go through the various parts of it, from the human genome epidemiology database I talked to you about earlier, to all kinds of information that you see on it.

So I just want to leave you with some parting thoughts here, because as I was preparing my talk here, I wanted to remember what SACGT asked us to do. After two or three years of deliberations, you have identified three processes for HHS to act on to improve the oversight and the quality of testing. One is an FDA process, which has taken on a life of its own; a CLIA process, which is taking a life of its own; and this so-called postmarket data collection effort. As you can see from all of our presentations this morning, this is truly a multi-agency effort. We see the CDC's role in this multi-agency effort as providing the population-level information before and after marketing of the genetic test. So when we talk at the end of the day about

genetic information in the real world, this is what CDC is about. In order to do this, partnerships are very crucial. As I said, most of these projects involve partnerships with other agencies and with the state public health infrastructure. Therefore, we need an interagency coordination for this. Thank you.

DR. McCABE: Thank you. Our next report is from Dr. Puryear on HRSA.

DR. LLOYD-PURYEAR: Good morning. The mission of our agency is listed here, and you have our vision in your handouts. But our agency is focused on assuring quality healthcare to underserved families and individuals nationwide. We've come to be known as the access agency, moving towards 100 percent access to healthcare and 0 percent health disparities for all Americans. We have four bureaus and a few offices and centers in the agency. The bureaus that are highlighted are the ones that contributed to this report. The HIV/AIDS Bureau and the Bureau of Primary Healthcare did not identify any genetics projects.

This is just to interject a little bit of humor. It says, "What will we ever think about now that the Genome Project is almost complete?" In actuality, we'll probably never stop talking about the Genome Project, just to reassure NIH, because it seems like all the other agencies that are here are asking for more money. I think it's a two-step process of continuing on with the research, but also engaging in conversations and concrete actions for the translation of that research.

Our agency has divided the translation process into four different areas. The relevant areas here are, again, highlighted. But our agency also has the only Federally funded and legislatively mandated genetics services program in the Public Health Service, and this has focused historically on -- again because of our legislation – public health infrastructure for genetics and newborn screening. Newborn screening is an integral part of that legislation. We

have also had programs to look at the financial, ethical and legal social implications of new technology, again within newborn screening programs. We have limited our focus to that.

We have looked at genetics education and defining the educational needs for health professionals and the public at large. We also have a particular focus on integrating genetics services into comprehensive systems of care, and historically, again because of legislation, we have focused on sickle cell disease, thalassemia and hemophilia. Of course, our programs are geared, especially over the past four years, to bring national leadership to expand and enhance genetics services for the entire population, beyond the traditional concept of the maternal and child health program. Our educational programs have been done in collaboration, in general, with the Bureau of Health Professions. Both the Bureau of Health Professions and the Maternal and Child Health Bureau have programs for funding education and training. Our projects are listed here relevant to the SACGT request. As you can see, most of our effort has been in the area of information dissemination and information development. The funding is categorized here. Again, most of the funding goes for information dissemination and information development.

We've had a few projects with primary research and secondary analysis looking at generally clinical utility and clinical validity. Again, these have been focused around newborn screening programs. We have two projects that are developing mutation analysis panels for cystic fibrosis and hemoglobinopathies in a multi-ethnic population for use in newborn screening panels. We contributed to the NIH consensus development conference for PKU, which we also supported with secondary analysis, a meta-analysis looking at health outcomes. But our primary effort has been with the evaluation of tandem mass spectrometry in the newborn screening programs. We have right now two multi-state grants to develop models to evaluate the clinical utility and validity of that technology in newborn screening programs. The main states that they're with are California and New York, but each of those states are collaborating

with surrounding states. We also have a contract with the American College of Medical Genetics to develop guidelines for newborn screening programs. A part of that effort will be using secondary analysis to again look at the clinical utility and validity of the testing technologies that are used in those newborn screening programs.

Information development has focused on faculty development, curriculum development, continuing education, and graduate and undergraduate education. Again, our bureaus interpreted the SACGT's request broadly. We feel that in order to use testing technology appropriately, you're going to need a well-informed healthcare workforce and public health workforce that understands the concepts of clinical utility and validity.

Listed here are some of the projects that we have sponsored. As you can see, some of these are in collaboration with other Federal agencies. Our dissemination, again, we interpreted this broadly. We think genetics education goes beyond the healthcare workforce. We think you need a well-informed public that understands the concepts of clinical utility and validity. So we have workshops to engage education leaders, workshops to engage consumer advocates, and we're in the process of developing a community engagement program.

These have been some of the projects that we have sponsored. We were an early funder of the Genetic Alliance and will continue to be. We have sponsored with the March of Dimes the Genetic Education Needs Evaluation Project, which will be a community engagement project. We hope to collaborate with NIH's Hap Map Project on that, and we're developing with NIH sponsorship of the National Coalition for Health Professional Education in Genetics. We are also sponsoring GeneTests/GeneClinics, and this is actually I think an interesting example of the cross-collaboration between federal agencies.

GeneClinics began with early funding of ours, and GeneTests was funded by NIH and the

National Library of Medicine. Those two projects have now merged, and we're using the GeneTests/GeneClinics project for two of our primary care projects. Genetics and Primary Care is using that site for an interaction and also as a resource, and Looking at Genetics Through a Primary Care Lens is also using that site both as a resource and a communication vehicle. We've also held with other Federal agencies and ASTHO and NCSL several legislative genetics policy forums to educate state legislators and executive health officials on genetics and newborn screening.

Partnerships. As you can see from our presentation, partnerships are very valued by HRSA. Most of our work has been done in partnership with other Federal agencies. To illustrate our concept of how this translates out, we've had several projects that I think are important to mention under this partnership. One is a memorandum of understanding with AHRQ, CDC, NIH and HRSA. There have been several items that have come out of that partnership. CDC mentioned the national conferences. We've sponsored the Genetics and Primary Care Project with two other Federal agencies, the workforce analysis, the need for both the genetics workforce and a workforce that's educated in genetics with NIH.

I mentioned the NCHPEG sponsorship and GeneTests/GeneClinics, but we've also recently instituted another memorandum of understanding for the implementation of Title 26, which is a new act entitled Heritable Disorders for Infants and Children. That will, again, engage four agencies -- AHRQ, NIH, CDC and HRSA -- in collaboration.

We also value our public partnerships, and the majority of these have been with Genetic Alliance and March of Dimes. Again, the focus of these has been both genetics and newborn screening.

SACGT wanted to know what our plans were for the future. The most relevant in the HRSA

preview for this fiscal year are the funding of a genetics consumer organization, and again those grants to look at models to evaluate clinical utility and validity of genetic tests and technologies in newborn screening programs.

But I think from the five agencies that have presented so far, if you look at the advancement of research that's illustrated by this slide with the need for educating health professionals, the need for developing evidence-based medicine, the need for strengthening our public health programs and healthcare delivery systems, there's a huge gap. Some of the items that we've been discussing with other Federal agencies are looking at the notion of developing mini-fellowships for healthcare professionals in genetics, not to produce geneticists but to increase genetics practice knowledge for healthcare providers and public health professionals; looking at the development of a clinical network to do evidence-based medicine; and other projects in newborn screening specifically.

DR. McCABE: Thank you. Our next report is from Dr. Collins about NIH.

DR. COLLINS: Well, thank you. Good morning. Mindful of the fact that the time is quite constrained, I'm going to do this rather briefly. Even though the information that's covered in this analysis is truly mountainous, occupying several cardboard boxes worth of abstracts, you see here and I hope you have a copy of these slides that were placed on the table at the beginning of the morning. I will go through them quickly.

The NIH mission I think is familiar to virtually everyone. It is primarily to support and conduct basic and clinical biomedical research, and hence the analysis that we carried out, revealed primarily in studies that are in this particular category; although, as I'll come to, it is also the case that NIH does carry out quite a lot of research that's relevant to other issues such as clinical utility.

The process that was followed to do this very large undertaking was to utilize the system called the Computer Retrieval of Information on Scientific Projects, colloquially known as CRISP. CRISP is a computerized fashion that allows you to search the very large NIH grant database using a variety of key terms, but you have to be fairly clever about how you define the terms so that you get what you want instead of what you don't want. Some considerable effort was put into doing that search. That then yielded up a very large number of projects which were distributed out to the individual NIH institutes for them to review, asking them to look at the list and make certain that each of the projects on the list in fact fell into the request that SACGT had placed, and also to find out whether there were things not on the list that should have been. Just the same, given the volume of information, I'm sure there are examples of things that should have been picked up and were not, and vice-versa, there were probably things on this list that didn't entirely belong. But I think, in general, it gives a pretty good snapshot of what this very large research enterprise has been doing.

Relevant to Dr. Greene's remarks at the beginning about under- and over-calling, we did not try to include studies that were primarily involved with gene hunting, and there would have been a huge number of those if they had been included. Rather, we assumed that what SACGT was interested in were studies, once a gene variant had been found, to see what its phenotypic consequences might be. In that regard, pharmacogenetics studies that were aiming to uncover a variant associated with drug response we did not try to include, and that may account for, in part, why some of the pharmacogenetics studies at NIH did not make the list. I think, though, your comments about StrongHeart are well taken, and that's why it was on the list, because we think we learn a lot from those large-scale epidemiological studies about genotype-phenotype correlations, which is, after all, another way of determining what exactly is clinical validity.

So with that background, I can show you what the basic summary is of the amounts of dollars that have been spent in these various categories. This is over 1996 to 2000. It will not surprise

you that the primary place where the funds have been spent is in what we would call primary research, using SACGT's definitions. But even though these bars down below seem small in comparison, as I'll show you in a minute, it still represents the majority of the research that's going on in these other areas within the Department as well. You can see that the rate of growth in primary research and, in fact, in all these categories has been considerable and greater than the rate of growth of the NIH budget overall. So there is a shift of interest into this area that has been occurring over the last five years because of the exciting scientific opportunities that exist there.

I could have chosen a whole long list of examples here, and these are just a few. In primary research, for instance, one finds studies on Alzheimer's disease that the Aging Institute is carrying out, looking at genetic epidemiology and the correlation with presenilin and ApoE mutations. Secondary analyses would include things such as ELSI studies about the diffusion of genetic tests, which we considered as responsive to the request. There are lots of things going on in various institutes about information development. Here's an example from the NCI. There are many other examples that could have been put here. In information dissemination, you've already heard about GeneTests and GeneClinics, which is also, as you heard, contributed to by HRSA as another example of another way in which we are working with other HHS agencies.

Along those lines, hemochromatosis seems to have been a favorite topic for everybody so far this morning, and I will also mention that because I think it is a very good example of the way in which a lot of research is going on in a vigorous way in a circumstance where we do have a genetic test that is being considered for broad application. I think it's fair to say that the agencies have not failed to notice that, and NIH in particular is very deeply involved in studies to try to identify what the value would be of population screening of this common disorder, which is also a treatable disorder.

Again to remind you of what you've already heard, this began in part, the current phase, with a large discussion in 1997, shortly after the gene was identified, to explore the implications of that, and basically the conclusion was that a lot more research would be necessary before beginning something like large-scale population screening. We were grateful for the studies carried out by AHRQ and by CDC that have provided useful information in terms of the frequency of mutations and some notion about their penetrance, and NHLBI and NHGRI are now collaborating in a $30 million five-year study to try to discern, in a much more rigorous way, what exactly is the penetrance of the common mutations and what is the relative value of biochemical versus genetic testing. That has already now enrolled some 40,000 patients in its first year.

Another example of collaboration in the education department -- obviously, that's also been brought up, but I won't dwell on it. But certainly the National Coalition for Health Professional Education in Genetics is a major undertaking, and the collaboration here between NIH and HRSA I think is working out extremely well.

In that regard, I would say that as we talk about collaborations between agencies, the experience that I would point to would indicate that primarily these things have worked well when there's a specific project upon which a collaboration can be built. The notion of trying to have large, overarching, heavy-handed bureaucratic collaborations, as you can tell from the way I just described it, is somewhat less appealing. I think, in fact, these things work best when those involved are close to the action and there's a specific goal in mind. Having said that, I think it's noteworthy that there is this MOU between several of the agencies that Michele already mentioned which indicates our strong intention to collaborate with each other at every opportunity where that can arise.

Not to over-emphasize the 800-pound gorilla aspect of NIH here, I just thought I would quickly

show you, and Carol will go through this table with numbers in it, but just to emphasize that it doesn't surprise you, I don't think, when you look at primary research that NIH is by far the largest contributor to that. But when you look at secondary analysis, that is still the case even though the total dollar figure here is massively less than the one I just showed you. When you go to information development, it is still the case that NIH is contributing something over three-quarters of that, and for information dissemination something like two-thirds. So while primary research is, in fact, the place that NIH is carrying out its most major activities, we have significant investments in these other areas as well.

I would just like to finish by saying as far as the future, I think by talking to other institute directors, as I do on a very regular basis, there is very strong interest at NIH in supporting research studies that look at genetic testing, and that will apply I suspect to the postmarket interval as well. It should not be assumed that NIH is disinterested in that at all. There will be lots of research opportunities there that the various institutes will want to invest in, I'm sure.

Finally, I'd like to complete by thanking Karen Hajos in particular, who has worked for months and months since this request was first put out to try to collect all of this data from the various NIH institutes, under the able guidance of Kathy Hudson. Thank you.

DR. McCABE: Thank you very much. We do appreciate all the work that all the agencies have had to do to put this together for us. We feel that it is useful as we begin to plan on how we should move forward.

What we're going to do is I'm going to ask for burning questions, really burning questions from the Committee to any of the agencies, and then we're going to take a break and look at our schedule following the break, a very brief break. Yes, please, Reed.

DR. TUCKSON: Actually, a question to you. When do we talk about the implications of what we've heard?

DR. McCABE: We're going to try to make time for that later this morning.

DR. TUCKSON: All right. Then I'll wait until then.

DR. BURKE: I have a specific question to Francis. You made the point, which seems like a really important one, that collaboration between agencies works best with specific goals in mind. That makes a lot of sense. My question is how do those specific goals get identified? You showed a very interesting process for the hemochromatosis of NIH and CDC coming together, having a conference, out of that some clarity about the research agenda that led to a different collaboration between two NIH agencies for a large study. Is there something there that represents a model process that we can learn from in terms of identifying what the really important goals are?

DR. COLLINS: Yes. I think, in that instance, this was all driven by scientific opportunity and public health opportunity, and by the folks in those agencies with that specific expertise and information knowing each other, getting in touch with each other, agreeing that we have a shared need here and let's put together an initial conference effort, drawing in all the expertise that can be identified, then out of that come up with some goals, divide up what needs to happen next and assign it appropriately. I think that is a very good model. I didn't mean to be so negative perhaps about overarching interagency working groups, but if they become heavy-handed, or even if they become a bit nonfunctional, they may actually slow down the process, because everybody will say, oh, they should be taking care of that, and it may result in the people who are sort of the grassroots, close to the scientific opportunities, being more inhibited in being able to carry out the more productive kind of interagency collaborations than they

otherwise would.

DR. BURKE: But if I could just follow up, it does sound like that means that thought needs to be paid attention as to how that good interactive communication that lets the ideas bubble up should happen.

DR. COLLINS: Yes, I agree with that 100 percent. My comments were related to whether we should jump at the idea of having a high-level interagency coordinating committee as the right way to do this. I'm fond of a quotation that says that a committee is a cul-de-sac down which good ideas are lured and quietly strangled.

DR. KHOURY: Yes, I just wanted to second what Francis said. I think the hemochromatosis example is a good one. It came from the bottom-up, sort of from the staff who were simultaneously looking at public health issues and the gene discovery issues, which led to this collaboration.

I just wanted to follow up with Wylie. I don't know how many other hemochromatosis type examples we could be missing, and that's the issue that this Committee has to wrestle with, because many of these gene discoveries that are coming down the pike have public health implications, and if we have a good, successful model for collaboration, I think we need to capitalize on it and see how we can drive the other types, the other hemochromatosis, because the staff may not always be there to have that kind of interaction. We need to push it and nurture it somehow.

DR. McCABE: I'm going to make one final comment, and then we do have an hour later to discuss this. But it also was obvious to me, as everyone was going through the presentations and discussing partnerships, the MOU, that it does seem that while we would hate to be heavy-

handed, that there is some value in coordination of these partnerships, and that may be something we would wish to discuss during our period of open discussion later.

As many of you have heard me say wearing my other hat, we do a very good job of primary research, and even secondary research. But the true translation of that research into ways that will impact on the public's health I think is something that has fallen through the cracks frequently, and it's a general problem not only in genetics but, since we are given the focus of genetics in our discussions and deliberations, we can look to that later today and see how one could do it without stifling new idea development.

So with that, let's take a 10-minute break. We will resume shortly before 10:30, actually. I want to be sure we're in place at 10:30 when Dr. Slater joins us. Thank you.

(Recess.)

DR. McCABE: Let's get started, please. We're delighted to be joined this morning by Dr. Eve Slater, the Department's new Assistant Secretary for Health. As you know, according to the provisions of our charter, recommendations of this Committee are transmitted to the Secretary through the Assistant Secretary for Health. As a conveyor of our reports, Dr. Slater has a critical role in relation to the work of our Committee. As you would imagine, Dr. Slater brings an impressive set of credentials to her new post. Prior to her nomination last October, Dr. Slater was senior vice president of external policy and vice president of corporate public affairs at Merck Research Laboratories. Her career at Merck began in 1983 as a senior director of biochemical endocrinology. Over the next two decades she took on more and more responsibility, heading up divisions of regulatory affairs and clinical and regulatory development. She supervised worldwide regulatory activities for all Merck medicines and vaccines, which included responsibilities for FDA and international liaisons, all IND and NDA

submissions, product labeling, quality assurance, and postmarket surveillance. A long list of important new drugs and vaccines were licensed during her tenure in regulatory affairs, including Crixivan for HIV infection, which won FDA approval in 42 days, which must be some kind of a record.

DR. SLATER: Close to a record.

DR. McCABE: While at Merck, Dr. Slater also managed new editions of the Merck Manual, was responsible for over-the-counter clinical development programs, and served on a number of important boards and advisory groups, including several dedicated to advancing globalization of regulatory standards. Dr. Slater received her medical degree from the College of Physicians and Surgeons at Columbia University and completed residencies at the Massachusetts General Hospital. She is board certified in both internal medicine and cardiology. Following medical training, Dr. Slater served as chief of the hypertension unit at MGH and was on the faculty at Harvard Medical School. During this period she taught extensively, was active in patient care, and directed laboratory research funded by NIH. Dr. Slater, thank you very much for being with us today.

DR. SLATER: Dr. McCabe, thank you. Thank you very much. The one small omission in my resume that you neglected, actually, was that in the course of my duties, I logged many hours at this Bethesda Marriott Hotel, coming down for innumerable meetings to accomplish our goals. So it's a pleasure to be back, actually, and a pleasure to be here.

I bring greetings and apologies from both Secretary Thompson and the Deputy Secretary. As I've learned, the government way is to be booked to about three or four obligations that are concurrent at any given time, and they are at the moment testifying on the global AIDS program on the Hill, and then subsequently the Secretary is testifying on the proposed budget for

bioterrorism later on this afternoon. So they are busy but send their regards. They have also made it very clear to me that the deliberations and recommendations of this Committee are really extraordinarily important to them as they formulate their plans and their policies, and I wish to certainly endorse that, reaffirm that, and make myself as available to you as possible for both the learning and the understanding that I know you're going to provide us, and also to help in implementing the recommendations that the Committee develops.

It's a little bittersweet for me, because I would like nothing more than to stay for the day and learn about the interesting things you're doing, but apologies on my part. I have to go back.

In any event, what I'd like to do is recognize the accomplishments of the Committee that I have already learned in reading some of the briefing books that Susan has provided. But basically, you have already made a number of important recommendations to us. First, the need for Federal legislation to prohibit genetic discrimination, which is, of course, kind of the first principle of the recommendations that you make. Secondly, the adequacy of oversight for genetic testing. Having been in charge of quality assurance and pharmacovigilance for years, I know how important that is. The challenge of developing a classification methodology for genetic tests; the impact of patents and licensing practices, which I'm sure many of you have had quite a bit of experience on; and then also the need to clarify when third parties have become subjects and when their informed consent can be waived.

Your work on the oversight of genetic tests has been significant. Your recommendations on this issue were based on a careful review of the current oversight system and a consideration of public perspectives garnered through a broad-based outreach effort. You considered a range of possible oversight approaches before recommending the application of FDA regulations to home-brew tests, and even then you were careful to urge that a new paradigm for regulation be formulated to ensure the safe use of genetic tests without hampering their development and

application, which is the fine edge that always obviously has to be navigated. You recommended that the Clinical Laboratory Improvement Act regulations be augmented to provide specific requirements for quality assurance if a laboratory is conducting genetic tests, and I'm aware that CDC and CMS both are moving forward on the promulgation of a regulatory proposal to enhance the CLIA coverage of genetic testing laboratories. Finally, you pointed to a need for postmarket data collection, analysis and dissemination about the validity and utility of genetic tests, and all of these are very important recommendations, enhancing the safety and appropriate use and application.

Current projects, I'm aware of those. Just to iterate some of those -- it's not an all-inclusive list, but your education conference in May to assist the status of efforts to enhance genetics education for health professionals; a draft report on informed consent for genetic tests; a brochure to provide basic questions and answers for the general public; a study of issues related to rare diseases, including the need for common definitions of those; and a white paper on billing and reimbursement for patient education and counseling services for genetic testing.

I know that you're also planning to address how advances in genetics and healthcare disparities may affect access to genetic testing services, and tomorrow you will be exploring some challenging questions about how population data on race and ethnicity are collected, analyzed, and reported in genetic research and genetic testing.

These are weighty matters, and I want to commend you for taking them up and certainly reaffirm my, the Deputy Secretary and Secretary Thompson's willingness to be accessible to you and to be as helpful to you in implementation as we possibly can be.

We're going to be actually retiring a few members of the Committee in a moment who have served above and beyond their call of duty, I guess an extra year of service, and I want to

certainly thank Dr. McCabe for his service, his chair. In fact, he's going to be serving some additional time with us, which is really wonderful.

Before I proceed with the recognition and the certificates, I did want to just remind you of one of my favorite quotations that comes from one of Stephen Ambrose's pieces, and this is the one on undaunted courage regarding the Lewis and Clark expedition. There's a fascinating quote in one of the early chapters, as President Jefferson and his aide, Meriwether Lewis, were trying to plan this expedition. Lewis was clearly this burgeoning naturalist scientist, as was Jefferson, and apparently they would sit at dinner in whatever place in Washington they would and discuss how this expedition was going to proceed, and Jefferson said, you know, we've been a nation 25 years, and think how much we have accomplished. I find that to be just a very poignant reminder that, just think, 25 years ago -- I hate to confess when I had just finished my medical training -- we had no vision really of what you all would be discussing now 25 years hence. Even more amazing is the thought of what genetic testing will be 25 years from now. It's actually a rather thrilling but similarly daunting concept. So if we measure our pace by maybe not so much 25 years but 5-year increments, I thank you very much for the wisdom that you're conveying, the openness of your discussion, and I look forward to reading and working with you as you proceed. Shall we present the awards?

I guess Pat Barr is not here, but I want to recognize Pat. She brought critical and important insights and perspectives to the work of the Committee. She served as a bridge between the Committee and the NIH/DOE Task Force on Genetic Testing, and made especially important contributions to the Committee's work on oversight and informed consent. She will be receiving her certificate in absentia, I guess.

Kate Beardsley. Is Kate --

DR. BEARDSLEY: I'm here.

DR. SLATER: There you go, Kate. We can go up to the podium and do this. Kate is being recognized for her expertise in health law, knowledge of FDA device regulations, and she helped to lead and shape the Committee's review on oversight issues and made critical contributions to the Work Group on Informed Consent. So we've appreciated your service enormously and we wish you the best. Thank you very much, Kate.

(Applause.)

DR. BEARDSLEY: Thank you.

DR. SLATER: Ann Boldt, on behalf of the Secretary, thank you for your work and commitment to the Committee. As a genetic counselor on the front lines of clinical practice, you have brought forward issues relevant to the genetic education and counseling providers. You made the Committee more aware of the complexities of communicating genetic information to patients and families and the impact genetic knowledge can have on health and life decisions. We've appreciated your service enormously and wish you the best. Thank you, Ann.

(Applause.)

DR. SLATER: Barbara Koenig. Again, on behalf of the Secretary, thank you for your work and commitment to the Committee. You have brought to the Committee the insights and critical thinking skills of a social scientist and helped raise awareness of the social implications of genetic technology. Your leadership of the Committee's Informed Consent Work Group has been enormously valuable, and I know the group has produced draft guidelines for informed

consent for tests in clinical and public health settings that the committee will be reviewing tomorrow. Such draft guidelines on informed consent for clinical and public health genetic tests will be an important contribution. We've appreciated your service enormously and wish you the best, and we look forward to your future work.

DR. KOENIG: Thank you.

(Applause.)

DR. SLATER: And, Dr. McCabe, congratulations on your reappointment.

DR. McCABE: Thank you very much. I know you have to leave.

DR. SLATER: With regrets. We'll do our best to try to get me here. When is your next meeting?

DR. McCABE: In May.

DR. SLATER: In May, okay. I'll do my best to keep my schedule open for the next one. But thank you very much, and thank you all.

(Applause.)

DR. McCABE: We really do appreciate Dr. Slater taking time from her extremely busy schedule to be with us today, and we've appreciated the opportunity to serve with her, and we're looking forward to briefing her in the future. We're invited to do so during the break, so that will be also an important event for this Committee.

We now move on to begin to discuss our assessment of the adequacy of the scope and level of current activities. We need to determine whether gaps or unnecessary overlaps exist, whether additional efforts are warranted, how well the current efforts are being coordinated, and what, if any, recommendations should be made to the Secretary.

Before we move on to that, we're going to finish up this morning and have Carol give some discussion, some wrap-up from this morning's events.

DR. GREENE: Thank you. There were 1,068 projects identified in the survey. Of them, as you can see, a majority were disease specific. I should say that those disease-specific studies were the ones that, in some interpretation, most directly address the question of analytical and clinical utility and validity for a genetic test for a condition. The non-disease topics included things that you've heard about from the agencies -- education, technology development, quality assurance, gene protein-specific interactions, which are essential to the process, viewed broadly.

I want to point out that 184 of these diseases and conditions that were listed, very specific ones, of that 700-some-odd, there were 184 conditions and diseases. Of those, 45 have tests that are listed on GeneClinics, and it's very interesting to note that while there were a few traditional diseases, sort of single-gene diseases funded, there were a handful for hereditary hemochromatosis, as you've heard, and the top five conditions that were funded were all cancer.

Types of projects break down into general -- I'll just tell you what the abbreviations are. The first is general studies. Those were studies in which the word "genetics" was not included in the title of the project, and you've heard examples of those. They might be the natural history of diabetes and include an emphasis on looking at genetic factors to see how they contribute. Genetic studies includes in the title words such as "identifying genes for" or "the genetic

epidemiology of" or "the genetic basis of." The next category is genotype-phenotype studies and structure-function analysis. The next stands for technology and testing development, projects to develop new tests or technologies. Then treatment and therapy or outcomes projects, projects that are studying treatments or therapies for genetic diseases, following patients, looking at outcomes. That's relevant, of course, to clinical utility. Cost effectiveness. The title speaks for itself, as does ELSI. The next one, 12 studies were specifically looking at tools for informed consent, two studies specifically on access, then quality assurance and more generally focused education.

As Dr. Collins said, this is the slide you were expecting. There was a total of 1,068 topics. The vast majority are from NIH, and the vast majority are primary research. If you want to see that later, we can come back to that one, but I want to show you how the funding breaks down. It's in the books.

DR. McCABE: I think it's impressive to look at the volumes of books on the table back there. Those are the abstracts that were accumulated by the NIH staff.

DR. GREENE: It's fairly impressive. The funding, of course, tends to follow the number of projects. Again, I should remind you, as I told you earlier, that some of the projects from FDA and from HRSA, we chose whether they would be listed as primary, secondary, informational development. Justifiably, some of the HRSA projects were listed as, for example, primary research and also information development and information dissemination. But in order to build a table, we had to choose one. The same is true for funding.

As you can see if you look at the funding, again the vast majority of the funding is from NIH. This is again looking over five years. I should also point out that FDA, CDC and HRSA all reported, in addition to their projects from 1996 through 2000, those three agencies also

reported some projects that were funded in 2001. That doesn't make a significant change in the budget because they were relatively small contributors to the overall budget, but it does change the numbers a little bit.

I should tell you that in the primary research category, 937 projects. That averages out to a little more than $1 million per project. In the secondary research category there are 42 projects, for a total of about $30.5 million. That's about $700,000 per project. Information development category, 32 projects, $28.4 million, about $875,000 per project, and information dissemination, 57 projects, $56 million, approximately $1 million per project.

Project funding over time, another look at the same thing. If you look at the primary research, that's in blue. It is going up, as many of us think it should, because of the increasing interest in the power of genetics to elucidate disease, and you do not see a comparable rise in the number of projects on secondary analysis. I should say that there may be a comparable rise, but there's still a widening gap would be a more fair statement, between the effort and funding dedicated to secondary analysis information development and information dissemination.

A couple more slides. This one is looking at sort of a pyramid model. We do that a lot in public health. This is an attempt to look at the agency's missions and give our best judgment about what we expect the agencies ought to be doing. You see the large letters is where their mission would lead them to be focused primarily. The smaller italicized letters would show appropriate overlap. For example, CDC is involved in oversight both through CLIA and by programs providing lab quality assurance.

I should tell you that application means a great many things. It includes many of the elements of translation, including the infrastructure to deliver service, and sometimes actually the funding of delivery of services itself. You can certainly make a good case, even though we

didn't put it up there, for a traditional role of NIH in some of the application in the sense that it's NIH that traditionally pulls together the consensus conferences, which often lead to guidance for primary care providers, what to do with a piece of genetic information.

Here's the actual outcomes based upon the number of projects. This is the number, not the funding. It would look even more dramatic if we looked at the funding. In terms of primary research, you can see the majority is NIH. This is very similar to what Dr. Collins showed you in a circular kind of presentation. The majority is NIH, with a smaller fraction of CDC, and a smaller yet fraction from the other agencies. In terms of everything that isn't primary research, the other agencies; but again, NIH still doing the lion's share of the number of projects.

With respect to agency collaboration, I want to mention first something that I think the committee is probably familiar with but the HHS working group and briefly review for you the history. The HHS Working Group on Genetic Testing includes basically the agencies that you see represented here, plus a few other elements of HHS. This working group was basically, as I understand it, evolved or developed or was created as a response to the NIH/DOE Task Force recommendations. That working group developed the framework which led to the creation of SACGT. In that working group, the agencies have explored intersection and potential for collaboration around data collection issues, and that is also the working group that developed the response to SACGT's oversight report that has led to the next step that's being considered by FDA and CLIA.

Also with respect to agency collaboration, you've already heard about the MOU and the more specific MOU for implementation of Title 26. I don't need to repeat the wide variety of different kinds of co-funded studies and projects. You've seen examples.

I do want to point out two things about this slide. One is that in formulating this summary

slide, this last slide, we could not identify in all cases exactly which agency was the lead or had the largest share of the funding, so it's in alphabetical order. My apologies if I've left somebody off a specific project. Examples of different kinds of collaborations range from cross-participation in review groups, so that CDC might invite somebody from HRSA to be part of the process of evaluating competitive project applications, to co-funding specific conferences, co-funding working groups, and co-funding or developing a variety of resources that you've already heard about.

I think that the agencies and I are ready to take any questions that you have.

DR. McCABE: Thank you very much. I really want to thank the agencies and Dr. Greene for all of your efforts in responding to our request. We know that pulling this material together has been a great deal of work, as I said before, and took many, many hours of time. I also want to thank Dr. Greene for presenting the overarching analysis, and I especially want to commend Dr. Susanne Haga for the work that I know she did in synthesizing this enormous amount of data. The broad view from the agencies has been extremely important and certainly informs our discussion that we will now have.

DR. TUCKSON: I, too, want to not only commend the work but also commend the leadership on your part to get this done. I think it's the right time to do it. I'm finding that this is the right moment for this kind of material to come in front of us, because I think we're all getting to a level of maturity on this that we can start to move to the next level. I don't know whether I agree with Francis and Muin or not. From the private sector side, we don't like all that government bureaucracy either. It's horrible.

What I think is missing from this discussion, or maybe I missed it because I came in a couple of minutes late. Dr. Greene, I missed the first part of your presentation. What I don't think I see

in government yet is an overarching vision for what it is we're trying to achieve, and what the role of government is to achieve it. I can't analyze -- well, first, we needed the statistics. I don't know what they mean, because I'm not sure what it is that we view. I'm going to truncate this quickly to say that one level where I'm confused is whether or not the government has decided to view genetics and genetic testing as a -- again, this genetic exceptionalism discussion that we keep having when we began, versus a targeted thing like HIV disease or the fight against cancer, or the fight against, so that you can sort of trace this NIH-ness that then gets dealt with, sequenced out, and then you can sort of see it through to a very specific line. Or do we view, or does government view, this effort as fundamentally the genetic revolution redefines the practice of medicine in its very heart, marrow and soul? And so you can't tease it out. Therefore, there is a different set of ways of viewing what this ultimately has to be.

I will conclude and listen to others by saying that I am alarmed and concerned about AHRQ and the lack of resource attentiveness to this issue. I cannot imagine that anyone could be comfortable -- and, by the way, I'm not into the budget fights, and I don't want to take a dime from NIH. I don't want to take a dime from anybody else, and there ain't no money nowhere, anywhere. It's a zero-sum game, and I'm not dumb about that.

At the end of the day, this country has this enormous machinery for putting forward every new kind of wonderful sophistication, and nobody knows diddly-squat about how to get access to it in a cost effective way. This revolution here is going to just drive these issues straight forward into the ground like a rocket, and to not have somebody on the front end figuring this thing out is scary and frightening, and what it's going to mean is that you're going to leave it to others in this healthcare industry that you're not going to want to make these decisions. Everybody is going to be mad.

DR. McCABE: Thank you. Other comments?

DR. COLLINS: I appreciate Reed's comments, and I guess it also raises a general question that maybe I'd like to hear the Committee wrestle with a little bit, which was a more careful enunciation of why we did this survey. What was it that we were aiming to learn? And now that we have the data in front of us, did it turn out the way we thought it would, or does it, in fact, come out differently than that? And perhaps most pressingly, from what we have done here as far as this survey, what is the evidence presently that critical pre- or postmarket research on genetic testing of a quality that would pass rigorous peer review is not finding an adequate home for funding? Is there a problem in terms of the support of pre- and postmarket research on genetic testing, or have we identified that a lot of this is going on? I'm sort of left with this mass of data not being quite clear, first of all, what was the motivation for asking the question, what do we hope to learn, and then what did we learn? I would love it if the members of the Committee would talk a bit about that.

DR. McCABE: Well, I'll respond, since I signed the letter that went out to all of you. We've been looking at oversight for genetic testing. That's one of the primary issues that we were charged with. We really, I think, took on or asked you to take on this task, because we wanted to look at the generation, collection, analysis, and dissemination of data on validity and utility of genetic tests from the perspective of the different agencies. What was each of the agencies doing that would contribute to the knowledge base for the oversight? Because we recognize that the rules should not be made in a vacuum, they ought to be data based, evidence based. So it was really to find out what was being done by the agencies, and then what were gaps, perhaps, in the agency funding, the agency responses, and how could we then make recommendations to the Secretary regarding additional data that needed to be collected or, if there were gaps, how could those gaps be filled.

I'll return to my comments at the end of the presentations this morning. As I listened to each of the presentations, it became clear that the problem is in the translation, what Reed said, the

access. How do we take the science that is really such a richness that has come out of NIH and the other institutes, or the other agencies, how do we take that science and now make it accessible in terms of healthcare for the American public, and by that nature, then, for the public more broadly throughout the world as it would be disseminated? It became clear to me also that in addition to developing ways to improve translation, we also need to develop ways to look at how the activities can be better coordinated if we are to achieve that goal. So that's my perspective on it as the individual who signed that request.

DR. LEWIS: I guess what I'm still not clear about is where there is duplication, where there is overlap that's duplicative and where there's overlap that's synergistic. To me, those are two very different issues, especially in light of what Reed said, which I agree with, the fact that there really are scarce resources, and that what we have to do is really look at resources to make sure that we're utilizing them maximally. There are areas where I hear collaborative efforts that seem to be parallel, and there are areas where I see collaborative efforts where the collaboration is really synergistic and moves things forward. I don't know how we identify that before the fact as opposed to after the fact, because I don't know that you know that. But what I want to be really sure about is that we're not using those scarce dollars the same way twice and that we're using them in ways that move us forward. I agree with Francis that we don't want any kind of heavy-handed bureaucratic master plan, but I think the communication piece is critical so that we don't have parallel work going on when those dollars could best be used and there's a huge opportunity cost to that.

DR. McCABE: Thank you. Wylie, this really came out of your work group presentation in August, so it's appropriate that you make the next comment.

DR. BURKE: Yes, and I wanted to comment from that perspective. I think why we got to where we are now is that in our discussions in the data committee, we could identify four

important areas of effort that all had to be in place if appropriate oversight, if appropriate translation was going to occur, and those were the four areas we asked people to comment on: primary and secondary research, education, or information development and information dissemination.

I want to comment about a little bit of an arbitrariness between what you call primary research and what you call secondary research. I don't think the line is necessarily easy to draw, and primary research could be genotype-phenotype correlation, but it could also be a primary data collection on how docs use information or how patients understand information. So I think there are nuances there that our data analysis doesn't give us yet.

That said, I think the Committee started with the four areas that are essential and all have to be present, so we wanted to understand what the mission of each agency was with respect to those different kinds of research and the relative activity in those different kinds of research. We now have, I think, extremely important data that still is just a starting point. To address the question that Francis raised, what we don't know is what the right ratio should be. In other words, we don't really know what the shape of the triangle should be, of the pyramid should be. What I think we now are able to say or inform our discussion about is that we know what the shape of the pyramid is, and knowing what the shape of the pyramid is, we can I think be better positioned to ask some critical questions, and I think Reed just asked one of them. That is, where the resources are relatively limited, where the activity is quite limited, at the tip of the pyramid, we have to ask ourselves whether that's enough. So I think we really need to start with where there's the least activity and ask if it's enough. In a sense, there's always going to be more justification for primary research, and I feel as Reed does that there's nothing I want to do to put brakes on that, but I think we have to ask ourselves where resources are limited, is it enough.

The other thing that I think is interesting that comes out of this data and informs our discussion is that even though NIH has as its primary mission primary research, it is the major funder of every other element of research as well, and I suspect that reflects that an agency that's trying to do a good job with a primary research agenda, an agency that's a big complicated multi-institute agency, finds that it must do those other things because they're essential. So I think we've got some agencies where there's a primary mission in one of the other areas, and those agencies have a tremendous contribution to make to identifying the agenda, but in a sense we've discovered that every activity on the list has to involve NIH, as well.

DR. McCABE: I'm just also going to warn everyone that we're going to stop about 15 minutes early in this discussion, so about 11:40, and really begin to get very concrete in terms of what our recommendations ought to be. So in terms of the discussion, the discussion will flow until about 11:40, and then I want people to be thinking about very concrete recommendations.

DR. KHOURY: Yes, just to react to a couple of things that I heard earlier, remember that SACGT has recommended a three-pronged approach to improve the oversight of genetic testing. It's sort of a new FDA paradigm for the regulation of home brews, the CLIA process, and what we call the postmarket data process. The reason why this is now important is because you want to move genetic tests in the real world more quickly than the usual, even with incomplete data. So that third arm becomes even more important, and more important to do in a coordinated fashion across the agencies and with the private sector, so that people don't get hurt by the premature use of genetic tests. So there is a certain threshold that the FDA process will exercise and will release things even with incomplete data, and that's why this arm here, the third leg of the stool, is so important. You have to ask yourselves that if there is something, a genetic test for cancer or whatever that is released through an FDA process and CLIA exercises its authority, whether or not there will be information on a timely basis that consumers and policymakers and physicians and healthcare providers can access so that people

aren't hurt by that.

Just reacting to Reed's genetic exceptionalism, this is very important, and the way we approach it at CDC is it's not about genetics, it's about the prevention of all diseases. So we approach it primarily through chronic disease programs. I mean, we don't even have a single line item for genetics in CDC's budget, believe it or not. It's all because of the prevention of the major killers -- cardiovascular, cancer, et cetera.

Just in closing, I wanted to give an example of this kind of, if you will, smooth transition between research and practice. We know smoking causes lung cancer. We've known that for 50 years. We know that physical activity can reduce the risk of cardiovascular disease. The primary research that has been done over many years has documented that. We have evidence-based guidelines that people should exercise daily or whatever, that maybe in an ideal world, through an AHRQ process or a consensus panel, that can be developed. But the real world -- and what I mean by the real world is what's actually happening in the real world. I mean, we still have 25 percent of people smoke, only 15 percent of people exercise daily, and to move things that work into the real world and really actually prevent morbidity and mortality requires an additional step working with the healthcare system, with the public health system, to make that happen. For example, the other evidence-based guidelines that we talked about which are really never mentioned is the Community Preventive Services Task Force. So we know that physical activity works, but do we know the processes by which we disseminate that recommendation to the communities, and what is it that works? I mean, if you go on TV and have advertisements for exercise daily, you'll save your life, will that work better than if you go to schools and you do different kinds of implementation? I think genetics is no exception. Genetics is going to be used for medicine and public health, occasionally for population screening, but mostly within the domain of the healthcare system, and we need to identify those various points along the way by which research can become a test and the test can become

diffused and evidence-based guidelines developed, continuous monitoring for what's going on in the real world to feed back into the system so that people don't get hurt by premature technology, and that's all there is to it.

DR. KOENIG: I'm basically in agreement with everything that's been said, particularly Reed's point, but also Wylie and Muin, but just want to remind everyone, since this is going to be my last meeting, I hope we'll have another social science perspective on the Committee.

But last night, as Muin and I were next to each other on the treadmill and I was watching the evening news, which I don't usually do, in the hotel, there were fully five, I think, direct-to-consumer ads for drugs and one that involved a device that were on one of the main network news programs. Just to throw out the point how important these things are because of the fundamental changes in the context of healthcare delivery and what's happening in that arena. We've been thinking about that an enormous amount in the context of informed consent in the Informed Consent Working Group, but just to remind you and to second what Muin says, that when we think about the relationship between, say, primary and secondary research, that there is also primary research on some of these other issues, like what are the broad social forces that are now affecting the way these technologies will come into existence, and I think that speaks to the need for some research that involves factors of political economy, as well as just things that focus on individual behavior. I think that's a really important distinction that we need to keep in mind. There are also other government agencies involved and other trends, as we found out many times, like the FTC in terms of how these messages get out to the public. Muin made the important point with the smoking example, that if you did direct-to-consumer public health saying exercise every day, that's a useful thing, but how is all of this going to play out in practice? I think we're not really clear about that. So I think, as we're thinking about the balance of how funding should go for research, to remember that there are many different kinds of primary research, not just in genetics as well. So that's perhaps a simple point but hopefully

helpful.

DR. LLOYD-PURYEAR: I want to question, actually, a little bit of what Wylie said. When you spoke about not knowing what the ratios are, but you also limited yourself to using a vision of the pyramid structure, and I think that pyramid, the structure was driven by the numbers of funding and the numbers of projects. But I'm asking the Committee to go back and actually look at the projects that have been put forward to see if a different kind of infrastructure is really needed than a pyramid. Maybe it's a circle, maybe it's a series of interlocking circles or concentric circles, but I think whatever shape that structure is should be driven by an overarching vision that Reed spoke about, and I think if we could go back and look at those projects that have mirrored successful collaboration between the agencies to see what's key there and what structure needed to be in place, what infrastructure needed to be in place, what vision needed to be in place to make that a positive force. For instance, we may be collaborating with not the Genome Institute but another institute at NIH on a project to develop a screening tool and to do primary care research and health outcomes for a specific disease. But it's going to require not only that kind of primary research but also a collaborative effort between state public health programs to carry that out. So in the very immediate part of the project, the initial stages of the project, it will require a collaboration between NIH and HRSA. But for that to be effective, we'll need to bring in CDC, we'll need to bring in FDA and CMS. So I think it's recognizing all the parts, and I don't think it's necessarily a pyramid.

DR. PENCHASZADEH: Well, first of all, I'm very impressed about all the data that we were given by the agencies, and suddenly I am a little bit -- in contrast with Reed, I think that I welcome the involvement of government in a number of issues, primarily in trying to protect the American people with the proper use of -- in this case we are concerned specifically about genetic testing. Of course, I'm not an advocate of bureaucracy nor any heavy-handed type of things, but it's obviously that someone, and I don't see anyone other than the government,

should be involved, and all these agencies have their role, mandated by law, to ensure the most rational possible use of developing technologies. I know about the role of NIH regarding basic research or primary research, and probably no one else can fill that gap, and I think that should continue to be a major thrust of NIH regarding biomedical research. I think, in talking about that pyramid, that probably I would like to see more budget and more funds and more attention directed to the translation of whatever basic knowledge is generated for implementation of evidence-based testing or therapeutics to improve the health of the people. I was reflecting on something that Reed said about the scarcity of funds and the perspective of the private sector, but we have to remember that if anyone is driving health costs to the sky, it's essentially the private sector, essentially because of the development of new technologies, the costs and the wasting that goes on in many cases. If you compare the healthcare money spent in all the developed countries, the U.S. probably spends twice as much as the next developed country, and I don't think we have better health than many other countries like in Western Europe, Canada, Japan, or whatever. So there is a lot to do in terms of determining priorities of how to spend money both in research and in the application of research -- that is, in medical care.

So I'm not so concerned about the role of the government. If anything, I think the government has a responsibility to make sure that tests -- and I'm going to restrict my comments to genetic testing, which is what this Committee is all about -- are safe and effective, as the mandate of this Committee states.

In that regard, I think that it is essential not only that the recommendations of this Committee in terms of oversight and regulation of effective and safe use are really implemented by Federal regulations, by law or whatever, but also to provide all the postmarket information that Muin always talks about, and I fully support that, in terms of the effectiveness and how really genetic testing will eventually improve the health of the population.

I'm not a genetic exceptionalist at all. I think that genetics is just part of health and medicine, and that's all. But we are living in an era in which most of the new developments in biomedicine come from the knowledge of the human genome and its applications, and it's logical that we take a close look at how those things are translated into practice. If our closer look at genetic testing, as compared with other testing or other therapeutics, brings up a new vision of how to conduct business in medical care, I would welcome that.

DR. McCABE: Thank you.

DR. TUCKSON: One comment and a question for me to help think about the specifics you want in a couple of minutes. Victor, I think, actually, I spoke so rapidly that I may not have been as clear. I think I actually sort of agree with you that there is a legitimate role for government. I'm calling for a legitimate role for government, and I think that it has to play that role. By the way, that role may not always be money. That role may be leadership. So while some of these things require funding, part of what I'm looking for in addition to funding issues is a certain leadership role, a certain coordination, just like you have an education summit to get all the parties together to start to focus on a big issue. Maybe that's also what's required here. My question ultimately is that – and it's sort of with Francis and Muin earlier that I was sort of saying I don't want to see big government. But at the end of the day, I want to feel like there's somebody in charge, that there's somebody thinking through the bigger picture here, and it's not only the academic model of collegiality among smart faculty members in different departments, and if you put all the folk in the lunchroom, the natural liaisons will, Brownian motion-like, covalently bond. Anyway, so the question becomes – one of the data sets that may not be captured here in the data is not project but infrastructure. Muin really helped me out when he took us back to first principles: FDA role for regulatory oversight, CLIA role, new role for oversight, and then this postmarket data collection. I don't know how much money that is, but I don't think that's captured in the analysis. So maybe what we need to do is ask a second

question, now that we have this, is where is the money? Number two is what's in the President's budget? This is where I'm scared, because we've made these recommendations. Dr. Slater, who clearly was wonderful to come here -- she felt like she had 10 milliseconds, and she felt like it was important to jump all the way up here to see us. So clearly, she's attentive. But at the end of the day, I would suspect that there isn't any of this reflected in the budget. So I don't know what recommendations we've been making, and people have been very polite to us. They treat us very nicely. They pat us on the head and they're just very political, and they come in and they leave, and it's all wonderful. We are doing all this work, and it didn't get reflected in the budget. So maybe I'm getting towards a reserve for recommendations.

DR. LEWIS: Again, I'm looking at the budget, I'm looking at the issues that other people have talked about, but I think the one thing that I don't see and that maybe it's another question that we need to ask is so what? What effect has all of this effort had at the level of the public's health and at the level of the health of individuals, and what are the outcomes that we're actually seeing that are changing practices and that are changing outcomes for individuals? It's wonderful to look at all the projects, but the question I always ask is so what? We've seen some examples of specific outcomes, and I believe they're there, but in terms of looking at projects and looking at the pyramid, it seems to me that some parts of the pyramid are really getting to the point where that's being translated to the level of the individual more effectively, and those are the things that interest me when I'm dealing with individuals humans in my daily practice. What are the things that I have to bring to them that are really going to change and that are things that are acceptable to the people I'm working with?

DR. McCABE: Okay, I'd just alert everybody, I've cut off discussion. I'll take the people who have raised their hands up to this point, but if you raise your hand now, it's got to be on the concrete side, please.

DR. CHARACHE: I'd like to join everybody in the emphasis on structure that Reed has just pointed out. Certainly, one of the key gaps is in this translational area, and that clearly needs attention to both quality and oversight of testing, and to the clinical validity and utility. What I've heard here, which has been extremely helpful, is that perhaps there could be more coordination in the educational area, where a lot of people are approaching it in a very productive way. But in the area of establishing clinical validity and utility, we've heard some gems of hemochromatosis from NIH, the cystic fibrosis from CDC, the HRSA work on sickle cell and other diseases. But to me, when you look at the number of genetic tests and the number of genetic disorders that we have to address, we're kind of looking at a bunch of gems in a sack, and they need to be strung if we can wear them.

DR. GREENE: Thank you. I really appreciate the discussion so far, and I think all of us are probably agreeing with most of what is being said. I think an important issue that needs to be dealt with in translation and implementation of genetic testing and specific genetics more generally – and, frankly, any new technology as we're moving into higher and higher tech -- is that much of the driving force is in the private sector, we've heard that, and then much of the demand comes from the public, which maybe have inflated or inappropriate expectations. On the one hand, we all want to do no harm. We need evidence-based decision making, and everybody will agree with that. On the other hand, we need equal access in the private sector, and the public demand has things out there, and we're seeing widening gaps between what people have access to. In genetic testing, in order to establish the clinical validity and the clinical utility of even a simple Mendelian disease is often a very complex problem and it takes many, many years, and that's a given for any of the complex diseases. This is not a simple question, so we are obliged to move forward when we have uncertainty. People have said this, but I want to look at this issue from a slightly different point of view. It is not always easy to move forward, except for certain kinds of primary research, with public dollars. It's easy to say let's do a study and find out. It's a lot harder to move forward with certain kinds of translational

research which basically implies it's out there, now let's do the postmarket data collection. But to move forward with public dollars when there's uncertainty is sometimes very hard to do. To do that, you need to have what people have already alluded to, this very big picture, and that can be viewed in the budget. It can also be viewed in things like departmental strategic plans and those kinds of overarching values or missions or different words that people have used drives what goes forward. Then you have different mechanisms that come into place that are very rich and very well developed in HHS that go beyond the important but not by itself adequate Brownian motion description. But when there is an overarching goal, then things do come together, as I think you saw in the description of the working group that HHS was never particularly directed to create, but there was a role and it was created for a purpose, and it accomplished its purpose, and I think you sit here in response to some of that. It comes down to that overarching vision.

MS. BOLDT: I'm really very supportive of having some type of interagency coordinating body. It seems to help the communication. I guess my question is there was a working group, an interagency working group that did review our oversight document. Was that a one-time thing or is that something ongoing? I guess I thought that this body was somewhat already created.

DR. GREENE: I'm sorry if I didn't make that clear. That was a group that basically was created by the Department, within the Department, in response to a need, in response to a driving force, and so long as the need for it exists, it will continue to do work. If and when the need doesn't exist, it's more or less active according to the perceived needs. I invite any of the agencies to elaborate on that.

DR. McCABE: As we segue into the more concrete recommendations, I just want to come back to something that was said this morning by one of the agencies, specifically FDA. Dr. Gutman said that the regulatory program was under review at the highest levels in the FDA, and

he was unable to share at this time with us. Given that really the linchpin of what we've accomplished so far and how we move forward had to do with the recommendations regarding oversight, recognizing you may be constrained to some extent in terms of what you can tell us, I'd ask you, though, to elaborate on this, because it seems like we've gotten stuck here, Steve.

DR. GUTMAN: Sure. Well, the regulatory plan that was framed by the center, by the division in response to the SACGT requirements was, we like to think, flexible and, we like to think, clever, but whatever we like to think, we're absolutely convinced it certainly is novel, and it is the novel nature of that plan that has created interest and attention by our management. It's under review in the commissioner's office and being looked at by the head of our legal staff and being evaluated as a matter of both law and a matter of policy. Although I wish I could provide you with insights into that discussion, I don't regularly interact with people quite at that level, so I can't.

DR. McCABE: Is there anything that we could do to at least make inquiry regarding the status? Because I'm sure that the leadership of FDA has a lot of things on its plate, and while this may not seem important in the overall view of the agency, it's extremely important for the work of this Committee.

DR. GUTMAN: I certainly wouldn't discourage any kind of formal or informal query or reminder, but it is certainly my impression that this is certainly not the highest priority item. Maybe bioterrorism will trump it, but I certainly don't think it's not on the active plate of issues under deliberation. I would reflect the time it's taking, not through a lack of priority but due to the complexity of the issues, both from a legal and policy perspective.

DR. McCABE: Thank you. Wylie, you wanted to begin to make some concrete recommendations.

DR. BURKE: Yes, I want to move to what should we do next. I feel as though we see a lot of things more clearly as a result of this data collection and presentation. From my perspective on the data committee, it's been incredibly helpful. As often is the case when you're trying to explore a new area, I think we need to do a little bit more investigation.

What I actually would like to propose as a concrete task is for the Committee to consider charging the data committee, so I'm proposing a task for my group and therefore input from other members of the group as well as from the Committee as a whole as to whether this seems reasonable. I think what we're hearing is that there's a felt need for more of an overarching vision about how you go from primary research to all the different steps in translation, and that we might be able to provide better advice about how to develop that vision if we examine some case examples. The case examples would, I think, address these questions: What is being done in each of these particular case examples? They would all be genetic testing examples. Are or were the downstream questions being addressed in a timely fashion as they arose? And if yes in a given particular case example, how did that happen? How did it happen that things did go smoothly and you went from a more primary question to the next question to the next question? If no, it's tempting to ask why not, but I don't think we can ask that question meaningfully. What I think we can ask is in a given case example where we don't see a sort of smooth transition, what elements tend to be missing? I think the elements that tend to be missing may be very informative to us about what kind of either coordination activities or discussion activities or just plain vision need to be developed. I guess my assumption here is that we all have the same goal and it's just a matter of figuring out why things aren't moving along nicely or what's missing when they aren't.

The examples that I propose are examples that I think would represent an interesting spectrum, and also I'm mindful of the fact that if the data group were to take on a task like this, we'd want to be sure that we had the right kind of help, so I'm thinking of examples where I think we

would be able to get the right kind of help from different personnel and agencies, and also partly from expertise in our group. It seems like we've got to look at hemochromatosis. That's a pretty powerful example and we want to understand how that's worked. We really need a cancer example because we heard that there's a lot of research going on in cancer, and I think we need to know how that's moving along up the pyramid. Newborn screening equally is a crucially important issue. We've also heard that there's important work going on. I'm not sure what the right newborn screening case example would be, but I think Michele could help with that. I've been told many times that Factor V Leiden is the most ordered genetic test in the country, so I'm curious about that one. Then it seems to me we need an example of a rare disease, and I would suggest the rare disease committee might help us. So I'm proposing a task for the data committee, if others think that's useful.

DR. McCABE: Thank you for that and for your willingness to take it on. For the newborn screening example, I'll throw in my two cents. I would look at two, and I would look at sickle cell disease as one because it always astounds me that recommendations came out from an NIH consensus development conference in 1987 that we should have universal screening for sickle cell disease and we still don't have it in this country. So what were the barriers to the implementation of that high-level recommendation? Then the other one that is obvious, the one that's rolling out currently at very high speed, is tandem mass spectrometry. So that would be an example in process. Michele, would those be acceptable to you?

DR. LLOYD-PURYEAR: Except that I might also include hemoglobinopathies broadly.

DR. McCABE: Yes, hemoglobinopathies broadly, but recognizing that this --

DR. LLOYD-PURYEAR: Because there's also a problem with quality testing.

DR. McCABE: Okay.

DR. TUCKSON: I think I like that last suggestion. I think my recommendation would be somewhat related but maybe a little different tack, and that is I would like us to send another letter to the Secretary, and I would like to specifically ask the Secretary who is in charge. I mean that not negatively, and I don't want to waste a lot of time on the diplomacy. I mean, given that the Secretary of Health has empowered us and has moved on to other things, and we're in this wonderful moment of transition, and so forth and so on, and we have the wonderful Dr. Slater who has just joined the administration -- we're in a moment where nobody knows who is in charge. So, who is in charge? Number two, what is the relationship between who is in charge and the HHS Working Group on Genetic Testing? Number three is that we would like to ask a set of questions that we want to use as a discussion in actual real time with whoever it is that is in charge. So I don't want to have somebody come and say nice things to us. I want to talk to somebody so that whoever it is who is in charge actually knows what we're talking about, or that we can learn from and have an interaction where we might actually be able to make better recommendations. So let's bring whoever is in charge here and not ask them to give a presentation but let's have a conversation. Number four, we want to ask them in preparation for that conversation what is the Department's philosophy regarding this issue of genetic testing and its relationship to other ongoing activities, or is this a separate bucket of things? We want to ask specifically how did our recommendations get translated into the budget, and if they did not, why not, and what can we learn about either the impracticality of our recommendation, the poor timing of it, or the fact that, unfortunately, in the scheme of bioterrorism and other things, just didn't make it? I mean, we're reasonable people here.

So what is the answer? It's not provocative. It's just teach us. Specifically we want to know in terms of that budget. We want to start with, although we didn't ask for it but I think it's important just to do it because I think we want to make a celebration of it, give us the budget

for the NIH basic science part, because I think that's important. I don't want to lose, plus I don't want Francis to hit me upside the head on the break. But what's the NIH budget? We know that's wonderful, it's robust, it's great. So we want to document that. Number two, what is the budget, then, for the FDA, CLIA, and postmarket recommendations? What's in the budget? Number three is what resources, if any, have you put forward for health services research to help us to think through how do we use these tests, how do you provide physicians and the public with an information base that they can use to make choices when healthcare costs are going up to an unaffordable level? So you've got to have some database around which docs and others can learn. And then finally, what is the budget for education of doctors, nurses, counselors, and the American people, so we can see those things? So at the end of the day, we have that information in front of us, robust or un-robust, unapologetic or whatever it is, and we now have a sense that this is what the deal is. I want to do what Wylie is saying to do in addition, but what I don't want to do is have us do another exercise outside of the context of what's the real deal.

DR. McCABE: Can I clarify just in the second paragraph of your letter, when you said who is in charge, and specifically in charge of what? The oversight of genetic testing or is it the translation from basic research? I just want to clarify.

DR. TUCKSON: I think you really asked the right question. I think in some way the answer to that is it is who is in charge, I guess, of the overarching genetic agenda for the Administration. That may mean to them -- and that's why I started at the beginning with what's the philosophy. That's what I don't understand. Is there a person in charge of genetics testing versus genetic issues? But that's what I'm looking for, Ed. It ultimately comes down to what is the philosophy.

DR. GREENE: Sarah reminded me of something that we looked at before, and that is that I did

a read-through of the previous Administration's strategic plan for HHS, and I unfortunately have to report that the word "genetics" does not appear in the strategic plan. The one mention of genetics is in the context of making sure that laboratories have the highest quality technology for detection of diseases, and an example was given which included molecular analysis of pathogens. That was the only mention of genetics that I found in the strategic plan. So I think that will be a very interesting question: What is the overarching question or view or approach to genetics? I might not frame it as who is in charge. You're likely to get a high-level answer like Secretary Thompson, and I'm not sure that the answer would be as meaningful as you might desire.

DR. McCABE: We'd probably cast it more as an opportunity to define. I'm sure that we could approach that.

DR. COLLINS: I guess I would like to endorse both of the proposals that are on the table, one from Reed and one from Wylie. I do think it's an opportune time to try to define the connectedness of this particular Committee with the Department with Dr. Slater's arrival, with the fact that it's not clear in a very busy agenda that's been occurring in the Department's leadership whether genetics has gotten on the screen very frequently. I suspect the answer is no, and many of the reasons for that are understandable. But this would be an opportune moment, it would seem, to try to define that pathway so that things both go up and they come back again. That would be timely.

But I think actually these are both connected, because I strongly endorse Wylie's suggestion of the charge to give to her data committee. In fact, I had written down almost exactly the same ideas, and then she put them forward. As usual, Wylie is thinking about the practicalities of how do we take this exercise, which has given us some information, and have it give us really the information that would be most useful, which is for a series of case examples, where are the

gaps. I think we have the sense that there are gaps, and we all are speaking passionately about the need to fill them, but frankly, when I think about a particular problem -- let's say BRCA1 and 2 testing -- it's a little hard for me to know what's missing, because there's a lot going on there, including what I think you could call postmarket evaluation, since that test is very much being marketed. But is it being done right? Is it being done in a fashion that's properly coordinated? Are we getting the answers we need as quickly as we need them? I'm not quite sure I know the answer to that part. If you chose an appropriate set of examples, and I like the array that you proposed, and I would hope that you would focus specifically on ones where we are pretty close to a postmarket situation, because I think that is the area that is most in need of attention, then we would learn a lot. That, in turn, would put us on much firmer footing if we are going to the Department or going to the Administration and saying, "There's a problem here." We've got to have the data to support that. Frankly, right now, we have ideas and a sense of this, but I don't think we have the examples to prove our point, and this next step ought to accomplish that.

DR. McCABE: So do I have a consensus from the Committee that we should move forward on both of these points, both what Wylie has suggested through the data collection committee, and then also with what Reed has suggested in terms of communication with the Department? Is there anyone who disagrees with that? Because we would move forward on a letter between now and May and try to get that out.

DR. BOUGHMAN: I would just like to reiterate one of the principles that I learned in my course on genetic counseling, my first course. I'm not going to tell you how many years ago, and you never ask a question that you are not ready, willing, and able to handle the answer to. So while I concur with the idea that we should not delay in addressing a communication with the highest levels of the government, I think it may be very important that if we can't answer the question where are the gaps and what should be done about it, I think that we need to be very

careful in how we ask those who are not as familiar with this area as those of us around the table. So some questions about general vision and interactions I think might be very important, but I would just urge us to word those statements and questions very carefully.

DR. McCABE: Well, one of the things we could do is prepare this. Hopefully we will have a briefing in the interval before the next meeting, and we would certainly prepare Dr. Slater ahead of time for that briefing and could cast it in that light as one of the important aspects of that briefing. So that would be a way we could move forward.

Again, anyone have any concerns with this before we move forward on it? Wylie, please consider your committee charged with moving ahead with that agenda, as well.

Some brief comments, then, because we need to move on.

DR. KHOURY: I don't have anything.

DR. CHARACHE: Yes. I just wanted to ask Wylie if it's practical in getting the data collection on these particular diseases, it would be very helpful if you could also get a sense of the quality of the test being done. I think this oversight issue and test quality of what's being offered, these are very good examples to look at that.

DR. BURKE: I agree strongly with that statement, and I actually think the position we're in is one where we can get help with all of the questions, including that one, obviously with your help to some extent on those issues.

DR. McCABE: In the spirit of no good deed goes unrewarded, I'll just mention to the agencies, then, that as part of the data working group, we will probably be asking for more data from you.

We very much appreciate all of the time that you put in bringing these data before us, and it certainly has sparked a very good discussion this morning and will lead to additional requests in the future. So thank you now and for the future requests.

DR. CHARACHE: I just wanted to thank the Secretary committee group for not sending us that with our briefing books.

DR. McCABE: For the record, Pat pointed to the probably approximately 40 pounds of paper arrayed on the table there. Thank you all. I really do appreciate all of the work that was put into this, and we all do on the Committee.

We're now going to move on to the next topic. In June of 2000, SACGT convened a panel of experts to discuss questions about whether third parties in research – at that time they were referred to as secondary subjects -- were considered human subjects under the Federal regulations governing the protection of human subjects. After subsequent deliberations, we concluded that the mandate of the National Human Research Protections Advisory Committee, or NHRPAC, was more appropriately suited to a fuller consideration of the issue, and we recommended to the Assistant Secretary for Health that NHRPAC be asked to carry out a review of Federal policy in this area. NHRPAC took up the issue last year, deliberated for several months, and at its last meeting just a few weeks ago finalized a consensus statement on the issue. The National Institutes of Health has also made recommendations on this issue to the Office for Human Research Protections. Both statements are at Tab 9.

We're very pleased that Dr. Mary Faith Marshall, chair of NHRPAC, and its executive director, Ms. Kate Gottfried, are here to discuss NHRPAC's statement, as well as the committee's plans to address ethical issues in genetics research. Sarah Carr, wearing a different hat now, and Dr. James Hanson, chief of the Mental Retardation and Developmental Disabilities Branch at the

National Institute of Child Health and Human Development within NIH, will discuss the NIH recommendations. We'll begin with Dr. Marshall and Ms. Gottfried. Ms. Gottfried briefed us at our August meeting, but I want to take a moment to introduce and extend a special welcome to Dr. Marshall, since we've already had Ms. Gottfried introduced before the Committee.

Dr. Marshall is professor of medicine and bioethics officer at the Kansas University Medical Center. She holds joint appointments there in the School of Nursing and Allied Health and the Department of History and Philosophy of Medicine. She is also a program associate of the Midwest Bioethics Center, where she leads the Kansas City initiative to promote integrity in biomedical research, which includes an IRB consortium representing 30 institutions. She is past president of the American Association for Bioethics and Humanities, and past president of the American Association of Bioethics. Her current research interests include human subjects research, perinatal substance abuse, and ethical issues associated with cybernetics and artificial intelligence. Ms. Gottfried and Dr. Marshall, welcome.

DR. MARSHALL: Thank you very much. It's nice to be sitting on this end of the table. I do want to say thank you to the Committee for sending us this issue to deal with. We certainly did not see it as a turf in any way, but actually as a gift, even though I think relative to our committee it's probably the most potentially divisive issue that we have taken up yet, although, as you have reported and I'm happy to report, we did, just two and a half weeks ago, achieve consensus as a committee on the issue of the clarification of the status of third parties as human subjects research. There was no blood on the floor. I think it was a miracle on the order of the fishes and the loaves. Actually, after we voted, the folks who were in the audience attending the meeting actually gave us some applause for bringing it to closure.

Just a little bit of background in terms of how we arrived at our advice relative to third parties. Because we are primarily a body that does public bioethics, we try to be very careful in terms

of our procedure and that we are as inclusive as we possibly can be, not only at our meetings with our public members but in terms of our working groups and those whom we consult along the way as the working groups are doing their hard work.

We created a specific work group to look at the issue of when third parties might become research subjects and under what circumstances. We already had in place a social and behavioral sciences working group. Early on, these two work groups, the third party work group and the social and behavioral sciences work group, both addressed this issue somewhat independently, and then we brought them together after they had had a chance to wrap their collective minds around the issue, to work as a whole to bring advice back to the committee. These were large working groups. I think they comprised together probably 30 people or so. I would also like to say that Felice Levine, who chaired the social and behavioral sciences working group, was very careful to actually reach out to the community of scholars who live in the social and behavioral sciences world at their professional meetings during the fall of 2001 to make sure that we could receive as much input from those folks as we possibly could. So I feel as though our process was as good as it could be.

The working groups did bring a draft to us at our October meeting. We had some lively discussion and debate about the third party issue, and really it seemed as though the crux of the issue had to do with whether information about a third party, when the third party was identifiable and when the information was of a private nature, had to be referenced by a research subject himself or herself, or whether third parties could be defined as those about whom information existed either in tissue samples or stored data in medical files and so forth. So the issue really, for us, had to do with the phrase "when referenced by," and that took a lot of attention at our October meeting, and then subsequently as our January meeting. We found a way to come together and to achieve consensus. We decided as a group that when one is talking about situations where information about a research subject is gathered through indirect

means -- this would be chart review, for example, or tissue samples -- that these situations are already covered in the regulations and that we were really talking specifically about when an individual might be referenced by a research subject, so by a person who is the subject of research.

You all have the clarification in our document in front of you, but basically what we decided was that when an IRB might be considering the question of third parties in research, the people who were pertinent to the discussion were investigators or their agents, the human subjects themselves who interact personally with investigators, and then the third parties again, the primary language here being "about whom researchers obtain information from human subjects, but who themselves have no interaction with research investigators or their agents."

We decided that reference to a third party, when it is contemplated in a research design or a third party's information is recorded in research records, that doesn't necessarily mean that a third party is a research subject. However, IRBs should consider in their prospective review of protocols and in conducting their continuing review how the research design itself might focus not only on the identified third party but on perhaps other persons as well.

In the case that the methodology of a protocol allows for collecting a significant -- and I realize that could be a fuzzy word -- a significant amount of private information is identified, that the IRB needs to seriously consider whether any of the third parties should be regarded and treated as research subjects themselves, thus raising the issue of whether one needs to obtain informed consent from those individuals.

So we provided what we considered to be important factors that IRBs should use in arriving at these decisions, and they included the quantity of the information that would be collected about the third party, the nature of that information, especially whether it is sensitive, the degree of its

sensitivity, the quality of its sensitivity, and certainly the very real possibility that that information may cause harm in the future to the third party; the ability of the investigators, given their methodology, to record information on those individuals in a manner in which their identity could be protected. We had large and I think fruitful discussions about the very real possibility of ever anonymizing anything or the ability that any investigator might have to protect information about a third party. Then, finally, the possibility that classifying this third party as a subject might actually reflect back on the original research subject himself or herself in a way that could harm both the individual subject and the third party, and how the IRB might deal with the issue of protecting the interests of both of those persons.

So I'm happy to say we did arrive at consensus, and our approach to it I think was somewhat different than that of NIH, who I believe at some point had a moment of gestalt in their approach in thinking not whether a third party is a research subject but how one might become a research subject if one were a third party.

So this is our advice to OHRP. It will I believe today or tomorrow go up on our Website for public comment.

I wanted to say, then, at the last that as part of our methodology, we tried and be as concrete as possible in thinking along the lines of the process of IRBs and others in the future being able to use any advice that comes not only from us but would go to the OHRP and be made into some form of guidance from OHRP to the research community; that we give concrete examples so that understanding the regulations, applying the guidance is easier than it has been in the past. We factor this into all of our processes in our working groups, and we actually asked all of the committee members, regardless of where they fell out on this issue, to provide us with concrete examples, scenarios, of research projects where a third party may or may not be a human subject. So we have a long list of those. We will be putting those on the Web as well for

public comment, and then certainly suggesting, as we always do to OHRP, that if it will prefer guidance to the community, that they be explicit in giving examples of how that guidance could be applied. Thank you very much.

DR. McCABE: Thank you very much. Perhaps when that set comes up on your Website, perhaps you could get the link out to all the members of this Committee so that it would be easy for us to access. Thank you.

We'll now turn to Sarah Carr and Jim Hanson for explanation of the NIH recommendations. Sarah, who you know works extremely hard for this Committee, and I know the hours she keeps because it's frequently late on the West Coast when she's still working here, so I assume that she accomplished this task sometime between 1:00 a.m. and 3:00 a.m. to help craft the NIH recommendations. But thank you both for being here to present them.

DR. HANSON: Sarah has kindly put together some summary slides to facilitate this. What we're going to do is I'm going to present a little bit of the background and overview of our efforts, and then Sarah is going to go through the document in a little bit more detail with regard to some specific issues, with which I'm sure you will all have an interest. I would point out that the handout that you have has one slide out of order, and that is the summary of recommendations slide, which I think is number 8 in your handout. That will be presented at the end by Sarah. I also want to acknowledge the contributions of a number of persons in this room, and in particular I think it is important that we acknowledge the spirit of cooperation and the environment created by NHRPAC in welcoming us into their discussions to participation in their group activity. I think this was healthy for all of us and has led to a set of documents that I think are essentially compatible and speak to an emerging, I hope, consensus between the scientific and ethics communities, and perhaps one that will be appealing to the public, to research subjects as well.

It's now over a year since our NIH efforts started, and I am very pleased now to be able to bring to you a final work product. I must admit there were several occasions during the past 12 months when I ruminated on Francis Collins' definition of a committee earlier this morning, but fortunately the cul-de-sac turned out to have a two-way entrance. So let me move on to the first slide, and that is why did NIH make recommendations to OHRP in the first place.

Obviously, this was triggered by the concerns that were expressed by investigators following the Virginia Commonwealth case, but they were not exclusively related to that particular case. A bad case doesn't necessarily make good policy, but it did trigger and extend some national debate about whether third parties should be considered human subjects, both within this body here today and within NHRPAC. In January of last year, Dr. Greg Koski came to the National Cancer Institute to discuss high-priority issues for OHRP and NCI's perspectives, and in the course of that this particular issue arose and he invited NCI to make recommendations to him and to OHRP on this topic. NCI then asked all the other institutes and centers at NIH to participate in this activity.

I want to emphasize that our document presents recommendations, not guidance. Our goal was to suggest a basis for guidance to help researchers and IRBs determine when third parties are or might become human subjects. In order to do that, we determined that we wanted to be able to work within the current regulations framework, so we felt there were two key questions. One is when is information individually identifiable, and the other is when is information private? We also felt that it was very important to enunciate clearly two guiding principles for our deliberations. One was that the protection of human research subjects is paramount, and the other is that research to advance scientific knowledge is a public good that we wish to protect and extend.

Our process was a trans-NIH bioethics committee subcommittee which met a number of times

between March and August of this past year. We asked for examples of research involving third-party information, we conferred with a variety of experts on the intent, or at least their perceived intent of the original drafters of the Common Rule, and we went through many drafts, and for that I will be eternally grateful to the person I now refer to in my own mind as Saint Sarah, who kept track of the drafts and managed to make sense of the numerous comments that were delivered in unusual and challenging order.

We ended up with a proposal which was reviewed by the T-NBC in October. This led to further drafts, and fortunately we were then able to put together a document and get the concurrence of all the institutes and centers in November. That was shared with NHRPAC, with Dr. Marshall, and I think it has resulted in, as I said earlier, a wonderful pair of documents; or if not wonderful, at least a remarkable set of documents.

The issues that we tried to deal with in our discussions related to the question of whether or not the outcome of the VCU case had adversely affected research and IRBs. As I said, we asked about the original intent of the National Commission and the Common Rule drafters. Importantly, we tried to address the issue of third parties, and that was in part because we started off looking at genetics research and suddenly realized that this extended to a whole group of other kinds of research questions in particular in the behavioral and social sciences. We asked questions about the autonomy of the research subject, as to whether or not that person's autonomy was more important than other third parties, and whether or not we owed that subject greater respect than other individuals. We also explored other issues, including the definition of human subjects and whether or not it could, under certain circumstances, cover third parties. We asked when do third parties become human subjects, and we also asked questions, as I've suggested, about the identifiability and privacy of individually identifiable information. We asked what role the investigator may have in determining who is a human subject, and very importantly what role does the IRB have in determining who is a human

subject and how adequate is data security in particular research settings.

Now, having said that, I'd like to turn the rest of this over to Sarah to go through some of these issues in a bit more detail and present to you our summary recommendations.

MS. CARR: That's right, Jim. I'm going to get into the nitty-gritty a little bit. So before we do that, I think it might be beneficial just for the Committee to look at the regulatory definition of a human subject, because this is what our work was framed around. As Jim said, we explored what the original intent of the drafters of this definition was, and we questioned the intent, but in the end we accepted this definition and we agreed that it would probably not be worthwhile for NIH to recommend changes in this definition, that that would be a long and complicated process.

So anyway, according to the Common Rule, a human subject is a living individual about whom an investigator conducting research obtains either (a) data through intervention or interaction with the individual, or (b) identifiable private information. As we know, the third party issue arose because of confusion about what Part B means, what is identifiable private information and what it isn't. Other parts of the definition, as we'll see in a moment, do provide some clues about the meaning of identifiable and private. The Common Rule does not define a third party, and to address this gap, NIH developed this definition. A third party is a person about whom a human subject provides information during the subject's participation in a research study. This person could be, for example, a relative of the human subject, spouse, sexual partner, social acquaintance, friend, and so on.

The NIH recommendations articulate four rules of thumb, and these rules, as you might expect, state general points. They don't try to account for every specific situation. The first rule addresses the question of whether third parties are human subjects. In going back to the

wording of Part B of the Common Rule definition, NIH suggests that a third party is not or does not become a human subject unless the investigator obtains information about the third party that is both private and individually identifiable.

Our next task was to explore the meaning and scope of individually identifiable and private information. To be identifiable, according to the Common Rule, the identity of the subject is or may readily be ascertained by the investigator or associated with the information. We emphasize the word "readily" because we saw it as an important consideration in understanding the intent of the regulation, which seems to suggest that there is a distinction between information that can easily identify someone and information that might possibly identify someone. We proposed that readily identifiable would include unique identifiers, such as full name, address, other contact information, social security number, and identifiable photographic images. We suggest that identifiable information would not include information that on its own is not identifying and in order to become identifying would need to be linked with other information. We felt that these linkages required time and special effort, and therefore did not constitute readily identifiable information. We suggest that, in general, family or social relationship identified only by that association is not identifying information. We noted that while it might be possible to ascertain the identity of a third party by piecing bits of information together, making such linkages takes time and effort unless the third party's name or other identifying information is collected.

These considerations are summed up in our second rule of thumb, which says that readily identifiable information is the criterion in the Common Rule, and it should be distinguished from possibly or potentially identifiable information, which is significantly different in degree, we thought. For example, information about familial or social relationships identified only by that association should not usually be considered readily identifiable information.

Our next task was to explore the meaning of private information. The Common Rule defines private information as including information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public -- for example, a medical record. We've underscored medical record here because we view it as an important guide to what was intended to be covered by the definition. Thus, we suggest that information in private documents, such as a medical record, is private information, and many but not all of health information is private information. The kind of health-related information that we would generally not consider to be private might include information about a person's age, body build, ethnic or cultural background, family relationships structure, marital status, social networks, and occupation. We are also suggesting that information about a third party that is obtained from a subject as background information about the subject is generally not considered private. Rather, such information is contextual since it is usually unverified and is used to provide background important to the condition or circumstances of the subject.

This led us to our third rule of thumb, which says that information about third parties that is obtained from research subjects as contextual information about the subjects is not generally considered private. When information from private documents of a living third party is sought and private information from those documents is recorded in such a way that the third party can be identified, the third party becomes a human subject and the need to obtain the consent of that subject must be analyzed according to the Common Rule.

Our fourth rule of thumb emphasizes the importance of handling in a confidential way all identifying research information, whether about a human subject or a third party, and the need to keep such information secure and protected from inappropriate disclosure. In our paper we also discuss the need to secure identifying data at all stages of research and suggest specific

measures that can be taken to protect information.

NIH makes several other points in the paper regarding the relevance of data collected about third parties, methods of contacting third parties if they are to be recruited as subjects, and the need for further input and guidance on these issues.

I'll just sum up what NIH's recommendations were. What we did in these recommendations is provide a definition of a third party, assert that a third party is not, per se, a human subject. We provide these rules of thumb to help researchers and IRBs determine when a third party may be or become a human subject in the course of research. We discuss meanings of identifiable and private, as outlined in the Common Rule, and suggest commonsense limits to what should be considered identifiable and private in the context of third parties in research. Finally, we reiterate the importance of protecting confidentiality of all identifying data, whether about a human subject or a third party.

DR. McCABE: Thank you very much. I would like to now open this for discussion. But before doing that, I would like to ask whether the Committee feels that it would be appropriate for us to endorse these two recommendations. I see them as complementary. I don't see any conflicts between them. Whether that's an action that the Secretary's Advisory Committee on Genetic Testing, having requested that NHRPAC take this up specifically, would now wish to endorse. Any comments?

DR. BURKE: I would just strongly agree with the idea of endorsing these statements.

DR. COLLINS: I think they're both excellent statements, and I look forward to the chance to talk a little bit more about the details. I think certainly this is the kind of recommendations that we were hoping to see come forward. My only reservation would be that there is still a fair

amount of ambiguity in terms of the actual application of these in specific situations, and it would be lovely to see what the examples look like in order to see how these recommendations would play out. I think that's going to be a very critical part of just how successful this approach turns out to be in terms of instructing and informing IRBs, who are still pretty confused about what they're supposed to do.

DR. McCABE: We could certainly take the position that we supported the statements and that we would look forward to seeing the examples that might have some feedback from our Committee and its members on the examples.

DR. KOENIG: I agree in principle with the idea that we should endorse these, but I share Francis' concern about the actual application. Just to give one example based on Sarah Carr's presentation. Say I'm a research subject. What if the contextual information about me includes, say, potentially private health information about my brother. I have one brother. It would be pretty easy to determine that, and he happens to have been born with very serious bilateral club foot. That information is an important part of who I am and everything about my life. I'm a bit concerned about the fact that neither of these documents address the fact that that information really doesn't just belong to my brother, say, but also belongs to me because it's part of me. So I'm just wondering how that sort of dynamic played out in the discussions at both NIH and at NHRPAC. I'm sure it came up a lot in terms of the individual bias and focus. Then I would like to see a little more – and I actually agree with the final conclusion. I would perhaps go further and say that there can be situations where even potentially private health information, that the primary subject should be able to discuss that and disclose it to an investigator without having to get the permission of another person. But then I also think we should go further and to perhaps provide some additional guidelines to IRBs about the conditions under which the waiver – even if you want to define it statutorily as requiring the consent of the third party, that you might want to be more specific about the situations of when

an IRB can waive that, can actually waive that requirement that you treat the third party as a human subject.

DR. McCABE: Do you want to comment? Because I think part of that was in your use of the term "contextual," but maybe you could elaborate on that.

MS. CARR: These were the very kind of discussions that went on in the subcommittee, and if it wasn't clear, let me try to clarify. We chose the word "contextual" rather than using terms like "the information belongs to the human subject." But in effect, that's what we concluded, that we're social beings, we live in families, we're part of families and so forth, and all of those influences affect us, affect our health and so forth. We felt that as long as the questions were being asked to enhance understanding of a human subject or the condition under study that the human subject had, that that was appropriate and that you did not need to even consider the question of whether that third party needed to be consented because the third party is a third party, they're not a human subject. So I think we're in agreement, if that's what you are -- are you saying that, Barbara?

DR. KOENIG: Well, that's not what I heard. What I heard was that if it is potentially private medical information, then that trumps the contextual piece.

MS. CARR: No, no. If you heard that and if I said that, then I misstated, because that's not --

DR. KOENIG: Other people seem to have gotten that impression, too.

MS. CARR: No, I don't mean that. We didn't mean that.

DR. McCABE: Dr. Marshall, do you care to comment?

DR. MARSHALL: Yes. I guess I would say a couple of things procedurally. Those sorts of examples are the very things that we will be posting. We did only meet a couple of weeks ago, so not knowing how the committee was going to fall out on the issue or whether we would come to consensus or not, it wasn't necessarily appropriate to add examples when we didn't know where we would wind up. So those will be on our Website for public comment, and I would imagine that either as individuals, or even perhaps as a Committee if you all wanted to weigh in on any of those, that that would certainly be welcomed.

I guess the second thing or perhaps the final thing that I would say relative to your question is that we felt that it was important to give IRBs criteria or factors to use when making these decisions about the issue of waiver or whether, relative to a particular protocol, a third party would become a research subject or not. We feel as though we have given a process, here are the things that you need to take into account and factor into account, and certainly a large part of that would be the circumstance in which either the original subject or the third party might be harmed from the use or release of information.

So we did try to be procedural, knowing that it's impossible to parse things out so completely that they would speak to each and every protocol that might come along. So we really did try to be procedural, but there will be concrete examples in the future.

DR. HANSON: I would just like to add that it seems to me that, at least by implication if not explicitly, these documents are an affirmation that we believe that IRBs can and should have the authority and have the discretion and responsibility for examining these issues and that they can make decisions that are appropriate to the needs of a local situation and a particular protocol, and that one-size-fits-all rulings at a national level are not, in fact, always appropriate or desirable.

DR. McCABE: Thank you.

DR. LLOYD-PURYEAR: I'm interested in the informed consent process that will be tied to this. Are you going to be making specific recommendations for the IRBs to include in the informed consent process addressing the idea of third party identification or not?

MS. GOTTFRIED: Well, these are recommendations that we've made to the Secretary and the Office for Human Research Protections, and it's not at our option to determine what the policy will be by that office. In terms of the informed consent, as Jim was saying, this is the obligation of the IRB to make these assessments, and they know that once you deal with yes this person is or no this person isn't a human subject, then the informed consent issue is triggered, and then the four criteria outlined in the Common Rule must be applied appropriately.

DR. LLOYD-PURYEAR: So that will be made clear in your recommendations so it's all tied together?

MS. CARR: At least in the NIH recommendations, what we tried to do was, using the definition of a human subject, which is that you have a human subject if you've got identifiable private information, we tried to suggest when that might not be the case, what kind of information is and is not considered identifiable and what kind of information is and isn't considered private. If OHRP accepts these, as I called them, common sense limits to what is private and identifiable, then I think that could form the basis of guidance to IRBs, and I think what we're trying to suggest is that there are many cases where third parties clearly are not human subjects, and there are cases where they may be. We're trying to sort all that out, and hopefully that would be guidance for IRBs, and then they would know when they're coming close to having a human subject and then when the informed consent issues have to be

addressed.

MS. GOTTFRIED: Let me just address for a minute the issue of illustrations, because that did come up a couple of times at our meeting. At the October meeting there was somewhat of a split. I mean, the majority felt that illustrations would be useful as a guidance, but obviously it cuts both ways, because once you provide illustrations, then there's the concern that someone will adopt it as the gospel and can't deviate. Obviously, there is an element of subjectivity in assessing all of these situations. So ultimately, I think the committee as a whole thought illustrations could be useful, but we would say that they're not definitive, per se.

DR. McCABE: I have two comments, two individuals who will comment, and then I'm going to bring this section to a close, decide whether and how we will endorse this, and then I want to talk a little bit about the subcommittee on genetics for NHRPAC also before we break for lunch.

DR. COLLINS: I just want to raise a possible concern about what otherwise seems like complete harmony between these two documents, and I think it's really important to make certain that if there is a discrepancy and it wasn't intentional, that maybe it get looked at. The NHRPAC document, in its last paragraph on the first page, suggests that IRBs can make a decision about whether or not a particular individual should be treated as a human subject in a way that suggests that there may be circumstances where somebody on which individually identifiable private information is being collected could still be called not a subject. That differs from the NIH approach, which says that you do have to call them a subject in that circumstance, but it's possible that you might want to waive the requirement for consent because of the minimal risk.

I actually think the NHRPAC statement may not be completely in concordance with the

Common Rule in the way that that last paragraph on page 1 is stated, and it might be good to clarify that so that somebody doesn't get misled by what you're trying to say.

The other comment I would just say is that in addition to the examples, it might be useful to provide one of these simple little flow charts about what are the circumstances that one should consider in trying to decide is this third party a human subject, yes or no; if it looks as though they are a subject, then what are the circumstances under which the IRB might want to waive consent. I mean, it's all information that's very familiar to all of you because you think about this every day, but it would probably help those who were trying to get used to this new context to have that kind of algorithm, as well as some examples to guide them.

DR. McCABE: I'm impressed that anyone on this Committee would recommend a flow chart or a decision tree, having approached what we thought was a very simple approach to decision making in our own program. But I'm glad to see that you're so naive to continue to think that these things were simple.

DR. COLLINS: I'm still just a young idealist, I guess.

DR. GREENE: My question is actually very closely related to Dr. Collins' question, and I really want to second what he just said. As I look at the NHRPAC statement, it's got extremely clear laying out of process and a very clear laying out of the issues that need to be considered. But I think in the presentation you pointed out that there are some very subjective words, and the IRB is directed to consider these issues and then to make a decision -- and Francis pointed out a question there about what that decision would be -- but absent some examples or some specific suggestions for how an IRB might approach it, I think there's room for one IRB to say that information about my father's manic-depressive disease is so terribly confidential, if he were still alive, that it would require him to be consented and lead you into the whole

discussion of does my right to participate in a study trump his, where another IRB might take the entire opposite view. My question is that it's not clear to me whether these are looked at as a packet. My sense is that the NHRPAC document stands alone and that the NIH document stands alone, and I'm wondering whether the NHRPAC document, absent some more specifics, might be a little premature to endorse. I think you said you're putting it up on the Website for comments, and I think it might be appropriate to see how that evolves before going further.

DR. MARSHALL: I should remind you all that in terms of process, what you have in front of you is subject to some perhaps revision on the part of OHRP relative to the commentary that we receive. So where we are in the process in this sense is that we have approved of what is in front of you as a committee. We will be adding the concrete examples relative to the definition or the perspective that is here. But then our process requires that we put our documents on the Web for public commentary and input before they are sent in any final way to OHRP. The issue that you and Francis both raised is something that received considerable debate and consideration both within the separate work groups and then the combined work groups when they came together. I guess the realization on our part that there is, as Kate mentioned a moment ago, a very fine line between providing what some might consider to be overreaching rule making on the part of a Federal agency or an advisory committee and something that is really concrete, pragmatic and helpful to IRBs is a difficult thing, and we certainly are shooting for the latter. So it was, I think, uppermost in our minds that we not create something that also is not flexible over time, as the evolution of processes of research move forward. We would not want to constrain IRBs in any way in something that is so hard and fast that it doesn't evolve along with the research world.

DR. McCABE: Barbara, but I would ask people now to begin to address their comments about whether we wish to make this endorsement.

DR. KOENIG: On that point, I think that perhaps we should wait with the endorsement until the public comment period is past, just procedurally. Is that the case? Otherwise we'd be endorsing something of which we haven't seen the final version.

MS. GOTTFRIED: Just to clarify, now that the document is final, it gets transmitted officially by the chair to the Secretary and the director of OHRP. So although the material will be on the Web and we will welcome comment, there's no official end to the public comment period, because again, it's not a proposed rule per se.

DR. KOENIG: I just have a broad comment about the issue of the Common Rule and the human subjects protection mechanism more broadly. I just invited to Stanford to do a grand rounds talk one of the only people who was on both of the major presidential commissions starting in the early '80s that developed this whole regulatory mechanism, and he was reflecting on this over three decades. This was Al Johnson. He reminded me very, very strongly, and I want to get this into the record, that the whole research environment has changed fundamentally and profoundly over the last three decades, since some of this rule making was instituted. So I'm a little concerned that there's a lot of worry about the fact that we can't propose changes in something as fundamental as the Common Rule, but remember that the climate and the environment are so different that at some point we may need to reexamine those. So I understand the pragmatism of the desire to not futz with something that took so long to get into effect and which works in some ways. But on the other hand, I might like a little more boldness in some of these areas.

DR. MARSHALL: Thank you for making that observation. It's something that at our very first meeting we realized in terms of process. We're not defeatists in terms of the idea that the Common Rule cannot be changed. It's uppermost on our minds. So we actually have a process as we move along for identifying within any work group, be it the financial relationship conflict

of interest work group, genetics, third parties, children, that the work groups clearly articulate anything that they would recommend in the future relative to changes in the regs. So we very much plan on making those sorts of recommendations.

DR. McCABE: Thank you.

DR. BURKE: The question was raised by Ed whether we should endorse these documents. We've had very constructive conversation about ways in which there might be some value in further clarification about whether there are any real inconsistencies between the documents and examples that might illustrate the conclusions. That said, I actually think that it would be of value for this Committee to endorse the process that led to these two documents, to recognize them as complementary documents, and to basically support the spirit behind the documents. Perhaps with that kind of endorsement, also append our interest in further evolution of the documents based on public comment and further clarification of the documents based on specific examples.

DR. McCABE: I'll entertain that as a motion. Do I have a second to Wylie's motion?

DR. KOENIG: Second.

DR. McCABE: That was a second by Barbara Koenig. Further discussion of the motion?

(No response.)

DR. McCABE: And you were taking furious notes. You changed hats again, Sarah, and were taking furious notes. With no further discussion, all in favor of the motion say aye.

(Chorus of ayes.)

DR. McCABE: Any opposed?

(No response.)

DR. McCABE: Any abstain?

(No response.)

DR. McCABE: So it's unanimous. So we'll craft a letter to the Assistant Secretary of Health and Dr. Slater. Thank you both, Dr. Marshall and Ms. Gottfried. On behalf of the Committee, I want to thank you for NHRPAC's work on these third party issues and for taking time today to present the outcome of your deliberations. Your appearance really helps us to build bridges and a solid connection between our two advisory committees, and I'd like to suggest that we continue staff-to-staff, chair-to-chair, to communicate closely with another so that our issue agendas and work plans can continue to be complementary so that we're collaborating where appropriate and avoiding redundancy and overlap whenever possible.

I'd also like to suggest that, given the hour, perhaps the discussion of the genetics subcommittee could be held at some future date when we could give it adequate time on our schedule, if that would be acceptable to you.

I'd also like to thank Jim Hanson and Sarah Carr for your work and your colleagues' work at NIH, and for your presentation on the NIH recommendations. Thank you very much.

With that, we're now recessed for lunch. Members and presenters, please proceed to Bello

Mondo, and for other members of the audience there's another restaurant in the hotel for the public. We will resume sharply at 1:30, so please be back here at that time. We have an exciting afternoon. We have an international presentation of horizon-setting that will include both private sector and presentation from the Province of Ontario, so we're looking forward to that.

(Whereupon, at 12:52 p.m., the meeting was recessed for lunch, to reconvene at 1:30 p.m.)

AFTERNOON SESSION (1:45 p.m.)

DR. McCABE: Let's go ahead and get started. We're extremely pleased to have with us today two colleagues from Canada, Dr. Anne Summers and Dr. George Browman, who are here to inform us about some of the important work that the Ontario Provincial Advisory Committee on New Predictive Technologies has been doing to develop strategies and policies in the area of predictive genetic testing to help the Province of Ontario keep pace with this rapidly evolving area of healthcare services.

Dr. Summers is the committee's chair, and Dr. Browman is the chair of its evaluation subcommittee. I was honored to have been invited by Dr. Summers to present the SACGT's work to the Ontario committee in September 2001. I think you will see that although our healthcare systems differ significantly, the two committees have similar mandates, and the efforts that Dr. Summers' committee has been making to develop a framework for the Provincial Health Ministry to use in making decisions about the funding of new predictive genetic tests has some interesting elements in common with SACGT's efforts to enhance premarket review of genetic tests and the effort to develop a classification methodology for genetic tests. Background on the committee's work is at Tab 3.

Dr. Summers is director of the Maternal Serum Screening Program at North York General Hospital in Toronto. She is also director of the Familial Melanoma Clinic at the Toronto Sunnybrook Regional Cancer Center. She was responsible for the initiation, implementation and maintenance of the Ontario Maternal Serum Screening Program and the Integrated Prenatal Screening Program at North York General Hospital. Dr. Summers also serves as the chair of the Canadian College of Medical Geneticists' Committee on Prenatal Diagnosis. Her interests focus on the bioethical issues in genetics. She is board certified in medical genetics and pediatrics. Dr. Summers was appointed chair of the advisory committee in April 2000 by the Ontario Minister of Health.

Dr. George Browman is the chief executive officer of the Hamilton Regional Cancer Center and Cancer Care Ontario, Central West Region. He is also a professor in the Department of Clinical Epidemiology and Biostatistics at McMaster University, and the director of the Program in Evidence-Based Care for Cancer Care. His clinical specialty is cancer of the head and neck. Dr. Browman is interested in clinical practice guidelines development and implementation, evidence-based decision making, health information sciences, and evaluation of clinical interventions in cancer.

Dr. Summers will present the committee's work in developing principles, guidelines and criteria to guide decision making about the introduction of new genetic screening technologies. Dr. Browman will discuss in more detail the committee's efforts to develop an evaluation template to assess new genetic services. Dr. Summers, Dr. Browman, thank you very much for being here. Dr. Summers, please proceed. We will be having the discussion of their presentations later in the discussion period for the horizon-setting session.

DR. SUMMERS: Thank you very much, Dr. McCabe. I hope everybody can hear me. I'm just getting over the flu, so my voice is fading in and out. Dr. McCabe asked us actually several

months ago to present our work on mapping the future in genetics in Ontario, which we've called our report. What I'd like to do is talk first about the Canadian context, which is a little bit different than the American context, briefly review the impact of this huge change in genetics, which I think has precipitated both committees, and then the work of the Provincial Advisory Committee.

Now, just to let you know where Ontario is, if you don't happen to know, we consider that we're in the center of Canada, although other Canadians don't. We actually are the most populous province of Canada. We have about 11 million people.

Moving on to the Canada Health Act, which is basically what we all have to function under in Canada if we work in medicine in any way, the Canada Health Act was passed in 1984. This has formed the basis for our healthcare system, which most people are aware of. It has five basic principles. The first one is public administration, and this has to be done by each province or territory and should be non-profit. So for anybody who deals with molecular testing, we often have our health insurance plan pay for the molecular testing for out-of-province. Comprehensiveness. All insured services must be covered. There are some services, such as cosmetic surgery, which are not covered, but basic healthcare is definitely covered under this. Portability. So if a person moves from one province to another, they have to be covered in the new province as they were in the old province. Universality. Every single person in Canada must be covered. Accessibility. So within reason, all services must be accessible to all Canadians. Now, you can imagine that's a bit ambitious and is not exactly the case, but certainly for basic care it is.

This is just showing Ontario up close and showing the geographical problem, which is a problem for all of Canada, maybe less so for Ontario than for other provinces. But you can see down at the bottom the high-density area. Probably 9 million of the 11 million people live in

that very small area between Windsor and Ottawa, with the greater Toronto area having about 5 million, and then the other 2 million are spread out around the province. This is showing our genetic centers. The most northern genetic center is Thunder Bay, which is on the northern shore of Lake Superior, and that has to service probably another thousand miles to the far north point of Ontario. So you can imagine that geography is a big issue for Ontario, probably more than most states I would think.

Just briefly looking at the impact of change in genetics, I think this is probably the same everywhere when we're looking at medicine. We have to get more involvement of family physicians and non-genetic specialists. This is a big problem in Canada, and I don't know how it compares in the U.S. We have about 100 clinical geneticists in Canada. We have 28 in Ontario. So there's no way we can handle cancer and heart disease and all the things that are coming down the pike.

People have to start understanding the difference between prediction and diagnosis, and we find with our medical colleagues that this is still a big problem. Increased complexity of risk calculations, particularly starting with cancer, is only going to get worse with things like cardiac disease. Things like pre- and post-test counseling, which physicians don't generally do these days for things that they're dealing with, and long-term follow-up, physicians are going to have to take into account psychological and ethical concerns as well.

On society, again, probably the same everywhere in the world, a need for better understanding of genetics in the general population. The general population is going to have to take more responsibility in their understanding of healthcare. They also need to know the difference between prediction and diagnosis for a variety of ethical issues. Testing for disease versus trait has to be a public discussion, and ethical issues.

Government I think is a little bit different in Canada than in the U.S. I think for most democratic governments, we hope that the government reflects the views of society, and they do some of the time at least. We need more public debate on genetic issues. These are not issues that should be decided by 100 geneticists or 28 geneticists. We need a wider discussion.

For Canada, the particular issue is the funding of new or expanded services, because every test we fund has a whole series of downstream costs that have to be taken into account. Legislation and regulation have to be considered, where required.

So on to the Provincial Advisory Committee on New Predictive Genetic Technologies. We've tried to limit the scope by putting in predictive, and then we kind of expanded it by putting in technologies. We decided that we couldn't really define predictive when it came down to it, so we've all but dropped that word from the title. Our job was to develop principles, guidelines, and broad criteria to guide operational decision making by the Ministry of Health and Long-Term Care in introducing new genetic predictive technologies in Ontario. This, we felt, required a very broad expertise. I think you have the handout, so I'm not going to go through the whole list of the people who are on the committee, which are the next two slides, but you can see from your list that there was quite a wide representation. The second one on that list is representation from the private sector, which probably in the U.S. is not very surprising. In Canada, this is not something that we generally think about, but it is an up and coming sector.

The committee was announced by the then minister of health on April 19th, 2000. Our first meeting was September 2000. Our subcommittee's work was done over the following year, and the first draft of our report was October 2001. Now, the political imperative here was that our premiere, who would be similar to the governor of a state, took genetics to the table of the premiere's meeting in August of last year and promised to have a position paper by January of this year. So we felt that we had to get our report out in time for that. So our final report,

which I think was 28 drafts later, came out November 29th, 2001. I'm sorry I don't have that for you, but it's still not been made public by the Ministry, although they assure me it will be public within the next 10 days. When I have it, I'll forward it to Dr. McCabe.

We started with seven subcommittees and dropped back to six: ethical/legal, evaluation, lab, clinical, psychosocial and education. We also had a resource subcommittee, but given our change in time frame, we didn't have time to let them do their work. I think I'm going to kind of zip through these slides because you have them in front of you, and also I will discuss them later in the recommendations. But the ethical/legal subcommittee was asked to look at a whole host of ethical issues, from privacy and confidentiality, which I think is to be expected, down to the use of microarrays and multiple disease testing at the same time. The evaluation subcommittee Dr. Browman is going to speak about and I'm not going to touch on that at all.

The lab subcommittee had to look at the change in technology and when it would be appropriate to change to a new technology and when it would be appropriate to stay with what you're at. Obvious issues like quality assurance and regulatory issues, lab licensing. Incidentally, none of our molecular labs are licensed, so this is fairly important. Specimen and data management, development of laboratory expertise, and along with that the infrastructure and personnel issues, which are a big problem in Canada. Also, the necessary volumes per test, how do we maintain competence and expertise. Standardized reporting is, I think, a dream for those of us in the trenches, because it would be really nice to know what you're reading on a report. Very often they're quite obscure. And the role of the private sector.

The clinical subcommittee, again probably fairly obvious tasks that they were asked to address. The eligibility criteria for referral and testing, the reason this came up was we have an implementation committee for breast, ovarian and colon cancers, and that committee has taken 18 months to come up with referral and testing criteria. We really would like to streamline that

process as genetic testing comes online more and more. They had to look at access to testing, and this is, of course, a geographical issue to a great degree in Canada rather than a financial issue. Management of persons changing from at-risk to affected status; service standards and requirements within the clinic; counseling guidelines, patient follow-up plans, and regulatory requirements. The reason that's under here is in Ontario, all healthcare professionals are regulated, other than genetic counselors and Ph.D. lab directors, and that's quite an issue for liability.

The psychosocial subcommittee had to figure out a way to integrate psychosocial support into genetic services. They're obviously desperately needed. We have a lack of psychosocial support in all areas of medicine, and this is just somebody else grabbing at it. We asked them to come up with recommendations for screening persons at risk requiring psychosocial counseling. So who do we need to refer to the psychologist or psychiatrist, and who could we not refer, again trying to streamline services. Also, like the clinical committee, management of persons changing from at-risk to affected.

The education subcommittee had a massive job, and this was basically to look at all education of everybody in the province with genetics. This was to look at public education, and I've heard some discussion of that here, how could we educate the people of Ontario so that they could make informed decisions about genetic care. Professionals all need upgrading in genetics, and we needed some kind of education for specific disorders.

So, on to the recommendations. Our top recommendation, I think probably the most important is that we couldn't complete this work ourselves and there is definitely a need for an ongoing provincial genetics advisory committee, probably for the management of genetics.

We recommended an evaluation process, and we recommended that be based on Dr. Browman's

template, which he will be discussing with you after. Part of that evaluation is to look at genetic services rather than genetic tests, and this is very important, as I mentioned before, because of downstream costs. So a genetic service would include everything related to that service, including legal, ethical, social, psychosocial, epidemiologic, clinical and lab components. There were a number of other features of the evaluation process. One important one was balancing the costs of new tests versus other prevention strategies. So, for example, a new gene for a cardiovascular disorder, how much would that cost compared to an anti-smoking campaign. The idea of developing guidelines and care maps in the genetic management of whatever condition is being reviewed. This is kind of reiterating what I just said about programmatic genetic services. These have to be integrated, multidisciplinary depending on the particular service, and they must include genetic assessment and counseling, quality testing, psychosocial support, and follow-up services, including surveillance, prevention and treatment.

Education and information. Our education subcommittee recommended to the Ministry that there be a full education program which would involve more than the Ministry of Health. It would have to involve the Ministry of Colleges and Universities and the Ministry of Education, and possibly the Ministry of Social Services. So this would be a huge undertaking if the Ministry chooses to do it. We recommend public education, professional education at all levels, so starting in early medical school all the way through to residency and fellowship, but also all healthcare providers, not just physicians. Information for new genetic services for providers and the public as they come along.

Quality, again looking at the service rather than the test. Pre-test preparation. So the counseling and educational materials, obviously the laboratory test itself, follow-up, so the interpretation of the results and reporting to patients, and then, very importantly, patient monitoring following testing, because we do need to evaluate each service because we can't

keep adding and adding and adding in a publicly funded system. We have to subtract every now and then. One of the issues is out-of-province testing, which we use a lot, and we need to ensure quality for that. In the U.S., we only send to CLIA-approved labs. When we're sending to other countries, however, we're not quite as clear on their quality services.

Human resources. I would expect this is a big issue here. It's probably a bigger issue in Canada. As I said, we have very few geneticists in Canada. We're not training very many. Probably two or three come out per year, clinical geneticists, and probably the same number of molecular lab directors and cytogenetic lab directors. So we need to encourage retention and recruitment of personnel to genetics training programs, and we need to enhance those programs. We also need to ensure that all personnel directly involved in genetic services work in a regulated healthcare environment, and this is again covering the fact that counselors are not covered under our Regulated Health Professions Act.

The rest of the recommendations are from our legal and ethical subcommittee, and they've made a number of very specific recommendations to government with how to do things, not just to do things but how they can do them. For non-discrimination, they've recommended amending the Ontario Human Rights Code to prevent discrimination on the basis of genetic traits, and they've suggested several methods for doing this. They also suggested an approval system for the use of genetic testing and information in insurance and employment. They've gone further, actually. As a committee, we recommended a moratorium on the use of genetic information until this kind of approval system could be put in place. Research, somewhat of a motherhood statement. However, while we do have research guidelines in Canada, they have no actual mandate. So we would like something a little bit stronger, making sure that all genetic testing undertaken in the research context will have thorough research ethics approval. Patents, direct marketing, and commercialization of tests. We basically recommended discussions between the Ontario government and the federal government for this. Our

committee didn't take a strong stand on patents, probably because we had a representative from the public sector. Our premiere and our minister of health, however, have taken very strong stands on this, and I don't know if you had a look at this document, "Charting New Territory in Healthcare," which came from our premiere's office, but basically it's much about patents and not the concern about royalties but the concern about the restriction and control of testing in other countries, which it does not look kindly upon. Informed consent. This was an interesting discussion because the lawyers and the doctors were split down the middle. Basically, the lawyers wanted written consent, the doctors wanted implied consent. The law says implied consent, so we compromised at documented consent. Duty to warn. This was an issue that we felt needed revisiting. We felt overall this should not be a duty of the physician to disclose genetic information to high-risk relatives, that this should lie with the patient or the consultant. However, we would like the government or the power-that-be to have another look at this and look at the issue of liability when a physician does feel that the risk is high enough to breach that. Privacy and confidentiality. We are currently -- I'm not sure if I should say developing or have developed privacy legislation in Ontario. There's very little about genetics, and the part about genetics actually makes very little sense. So this is probably a good time to suggest they follow our wish list here and mention all of these things. Finally, genetic testing of minors. This very much follows the ASHG/ACMG statement on the testing of minors, that there should be no testing where there are no timely medical or psychosocial benefit or when such benefits accrue in adulthood. Generally, we felt parental consent should be obtained for newborn genetic screening and that it should be looked at when there are exceptions to this. When banking newborn screening data and samples, individual rights of privacy and confidentiality should be protected. Informed consent should be integral to the practice.

That's the recommendations. I should say there are many more recommendations in the text of the document that I couldn't possibly cover today but which do address many of the issues in the terms of reference. This is just a list of the members of the committee, and each and every

one of them did a huge amount of work in a very short time.

DR. McCABE: Thank you, Dr. Summers. Dr. Browman?

DR. BROWMAN: Well, thank you. Thank you for inviting me to address you. I hope everybody can hear me. This is the report just from the evaluation subcommittee. It will be difficult in the two hours that I have to do justice to this but I will do my best.

The report – this is the report here – and I wish I could share it with you, but once we submit this to the government, it becomes the property of the government of Ontario. Until they release it publicly, we can't share it. But I really hope that you'll be able to see it soon. The report is in eight sections, and I'm going to basically show you some highlights of each of these sections. The discussion papers at Section 7 are really five discussion papers that are written as scholarly pieces to examine various aspects of evaluation and genetic predictive testing, which are part of the report but will also be submitted for publication as independent papers.

I just want to acknowledge that the evaluation subcommittee was extremely grateful for the work that SACGT had already done and built along the lines of the work of SACGT, and I'll show you where some of our approaches might be slightly different from your approaches.

I'm going to say something about the Canadian context which I think complements what Anne was saying. First of all, the purpose of the evaluation subcommittee was to prepare an evaluation framework upon which decisions could be made, and these decisions will define access to people to these tests, which is different from the kinds of decisions I think that you're talking about. Access is, by legislation, universal and not based on ability to pay. We have a single payer system, which is the government, and therefore decisions compete with other allocation decisions. So any evaluation template has to take these issues into account. While

your committee, as I understand it, principally is concerned with federal approvals and oversight, with a focus on safety and effectiveness, resource allocation decisions basically are devolved to the individual level. In our particular case, Ontario principally is concerned with resource allocations from a societal perspective, where evaluation of a genetic test service as a whole must precede evaluations by individuals who wish to access those services, and therefore the evaluation strategies will be different.

We started off with some guiding assumptions, and there is actually a section in the report called Guiding Assumptions. The first is the unit of analysis. We decided early on that the unit of analysis was not the test itself but the whole service, the service being defined as the test, the population to which it applies, and the clinical condition or conditions of interest for this test.

We also examined methodological criteria similar to the ones that you examined in terms of analytical and clinical validity, clinical utility, and something we call social utility. I will say a bit more about that in a few minutes. At the beginning we decided to avoid, despite quite a bit of pressure, formulaic approaches with scoring systems, but to understand that an evaluation template should not replace a decision but inform a decision. We felt that an holistic and iterative, as opposed to linear hierarchical, approach should be used in terms of the steps used in evaluating these technologies.

The role of evidence is crucial to our particular report, the importance of looking at study quality, systematic reviews of bodies of evidence as opposed to individual studies. But we also understood that evidence doesn't exist in a vacuum and must be interpreted by different stakeholders, so evidence has to blend with experience and expertise in terms of coming up with decisions.

The term "jagged cutoffs and gray zones," and I'm going to show you what that means in a

minute or so, this is where we're avoiding formulaic approaches, and we feel it's the process of decision making with multiple stakeholders, guided by rigorous methodology, that allows groups to actually come up with the right decision in a political, social, and economic context that's important. That is, we can't impose decisions on people. So, in other words, despite the evidence-based philosophy, the decisions involve uncertainty, values and judgments, and our template tries to be explicit about what those values and judgments might be. Finally, we suggested a process for decision making with the features that there should be multiple stakeholders, transparency, and that specific circumstances needed to be taken into account.

Some of the principles that we addressed in terms of designing the template were, first, that the evaluation would actually be conducted by a group that would make a recommendation around making genetic tests available. The decisions are government decisions. So we're making recommendations, not decisions. Secondly, the evidence base has to include expert input. Third -- and I've talked about this -- a multidisciplinary process with stakeholder participation and explicit consideration of values. I've already discussed that.

Now, in terms of decision steps, and this is just sort of in rough form, the kind of issues we recommend the evaluators will go through, and I did provide a copy of our evaluation template which is not yet polished, but it just gives you a sense of what we were considering. Any evaluation group we felt had to start with what is the purpose of the test or the service, and what is its relevance and importance, and to whom. To the individual? To family members? To society as a whole? These are value judgments. So, for example, if there was a genetic test that could predict whether or not you would get widows peak, the question is should the public health system pay for such a test because people want that test? That would be an example where the answer would be no. Of course, there's a lot of gray areas in-between that.

Secondly, it was very important that once one decided that the purpose was appropriate, that we

needed to know what the effectiveness of the test was, or of the service, and how useful it was -- that is, what was its utility. Effectiveness is really measured in terms of analytical and clinical validity. Now, we do not actually define validity in the same way as SACGT, and I'll show you that in a minute. We look at, for instance, sensitivity/specificity and utility and accuracy as test performance characteristics, not validity characteristics. I'll show you something in a minute around that.

Also, in looking at effectiveness and usefulness, the important thing for evaluators to consider is what were the alternatives available to this particular technology, was there an attempt to compare the performance of the different alternatives, was study quality taken into account? In other words, you may have information on sensitivity and specificity. The question is were the studies upon which this information was based rigorous enough to ensure that these performance characteristics were properly determined?

Then in terms of effectiveness and expected use, what the desired outcomes would be, we looked at what I think your committee called social consequences or -- I don't remember what the term was, social something or other. We used the term "additional effects," that is both secondary and desired and undesirable effects or outcomes, such as labeling effects on individuals, personal, societal and cultural. Also, the additional effects would have positive or negative value depending on the perspectives of family members, the individuals being tested, and society as a whole. Finally, because in the end this is an affordability issue in a publicly funded healthcare system, we had to address issues of economic considerations, what would the costs of the technologies be or how would they evaluate the costs, the growth potential, and the economic benefits, as well as cost avoidance issues.

This is the process that we recommended for decision making. There are three levels here. You have the decision maker, which is the payer, which for us is government. Then we suggest

that establishment of an advisory committee, which is an arm's length, multi-stakeholder group which is a permanent committee, and then a series of expert panels that could be ad-hoc panels depending on the evaluation problem that they were given. The file would be identified. It could be identified through a horizon-scanning approach; that is, the advisory committee sees something coming down the pike and wants to get it into the evaluation system, or somebody could submit a file to the advisory committee, asking for it to be evaluated. The advisory committee could do a preliminary assessment. It would then identify an expert panel and ask them to evaluate purpose, effectiveness, and so on and so forth, and cost.

Once the evaluation committee completed its assessment, it would report back to the advisory committee, and then a recommendation would be made to the decision maker. Then finally, we feel that there should be ongoing review of the appropriateness of tests so that they don't necessarily become permanent if there's something else that can replace them or if they're not performing well.

Now this, I think, is probably one of the innovative parts of our evaluation process. This and the next slide I hope will be able to explain it to you. Basically, the conceptual framework is based on what we call confronting gray zones in the evaluation and coverage of genetic testing. The idea here is you're staring to develop an evaluation framework, there are certain black decisions and white decisions which are very easy, and then there are all these decisions in the gray, and that's where we haggle about what's an appropriate evaluation framework for figuring out differences at the margins in the gray area. The gray zones concept includes three components. We actually called them dimensions to begin with, but it's not three-dimensional because it doesn't fit into a cube, for example, so we're calling them components. Component 1 are the evaluation criteria, which I've already gone over – the purpose of the test, effectiveness, additional effects, expansion potential, and economics. Component 2 is what we're calling the coverage conditions in the gray. That is, if a test should be made available and it's pretty

obvious, that's white. If it should be rejected and it's pretty obvious, that's black. But where we're going to have difficulty is in the gray zones. We felt that the way to handle the gray was not to force a decision, yes or no, but to put conditions on how it should be covered, and the kinds of conditions that you might put would be, well, yes, introduce it but as a pilot study, or introduce it as a restricted protocol, or with scheduled review or with regulation, or against a certain set of priorities. That way, this doesn't stop a test from being introduced, but it does allow a more controlled introduction. Component 3 was what we called cutoffs and thresholds, and we divided these into deductive and inductive processes. That is, if we were going to establish cutoffs for decision making, if it's above this cutoff it gets funded and below it doesn't, then what are the kinds of decisions we've made previously, are there some basic principles that ought to guide us, and so on and so forth.

So those are the three components, and they're integrated into the gray zones. This is what the gray zones looks like. In fact, the whole thing is gray, but on my screen it's actually blue. The light gray is the gray. You can see the evaluation criteria on the first column, then the assessment of the test, and one would decide under "Intended Purpose" that it's either worthwhile or not worthwhile, or that it's unclear. So if the worthwhileness of the test is unclear, that's a gray area. You can see it's in a gray zone. Then we'd look at effectiveness, it's either effective or ineffective, or we don't really know, or it's on the margins. That's in the gray, as well.

In terms of additional effects that the test might have, they're either acceptable -- that is, we may find that a test performs extremely well but we're concerned that if it becomes available there's a huge potential for abuse and what you gain from the test is not worth what you're risking, therefore the additional effects might be unacceptable and you wouldn't approve it, or you'd wait before approving it. If the additional effects are worrisome or unknown, then you might go ahead under certain conditions. If the price is low, the expected demand is low and

the expanded potential is low, then there's no reason not to approve it if it meets all the other criteria. But if this is a high-priced item, then you might want to have some controlled introduction.

So basically what the gray zones concept does is allow decision makers to understand where they're going to have to -- and this is the concept that you folks came up with that we thought was very useful. This is the area where there's going to have to be some increased scrutiny because of the uncertainty around some of the decisions that have to be made.

There you see the jagged cutoffs. The jagged cutoffs conceptually -- basically the jagged cutoffs ask the question: If a test is worthwhile, what's worthwhile enough? Or if a test is effective, what's effective enough? Because we never have completely effective or ineffective tests, and our feeling was that we could not actually make judgments under current circumstances about what these thresholds would be, that these might vary by place, by the economic status of the province, by political issues, et cetera. So the idea is here's the concept, and really the decision around what the cutoffs are could vary, and they should be negotiated. That's what the jagged cutoffs are.

The evaluation toolkit -- and I think I provided you with that -- basically has six parts. One is an explanation about what the toolkit is. The second is a flow chart. I heard there was a comment that you folks have difficulty with flow charts, but we do have a flow chart. The flow chart is simply intended to provide people with an overview of what the template looks like. The evaluation template itself is really what the advisory committee or an expert panel would use. They don't actually have to use the template. They should be guided by it. We then have a summary evaluation template. This basically takes the very long template and summarizes it into several different statements that the committee can use as it puts its recommendations forward. I won't go into the other issues.

Here's the title, so a partial title of the discussion paper so you know what areas we researched and detailed in order to come up with this model. We have a document called "Assessing Validity: The Importance of Systematic Review Processes," "What Will They Really Cost? Economic Considerations," "Evaluating Predictive Genetic Technologies: The Ontario case in Perspective," where we compare our process to your process, and "Defining the Characteristics of Predictive Genetic Tests."

I'm going to end now with two slides which I'm going to try to highlight what we think are some of the differences we have to yours. This is our opinion, this is not truth. SACGT has not maintained a focus on development of categories, although you started out that way, but several insights were very useful. First of all, highlighting the role of analytical validity and noting challenges of orphan diseases, which we felt was very important. In terms of analytical validity and clinical validity, we have found that analytical and clinical validity are key evaluative criteria, extremely important, and the way that they have been positioned by this committee, we found that very useful. Our validity criteria, however, are slightly different. We refer to test performance, which encompasses both analytical and clinical validity, but it also focuses on study quality and whether or not systematic reviews were used. We have found the category of clinical utility one of the more important evaluation categories in a publicly funded system, and for us clinical utility is a function of both alternatives and outcomes. That is, there are various choices that you can make. You have to be explicit about what the choices are, what outcomes you want to achieve, and utility has to be defined by how the test will affect those who test positive, those who test negative, for both medical and non-medical outcomes. So it's quite a large evaluation problem.

SACGT defined a social consequences category, which we thought was important. We felt social consequences was a very hard concept to operationalize and we relabeled it as additional effects.

I now want to simply show you what I think is a very important concept for us, which is how we looked at validity. To us, sensitivity, specificity, accuracy, and the precision of risk estimation are really performance issues of a test. They're not validity criteria, per se. The issue is what is the quality of the studies that resulted in the claims for this level of performance? So if there's a claim that a test has 90 percent sensitivity, 90 percent specificity, and a certain positive predictive value, those characteristics were based on studies that were done. If those were poor studies, then these are not valid performance measures. So the next level is what is the quality and relevance of the studies from which the performance characteristics were derived? Were the appropriate study designs used? Was there a control for bias? Were the relevant populations studied? So you could have a test, for instance, whose performance characteristics are valid for a particular population, but they're not valid for another population to which they're supposed to be applied.

Thirdly, and we felt this was extraordinarily important, we felt that this area is very subject to publication bias and in particular to biased information being presented to evaluators where, for instance, companies who are proposing a test for evaluation will provide background information in which they select out the studies that make their product look good, and competitors will select the studies that make their product look not so good, and evaluators have to look at the consistency of the findings across studies for a particular technology. They have to look for unpublished studies, and they have to avoid publication bias by doing systematic reviews, which is a validity issue.

We've done some comparisons with the U.K. ACGT, and I'm not going to go over that. We also have something that I provided to you, that each discussion paper contains several key messages. You probably won't understand them completely without having read the papers, but I couldn't give you the papers, but I did give you a list of key messages, and I also, as a handout, gave you the rough copy of the evaluation template. Thank you.

DR. McCABE: Thank you, Dr. Browman. As I said, we will have discussion of these two presentations in the subsequent discussion period. Now we're going to hear three more presentations that together will provide us with a broad outlook on the economic future of genetic testing. Our next two presenters are from Frost & Sullivan, an international marketing, consulting, strategy and training firm whose clients include clinical diagnostic and medical device companies.

Mr. Dorman Followwill is vice president of healthcare and life sciences practice at Frost & Sullivan. Mr. Followwill oversees custom market research consulting enterprises and manages the healthcare business unit. His group has carried out strategic analyses for a number of clients, including Bayer Diagnostics and Biologicals and GlaxoSmithKline. His current professional interests include helping companies translate demographic, genomic and proteomic data sets into market opportunities.

Mr. Manoj Kenkare is research manager of Frost & Sullivan's healthcare and life sciences practice. He is responsible for business planning, strategy development, and implementation of healthcare practice, as well as design and development of new research methodologies and models. Mr. Kenkare has been researching and analyzing healthcare and life sciences product and services markets for more than 10 years.

Mr. Followwill will discuss the impact of discovery and diagnostics on the healthcare industry, and Mr. Kenkare will provide an overview of the Frost & Sullivan 2001 analysis of the U.S. genetic testing market. Mr. Followwill?

MR. FOLLOWWILL: Our presentation is basically a two-part presentation. I want to thank the Committee for inviting us here. My part of the presentation is really at the 30,000-foot level, to look at the healthcare industry as a whole and the role that genetic testing plays within

the industry as a whole. Then my colleague, our research manager, Manoj Kenkare, he will come down to about the 3,000-foot level and will analyze the U.S. genetic testing market in terms of specific forecasts and the real economics of that market.

The title is "Genetic Testing: A Key to the Future of Healthcare." What I want to talk about on this slide, this is basically my thesis slide. If you look at the healthcare industry in the U.S. today, there are really three mega drivers. Driver 1, patients. There is a demand side wave coming into the marketplace with the increased aging of the population that we've all heard a great deal about. That's certainly a key driver. Everyone is concerned about that. But there's also an incredible increase in knowledge among the patient population, and specifically in terms of genetic profile information, therapy paths, and all of this is contributing to an increased self-determination of patient care. Driver 1 certainly is the patients.

Driver 2, data and technology. With the vast genomic and proteomic data sets that are now coming online, there will be obviously an incredible new development cycle that we're just on the beginning of this curve in terms of therapeutic developments by high-performance computing. I was just reflecting last February, I was invited to IBM Life Sciences analysts briefing, and looking at the type of resources that that company is bringing to bear in this space is truly awe-inspiring. They've invited me back. In a couple of weeks I'll be up in Armonk going through with them the review of the last year's work in this space. An amazing amount of work being done in this area, and the data sets are truly awe-inspiring. Clearly, the new wave of drug discovery and development will be driven by high-performance computing and server farms, no longer driven by the wet lab. But it's not just in drug discovery. It's in highly integrated healthcare information systems. We're going to talk in a minute about GE Medical Systems, some of the things that they're doing. So Driver 2 is data and technology.

Driver 3 is the supply-side race to market. Everybody sees the demand wave coming. That

represents huge opportunity, new products. It also represents concern. There have to be new streamlined regulatory reimbursement frameworks, the whole eNDA initiatives, and there also need to be updated new provider infrastructures.

Now, if you look at these drivers, it's very clear that you've got a demand side driver that is a wave of grave concern. You have supply side factors trying to race to meet that incredible wave in the market. And in between the two is data and technology. How will a coming demand-supply gap be closed? Technology will play an incredible role in that, and genetic testing will be, I believe, a key catalyst spurring and enabling each of these drivers in different ways. We're just seeing this emerging in the market. But over the long term, it will flex its muscles, increasingly so over time. A quote from Dr. Venter: "While unlocking genomes may not have the short-term effects that some biotech proponents have theorized, it is clear that there will be a long-range impact of genomic research on drug development," and I would want to expand that to not just drug development but diagnostics and a whole host of areas across the healthcare landscape.

So let's drill down a little bit. Driver 1, patients, patient need. We've all heard about the aging population. But with that aging population, there will be a coming increase in chronic illness prevalence over time. This creates an unprecedented wave of patients on the 5- to 10-year horizon. By the way, this is not just a U.S. issue. This is a global issue, as my next slide will show. Patient awareness, a vast increase in knowledge of patient diseases, new access to genetic profile data via genetic testing, growth of online support groups. All of these things drive an unprecedented level of patient awareness. Anyone in private practice knows that the patient today does not take the care provider's word as gospel any longer. There are questions and more questions. Unprecedented levels of patient awareness. Patients, therefore, becoming self-determining drivers of healthcare, dictating over time what technologies will be developed, demanding greater and easier access to care. We're seeing this all across the country.

Suggesting therapy alternatives, opting for alternative therapies, et cetera. Very interesting degree to which the patients are really the drivers. I was talking about the increase in the average life expectancy. Of course, we know that the aging population is a key driver in the U.S. It's true globally. Current global life expectancy is 68 years, but there's a 50 percent increase from 1955 to 2025. That's absolutely amazing. Then dramatic advances in medical technology, successfully applied, have driven the global increase.

Driver 2, data and technology. I had the privilege about two months ago of being at Oracle's life sciences day in San Francisco, where Dr. Venter presented, and he presented a basic thesis, that the future of biology today is really equated to the future of computing. This is what many of us have seen in the industry as the convergence that has been going on between the biological sciences and the computing sciences, where really drug discovery is driven increasingly today, and certainly in the foreseeable future, by high-performance computing, and the ultimate challenge is knowledge management because of the terabytes, the exabytes of data that we're going to start seeing coming out of the mapping of the human genome, et cetera, and then how we start translating that into new therapeutics. The data onset is truly awesome, and the challenge here is in knowledge management. Genetic testing is a great example of this driver, particularly in regards to cancer. It was interesting how much cancer has certainly dominated some of the conversation earlier today. Obviously, earlier detection will drive more cost effective treatment and reduce hospital stays, et cetera. Another example is minimally invasive surgical tools, MIS products, and then end-to-end healthcare information solutions. Everyone realizes that data management and information technology really is becoming increasingly important at every level within healthcare.

GE Medical Systems. I believe in the basic principle that if you want to understand the dynamics of an industry, you look at the industry leaders. You look at what IBM Life Sciences is doing in the life sciences. You look at what GE is doing. GE Medical Systems approached

us about six months ago asking us to co-author with them a press release about an entirely new strategic direction they're taking, and their new strategic direction is to divide their business into basically three strategic units. Well, one of those units is called GEMS-IT, GE Medical Systems Information Technologies, and it's for the express purpose of providing the healthcare system with better data management, streamlining care for the patient.

This is a huge driver, driver 2, data and technology. If anyone questions the role of IT in healthcare, you won't question it in five years. You certainly won't question it in ten years. This is a quote from the Institute for the Future: "Baby-boomers will impact healthcare in ways never seen before. They will place more demands on hospitals and clinics, not only for their own needs but also for the needs of their children and parents. At the same time, healthcare is expected to be revolutionized by advancements in information technologies that will help improve patient flow, information sharing, and administrative services."

Driver 3, the supply side race to the market, racing to overcome current supply side challenges. Certainly, there are regulatory challenges. There's an FDA head somewhere in our future; we hope so. Streamlining drug discovery and development on the manufacturer side, on the part of big pharma, on the part of biotech, on the part of the life sciences company, representing the fusion of IT and drug discovery. Streamlining that entire process. At IBM Life Sciences, for example, they're talking about drug discovery and development timelines being shrunk from the typical 10 to 12 years down to 4 to 5 years. All of that is fine and good, but if there's not a similarly streamlined approval process, we're going to have a far greater bottleneck even than what we have today. This is where the eNDA hopes and dreams come into play. Convergence products, meaning interdisciplinary products and services, are very well funded, a tremendous amount of investment capital being funneled into biotech and convergent type products right now. But those products, there's no guarantee they'll be marketed or sold well. It's a question: Do great scientists make great business people? Big questions in that area. Then current

provider infrastructure is certainly strapped. New and updated centers of care are required so the wave on the demand side doesn't become a tsunami and completely overwhelm the system.

Talking about approval times for FDA, we were interviewing one of the CEOs of one of the top 20 pharma companies, and I raised this question with them, that no matter how we shrink the drug development and discovery time frame, if the approval times are not shrinking as well, then we've got a gigantic bottleneck coming. He said, actually, you're dead right. In fact, approval times are getting longer, and here's an example of that. I think we're going to see that over time. So there are definitely challenges.

The way to look at the future in healthcare is to say that there is a demand-supply gap that is coming. Demand: more and smarter patients, older, sicker, chronic, multiple disease states, living longer, increasingly more educated, and therefore more demanding. Supply, overburdened infrastructure. Chronic conditions require more resources and time to address, insufficient resources and clinicians waiting less, and the worst-case scenario is really one that we have to consider as a possibility, ruthless prioritization in terms of access to care.

So another way to look at healthcare is with the increasing demand-supply gap, there are unprecedented opportunities, but the question is who will close the supply-demand gap? This is where technology, I believe, really sits between the demand side and the supply side forces in a key way. The supply-demand gap will narrow as sound technology is applied to address a wide range of patient needs, and this gets right to our topic.

There are more tools today than ever. I thought what Dr. Slater said was absolutely priceless. Certainly 25 years ago, did we ever imagine we'd be sitting here talking about these things? The convergence of scientific disciplines in the drug discovery world, all the cheminformatics, bioinformatics, pharmacogenomics work that's being done. And in genetic testing and

diagnostic technologies, the prediction, the avoidance, the earlier treatment of diseases at earlier stages, and therefore diminishing demand at chronic stages, the whole idea that we can really think about individually targeted treatments -- obviously these will take a long while to develop, but we already are seeing the seminal work being done in the area of pharmacogenomics.

This has given birth, obviously, to all the new industries. There are already multi-billion-dollar "-omics" industries that did not exist five years ago. Companies -- and this is a key point -- that do not use genomics probably will not be in business in 20 to 25 years. Genetic research has become, I believe and many of us believe, a fundamental technology underlying a vast array of new therapeutic approaches. I see the work that's being done here as really being critical for the future. This is changing how medicine is practiced. Instantaneous diagnostics for microbial infections, very specific antibiotics that target specific microbes, and vastly more rapid screening for genetic diseases.

But with all this, there are unprecedented challenges. Challenges are unprecedented, and there are no easy solutions in sight, scientific challenges. Quoting again from Dr. Venter: "If there's any question about the complexity of human traits" -- this quote sort of puts that to rest. Next time you read a story linking a human trait to a specific gene, remember this: There will be few simple answers for complex human traits. There are ethical challenges. Genetic engineering; how far do we go? Are we playing God? It's a very interesting thing for me personally. Not only am I vice president of Frost & Sullivan's healthcare practice, but I'm also a very passionate and devout Christian. I preach two out of four Sundays at my local church. I'm wondering about the ethical side of genetic engineering. Are we playing with the very seeds of life, and are we playing God? Technology for me is an amoral thing. Where we have to consider the ethical side of this is in the wise application of these technologies, and there are significant ethical challenges associated with this as a broad topic area.

Patient access to care. This is a gigantic concern to me personally. If demand outstrips supply, what then? Already in my county, I'm seeing that many of the older members of our county, and there are quite a few in my county in California, are being cut out of their insurance programs. Patient access to care is a serious, serious issue. Another serious issue on the ethical side is confidentiality of patient data. Who has access? This to me really cuts on both sides. I want to see the preservation of privacy on patient data. On the other hand, when I think about what a barrier that is to knowledge management and data mining and where we could go if we could figure this out is really an awe-inspiring thing to consider. Regulatory challenges. Commercial approval processes. One of the huge issues facing any drug development company is the huge development costs, with no guarantees at the back end. Strapped regulatory agencies, even headless in the case of FDA. Another challenge that I think is interesting is considering global harmonization of approval standards. Can a gap between U.S. approval times and, say, European approval times be narrowed? Challenges in that area. Obviously, these are grave concerns. Look at the increase in adverse events numbers, postmarketing adverse events reports, certainly a significant increase over time. Funding reimbursement challenges, the growing role of CMS and AMA in genetic testing. Commercial approval does not guarantee reimbursement. I'm concerned, again, about these issues devolving into ruthless prioritization, the emerging system of haves and have-nots, like I'm seeing in my own county, which, I believe, will bring, at the end of the day, unless something changes, an increase in out-of-pocket expenses. That has, for years, been going down. We're going to see, I'm afraid, that curve start to up-tick. Other challenges. Growing immunity to antibiotics. Obviously, the folks at CDC are very concerned about this. Undiscovered virus sequencing we all know raises as many questions as it answers. New ways of thinking about diseases will be adopted slowly, and the full promise of genetic testing has barely been tapped. There will be challenges in tapping this further.

The last two slides. What I see for the future of healthcare is a bumpy ride. Patients will

undoubtedly wield more power. Providers will undoubtedly be strapped and wield less power. There will be the continued convergence of data technology and unmet clinical needs. But I was very intrigued this morning to listen to Reed's concern about the coordinated effort being needed at your level. I see as being the fundamental issue at the total U.S. healthcare level that a coordinated effort alone can close this supply-demand gap as patients, providers, payers, regulators, and suppliers -- suppliers being big pharma, biotech, medical device companies -- come together in an Olympian effort to drive better healthcare. This is obviously a very timely slide, but it's an Olympian effort in two different ways. One, it will require a truly interlocking, united approach to be able to solve the healthcare dilemma, including patients, regulators, providers, payers, suppliers working together, Olympian in that sense. It's also Olympian in the sense that it's going to take a tremendously great amount of hard work to get there. When I think about this, every time I think about the future of healthcare, I'm forced to think to some extent about the past, and my mind often goes back to 1993 and the ill-fated attempt by Hillary Clinton and others to really provide some of the leadership that I think really the government can provide in this space. I always think about this in two ways. One, how absolutely right that problem was then, and how absolutely right that problem remains today, eight years later, and how unfortunately wrong the individual person was trying to solve that, and that was for a host of reasons. But the reality is this Olympian effort to put some leadership and some parameter around where we're going is, I think, a critical issue for the future of healthcare.

Now, my colleague, Manoj Kenkare, is going to drill down on the genetic testing side. He's going to reflect on our report at Frost & Sullivan in the U.S. genetic testing market. But our report starts with a quote that I want to use as a transitional quote because I think it has a great impact in talking about what we just talked about, and then focusing now on genetic testing. The quote is from bioethics scholar Arthur Caplan. He says this: "Genetics will be to the 21st century what physics was to the 20th. With biological warfare, new drugs, genetically engineered foods, it will touch every aspect of our lives. But people know nothing about it, and

I'm worried about that." Interesting. Manoj?

DR. McCABE: Thank you. And now Mr. Kenkare. Following up on that quote while we're changing the computers, our chancellor, Al Carnesale, has made the comment that the 20th century was the century of engineering and physics, that as a university you needed the basic science of building things, which was physics, and then you needed to translate it with engineering. He has said that this will be the century of biology, where you need strong fundamental biology, and I think we're recognizing more and more that that includes mathematics and biomath, and that you also then need the translation, which is through our medical schools and our health professions schools. Mr. Kenkare?

MR. KENKARE: Thank you, Dr. McCabe, and thank you, members of the Committee, and everyone here for inviting us today to make this presentation. Frost & Sullivan's report on genetic testing market was published in 2001. The report had a base year of 2000. The way we do our reports and products in Frost & Sullivan is based on the demand in the market. For example, the companies who were interested in a particular report or particular area, they come to us and request us to look into the market and come up with a report and research. This report is based on the demand that we had in 1999 and 2000 to learn more about the genetic testing market. The base year for this report was 2000. For the purposes of this report or this research, Frost & Sullivan has defined the genetic testing market to include prenatal genetic screening, genetic predisposition testing, genetic cancer testing, and technology and regulatory assessments. Data for this research was a compilation of information from manufacturer interviews, interviews with labs, lab technicians, Frost & Sullivan existing reports that we have, and also Internet resources and secondary data that already exist. Market growth was calculated based on analysis of market drivers, restraints and challenges that the labs and the manufacturers faced in the industry. Revenue numbers shown in the report or mentioned in this presentation include only fee-for-service, because most of the end users -- I mean,

manufacturers don't exist in this market, except for the cancer diagnostics area, where you'll see a lot of manufacturers introducing their kits and tests.

Preliminary findings. Research on the human genome, the genetic blueprint of human being, is paying off much faster for diagnostic companies than for the pharmaceuticals and the biotechnology companies that try to cure it. Industry-wide genetic tests already account for close to $319 million in revenues, and it's expected to reach $778.6 million in 2005. Right now, the competition is extremely diffuse. Most of the competition is at the lab level and very few at the manufacturer level. This slide shows the graphical representation of the market stages. The genetic predisposition segment stood at $42 million at the industry stage. The cancer testing market, which is the fastest growing market in the industry, stood at $75 million and was seen in an early growth stage with a lot of potential. The prenatal testing market at $203 million was the most developed segment of the market in its late growth stage. In this slide you'll see the trend in the revenue growth rate in the genetic testing market. Frost & Sullivan estimates that by 2006 this market will easily reach $1 billion, and there's a huge scope in the market.

Pricing trends by segment. The cost for the end user is significantly high, between $300 and $400 per assay, depending upon the provider and the agreement with the insurance company. As the market develops and the testing volume increases, many companies are expected to lower profit margins and decrease pricing to remain competitive. This figure describes the graphical decline in the pricing trend.

Some of the high-impact challenges that Frost & Sullivan have identified which would be impacting the genetic testing market for the next few years are communicating value of genetic screening, change to product driven market, Centers for Medicare & Medicaid services testing guidelines, and technical and biological complexities. I'll just highlight one impact or one

challenge right now, which is communicating the value of genetic screening. In order to achieve widespread adoption of genetic screening, every member of the healthcare chain must understand and believe in its value, both clinically and financially. The healthcare chain can be thought of as a type of food chain, and as with nature, every member feeds and prospers at the expense of the next member in the chain. In the genetic testing market, manufacturers have to prove the value of the assays to the health insurance providers, and also to the physicians, along with patients. The physician must be able to impress upon the patient the value of the genetic screening in order for them to give the physician permission to perform the assay. If every member does not believe in the value of genetic screening, it's likely to be more difficult to make it to the next step in the chain. Frost & Sullivan has identified some low-impact challenges that would impact the market, which are rising cost of lab operations, specifically labor costs; ethical issues, consolidation of testing labs; and education of healthcare providers.

I'll talk about the consolidation of testing labs. Recent developments in the clinical diagnostics market have seen consolidation of both hospitals and reference lab. During the past 10 years, numerous hospitals have closed, while surviving hospitals have absorbed their patients. Meanwhile there have been consolidation of reference lab. Two major lab chains, Quest and LabCorp, now control most of the reference lab market. Currently, genetic testing is a labor-intensive, expensive process, and to make it profitable business venture, economics of scale dictate that reference lab must have a large number of samples to process. Even with the high degree of consolidation in the clinical diagnostic market, some of the large reference labs, such as Quest, out-source genetic screening tests to genetic testing facilities.

Reimbursement for services. It's a major challenge, as Frost & Sullivan has identified in its report. Frost & Sullivan understands the role of Centers for Medicare & Medicaid Services going to be a decisive factor in the genetic testing industry. Various testing facilities today include reference labs, hospital labs, university labs, and specialty labs. The reason I have this

slide here is to show you how genetic testing market can actually neutralize the basic infrastructure and can mirror the IVD technology industry today. Eighty percent of the IVD tests are performed in labs on automated equipment. Twenty-six percent of the lab tests are done in commercial labs -- for example, Quest and LabCorp. Fifty-two percent of the tests are performed in hospital-based lab, and 22 percent of the tests are performed at the point of care by clinicians or patients themselves. So if we take this as a business model or a basic model, we can actually mirror this in the genetic testing market and take it as an example to work out the details and numbers for the market.

We called up GeneTests last week to find out the different types of tests available and the number of labs. According to GeneTests, 523 labs were registered with them last week, 907 diseases for which testing was available, of which 531 were available clinically and 376 were available on research basis.

Some of the competitive factors that Frost & Sullivan have identified include turnaround time, accuracy of results, and range of available tests. Cost of testing. The cost of testing can vary anywhere between $150 to $3,000 today. Factors that impact the cost of testing include complexity and technology. Fifty percent of the testing costs usually come from labor in the genetic testing market, and 80 percent of the labor costs can be eliminated with automation. This is based on the information which was derived through interviews with labs and physicians.

I'll go to the prenatal/newborn genetic screening segment. Some of the available tests today include Fragile X syndrome, cystic fibrosis, Tay-Sachs, sickle cell anemia, Gaucher, Klinefelter syndrome, and Down's syndrome. Market engineering analysis for this segment. The types of institutions that perform these tests include public health labs, commercial reference labs, hospital labs, university labs, and genetic testing centers. Some of the largest competitors in

this market include Genzyme and Quest Diagnostics. This type of testing is very expensive to perform, and unless the lab has significant volume of testing, it is not profitable to perform the testing in-house. The market for prenatal screening generated revenues of $203.3 million, which is an increase of 7 percent in 1999, with a growth rate of 8 percent. Revenues are expected to reach $293.2 million by 2005. Price range of assays/tests usually range between $200 to $400. Factors promoting growth in this market include adoption of screening practices by managed care organizations and increased knowledge of genetic basis of disease. Factors impeding growth are slow growth in percentage of women seeking prenatal care, cost of testing, and market saturation.

Diagnostic kits. The different diagnostic kits available today include home-brew assays. Market growth depends on using kits and automation. The main manufacturers actually participating in this market include Vysis, Bio-Rad, and Genzyme.

Genetic predisposition testing segment. Available tests include polycystic kidney disease, Alzheimer's disease, Huntington's disease, neurofibromatosis, and several forms of ataxia. The market age of this market was in the early development stage. The market revenues were already found to be $41.6 million, and it expected to reach $196.4 million in 2005. The potential growth rate for this market was identified at 27 percent. Price ranges varied from $200 to $400 for different tests available. Competitive structure. Competition between manufacturers and labs. Roche's Viral Load Monitoring Kit is the most important product in this market. Also, patent laws restrict direct competition in this market.

Genetic cancer testing segment. Available tests include breast cancer, bladder cancer, hematological cancer, lung cancer, and prostate cancers. Market engineering. The human genome project influences growth in the genetic cancer testing market in much the same way as all the other segments of this report. The market age of this market was at development stage.

Market revenues were identified to be $75 million, and the potential revenues was expected to reach $289 million. The annual growth rate of this market was 29 percent, and the price range of tests available varied between $200 and $3,000. Types of competitors in this market include IVD manufacturers, reference labs, university hospitals, teaching hospitals, and genomic centers.

Manufacturers of diagnostic kits. I'm just highlighting some of the tests available in the cancer diagnostics market, which is Vysis tests. Some of the major manufacturers in this diagnostic kits market include Vysis, Vental America Systems, CytoCell, Camvue, and Myriad Genetics. Vysis has been mentioned as an example. Some of the highlights of their products include Path Vysion, UroVysion, HemaVysion, LA Vysion, and ProVysion. They are available today in the market and can be purchased by the patients and can be recommended by the physicians. Products in development. Vysis has a FISH panel for cervical cancer, Millennium Pharmaceuticals is in collaboration with BD to produce diagnostics kits, and EXACT Sciences has colorectal cancer tests.

Direct sequencing tests. Today, Myriad Genetics has BRCAnalysis for breast and ovarian cancer, Colaris test for HNPCC, Melaris test for melanoma, and in development for Prolaris is test for prostate cancer.

Patent issues. Some of the important problems today are the patent issues because there have been several important cases that have come up recently. I'll highlight the Myriad Genetics case of patent on its BRCA1 and BRCA2 genes. Myriad Genetics charges anywhere between $2,400 to $3,400 to sequence a woman's DNA in search of BRCA mutations, which numbers in the hundreds and most insurance covers BRCA testing for women at high risk for breast cancer. Myriad did not attempt to enforce its patents against researchers until recently. Until January 2001, the patent covers methods for diagnosing a predisposition for breast and ovarian cancer

linked with BRCA1 gene. It covers all diagnosis methods based on comparing a high-risk individual's sequence to a known normal sequence. The Curie Institute is opposing the patent on three grounds: lack of novelty, lack of (unclear word or phrase), and insufficient description. According to the Institute's spokesperson, the main problem is that the patent is too large and this grants Myriad an unacceptable monopoly.

Technology and regulatory assessment. Emerging technologies that we see in the market include multiplex ISH assays, microarrays, and automation. FDA approves most of the commercially available reagents classified as analyte-specific reagents. ASRs do not possess diagnostic values, and manufacturers required to file PMA since there are no predicate devices. This is the most important problem today in the genetic testing industry. That's it. That concludes my presentation. Thank you.

DR. McCABE: Thank you very much, Mr. Kenkare and Mr. Followwill. What we're going to do now is take a break. We will resume in 10 minutes. So please, just a 10-minute break so we can get back on time and have plenty of time for our discussion. Members and presenters, please proceed to the Belle Mondo, where we had lunch, and we will be back here in 10 minutes sharp.

(Recess.)

DR. McCABE: Before I introduce Dr. Aubry, I just want to bring everyone's attention to the brochures that are outside, "Genetic Testing and Public Policy: Preparing Health Professionals." Registration is available out at today's registration desk for this meeting, which will be held May 13th at the Hyatt Regency in Baltimore. Our meeting will follow in the Hyatt in Baltimore the two days after that, the 14th and 15th. But please, if you'd like to participate in the meeting, join the meeting in Baltimore on "Genetic Testing and Public Policy: Preparing

Health Professionals," please register today.

Our third market analysis will be provided through a virtual presentation by Dr. Wade Aubry, senior advisor of the Health Technology Center. Health Tech, which is based in San Francisco, is a non-profit organization committed to advancing the use of new health technologies through technology assessment, forecasting policy development, and education. Last year, Health Tech produced a forecast of the impact of genetic testing on the healthcare delivery system.

Dr. Aubry is former senior vice president and chief medical officer for Blue Shield of California, as well as chairman of the Technology Evaluation Center Medical Advisory Panel of the Blue Cross/Blue Shield Association. He represented the BCBS system on matters related to technology assessment, coverage and reimbursement, current procedural terminology coding, clinical trials policy, performance measurement, and quality of care. He is a current member of the Centers for Medicare & Medicaid Systems Medicare Coverage Advisory Committee. He is also on the faculties of UCSF, UCSF's Institute for Health Policy Studies, and the Stanford Center for Health Policy and Center for Primary Care and Outcomes Research. Dr. Aubry is trained as an internist and endocrinologist. Dr. Aubry, thank you for being with us today from California to discuss Health Tech's recent analysis of the impact of genetic testing. Please proceed.

DR. AUBRY: Thank you very much. I appreciate the opportunity to be there virtually. I haven't done this before, so bear with me. I have some slides, which I presume are put up on the board. Is that right?

DR. McCABE: They look beautiful.

DR. AUBRY: Are the slides projected?

DR. McCABE: Yes, they are.

DR. AUBRY: Okay. I'd like to talk a little bit about Health Tech and then go into the forecast. As you mentioned, Dr. McCabe, the Health Technology Center is a non-profit organization in San Francisco. It's affiliated with the Institute for the Future, and the first slide says "The Vision," which is to advance the use of new technologies to make people healthier. That's the overall vision, and that is achieved by doing forecast reports and providing a variety of services that follow from that. It is funded by a number of organizations. Most of these are health delivery systems. There are some strategic partners, like ECRI, which is a non-profit technology assessment institute, and others, but most of them are delivery systems with some health plans.

The next slide gives you an idea of the different range of technologies that we're looking at over the first two or three years of this organization. The organization is a little more than a year old, and genetic testing is one of the subjects that we looked at.

The next slide is forecasting the impact of emerging healthcare technologies. This gives you an idea of the different sections that we look at in our forecast reports. The forecasts are normative forecasts as opposed to positive forecasts, meaning that we try to get a sense from research and from interviews and our expert panel process of what experts and evidence, what evidence there is, shows will happen, not what any individual wishes to happen, which is positive forecasting. But basically, we're looking at the nature of the scientific advance, the impact on clinical care, quality of care and delivery, impact on the delivery system, such as programs, specialty mix, facilities, workforce, impact on coverage and reimbursement, and we try to do a staging review of timelines for the rollout of different products.

The next slide shows the different reports we've done. Up to now we've had a total of actually

10. We've done one more after this, expert panels and reports which are put on the Website.

The next slide is our methodology. This is primarily, as I mentioned, an expert panel process. We start off by doing literature reviews and a stakeholder analysis, doing internal discussions of the impact of genetic testing, for example, on insurers, on policymakers, regulatory agencies, health plans, et cetera, and we do expert interviews. Many of the expert interviews are selected to be part of the expert panel. That sort of guides our research, and through the interviews and the research, we develop a draft forecast with forecast bullets on various different aspects, the different sections that I've mentioned. Then we convene the expert panel, and in a moment I'll show you the composition of the panel that we had for genetic testing. But this is an all-day session using a graphic facilitator in which we portray the forecast bullets for these different areas of the healthcare system, and then we have a facilitated interactive discussion to modify and revise the draft forecast, and then we develop our report after that.

Then, as I mentioned, we have a number of other products that come from that. The next slide shows some of the other things that come from the forecast, which basically go to the subscribers of the program, including databases of the new technologies and products under development and strategic planning tools.

The next slide, which is entitled "Genetic Testing Forecasts," describes the expert panel that we convened on August 23rd. It included academic and community practice geneticists, two genetic counselors, a laboratory medical director, a medical oncologist, a legal and medical ethicist, a representative from the American College of Medical Genetics, an IOM representative, a health plan medical director, and a former Medicare medical director. Then we developed the draft forecast that was presented at the meeting and modified and then put on the Website. So that's the basic process.

In the next several slides I'm going to go through some selected pieces of the forecast report and discuss them briefly. This doesn't include all aspects of it. We selected some of these which we thought would be of the most interest. So the first section would be the impact on quality of care or clinical care delivery, and it should be before you. In that we talk about much of the media, public and scientific focus on predictive testing for common complex diseases, multi-genetic diseases, multi-factorial genetic inheritance such as diabetes, cardiovascular disease, asthma. The panel felt that the greatest impact on genetic testing would be seen in the area of newborn screening rather than individual genetic testing, although there will certainly be an increased and continued application in genetic testing for the use of predictive genetic pieces caused by genes with high penetrance, such as Huntington's disease and others like that. But we felt that the greatest impact on genetic testing would be seen in the field of newborn screening in the next two to five years. With the implementation of tandem mass spectrometry, a greater number of inborn metabolic errors can be screened for and identify affected newborns for effective earlier intervention. This is one key area which I'm sure your Committee has discussed.

The next slide. I might say that these forecasts, we basically divided them into two sections. One is the two- to five-year period, and the other is beyond five years. Of course, it becomes more difficult to forecast beyond five years, and I might also mention that forecasting is somewhat of a young science, with the methodology continuously in evolution. It is different than a technology assessment in which you deal with evidence generally of products that are on the market and have an evidence base. Frequently in these areas of forecasting, there isn't a substantial evidence base. At any rate, family history we feel will continue to be the indication for genetic testing, excluding newborn screening, in the next two to five years. There are some changing demographics in the U.S. population, with more single-parent families, and of course this will make genetic histories sometimes incomplete, with more often maternal heredity present but not always paternal heredity.

As more effective treatments become available for cancers and neurodegenerative diseases, earlier, more accurate diagnostic methods for these diseases will be emphasized. In other words, as the science for the treatment of cancer and degenerative diseases like Parkinson's and Alzheimer's become improved, that will shift the emphasis to earlier detection, and that will spur the field of diagnostic testing, including genetic testing.

I'm going to shift to healthcare delivery systems, again the two- to five-year time frame. This again refers to newborn screening with tandem mass spectrometry, which identifies affected neonates at a greater rate than conventional methods. Again, this is the impact on the healthcare delivery system, so this is looking at it from that point of view. Children who had previously died from these inborn metabolic disorders will be identified earlier and will require significant healthcare services, placing demand upon the entire system. Genetic risk assessment programs will be developed slowly in this time frame and expand into centers of excellence focused around a disease set. Current programs for cancer risk can serve as prototypes for risk assessment programs for a neurodegenerative disease, for cardiovascular diseases. Some existing systems have greater experience running these programs than many academic centers, and as institutional support is critical, diffusion may be easier into the private hospital setting than to other academic settings. So this basically talks about a potential area of expansion for genetic risk assessment programs, primarily thought to be more likely to disseminate in community hospitals rather than --

(Dr. Aubry's telephone connection broken.)

DR. McCABE: We were able to pull this off between the U.S. and Canada when I did a virtual presentation, but it's difficult within the United States I guess.

DR. KOENIG: I was going to say at the end, just in case people were interested, that I was

actually part of the local group that advised them because the Institute for the Future is literally down the street from my office at Stanford. It actually is an interesting process that they use. The first step when they were setting up, before they did the final expert panel -- and I've actually seen the report. Have you actually read the report?

MS. CARR: We don't have it.

DR. KOENIG: I actually have it.

MS. CARR: We can get it.

DR. McCABE: I think it's proprietary.

DR. KOENIG: Yes, it's proprietary.

MS. CARR: It's part of why we've invited (inaudible).

DR. KOENIG: I see. Well, I guess because I participated, I can have it.

DR. KHOURY: So why is it proprietary?

DR. McCABE: It's proprietary because they're funded by the health systems that they listed at the outset. It's a non-profit, but they generate their funding by a dues system, in essence, and you have to pay in order to get the product. So what we're seeing here is a very superficial view of that product. The reason why we knew about it, in addition to Barbara being involved, was that several of us were involved in the process. It's quite an intriguing process, and one goes quite a long distance in the period of one day because of all the preparation that's been

done previously and the various feedback that occurs after that. But it was interesting because very shortly thereafter I was involved with the Ontario horizon scanning process also, and these are efforts to look at the near horizon and at the far horizon, both with the intent of looking at cost. For Health Tech, it's really trying to anticipate unanticipated cost to their health systems. For Ontario, obviously, with a single payer, really trying to assess where the costs are going in their single payer system. In both cases, it's how one can prepare ahead in order to offer these technologies without bankrupting the various systems.

DR. BURKE: While we're waiting, I just think it's an interesting comment on the value of the information that it's possible for proprietary reports of this sort to be created, that there's a market for them. But I think it also underscores, in fact, how important development of information and dissemination of information is. A proprietary report is never going to help inform public policy, and it may have very different and quite legitimate purposes other than public policy, like healthcare systems trying to prepare for what costs they need to bear. But I think it speaks to the tremendous importance of having the information that is appropriate to public policy in the public domain and thinking about investments in those kinds of procedures that generate good quality information.

DR. McCABE: Just since Dr. Aubry was cut off, I'll refer you to the handout which is in your red folder that has all of his slides so you can look through that. But I think that we probably should move forward with the discussion, and if he recontacts us, then we can continue his presentation. We have the speakers from the previous presentations at the table. Are there questions for either of the groups?

DR. LEWIS: I was really impressed with the parallel structure in terms of what's going on in Canada and what's going on in the States. But one of the things I found really interesting was that your group worked at the level of the province, and I'd be interested in knowing were there

any trans-Canadian efforts. Is there any kind of a mega-group that comes together that's all provincial, or are decisions made at the level of the province, so that each province is like a separate country? It shows my ignorance. I'm sorry.

DR. SUMMERS: It's actually a good question, because I think most Canadians wouldn't know the answer. In Canada, we have a Healthcare Act, which is Canadian, and the provinces are actually the payers and pay from their own funds for healthcare, except for a small amount of transfer from the federal government. The federal government does have a committee called CBAC, the Canadian Biotechnology Advisory Committee, and that advises a number of different ministries within the federal government. But it's an advisory committee and, in fact, they can't really form policy because the federal government can't tell the payers what to do. So it's a very odd kind of situation.

DR. LEWIS: So just to follow up, then, if you lived in Prince Edward Island, the services you get might be very different than if you lived in Vancouver.

DR. SUMMERS: Absolutely.

DR. KOENIG: I mentioned this. This is a comment on the Frost & Sullivan presentation, and I actually mentioned it to Mr. Followwill during the break, but I really feel it's important to correct one of his slides which attributed the increase in global life expectancy, the significant 50 percent increase in global life expectancy to medical services. Just to correct that, just to get that on the table, that's actually not the case.

DR. McCABE: What is it attributed to, Barbara?

DR. KOENIG: It's primarily attributable to public health and much more simple kinds of

changes. I mean, Muin could speak to this. Clean water, all sorts of other things, public health. I mean, it's definitely not medical services. Those numbers of what percentage is attributable to actual medical care itself are available, and it's much closer to about 5 percent. So just to make that case. This is related to my second point and question, which is to ask about the relationship between the -- what did you call them? – the first factor, which is the demand side, and the third factor, which is the supply side. I have some concerns about the fact that those were presented as being completely separate, whereas one might think of the fact that the supply side does a great deal to create the demand on the part of patients. I think that's an important dynamic to put on the table. I think it's not the case that they're totally separate.

DR. McCABE: Mr. Followwill, do you wish to comment? Excuse me one minute. Dr. Aubry, are you there?

DR. AUBRY: Yes. When I finished the end of it, I realized I was off the phone.

DR. McCABE: Yes, we were concerned that you might not be aware that we had been cut off.

DR. AUBRY: When were we cut off?

DR. McCABE: Let me just allow Mr. Followwill -- we had begun the discussion, pending your return. Mr. Followwill, do you wish to comment, reply to that? And then we'll continue with Dr. Aubry.

MR. FOLLOWWILL: I would agree with what Barbara has said. The distinctions that I was making really were in looking at the different factors. I think where I ended in terms of the combination of those factors is really speaking to your point, and I think in any market, obviously, supply side forces create demand. So in that sense, I would agree with that

comment. It puts some structure around the discussion which, obviously, when looking at the total healthcare industry, it's a discussion of infinite complexity in some ways.

DR. McCABE: I would comment that it would be interesting to look back 25 years from now and see how we perceived genetics and how much of it has moved into public health versus health services, because I think to some extent, when we were dealing with water-borne diseases and food and those sorts of things, it was very clear what public health's responsibilities were. But as we move into a new era, I think we may see the blurring of the distinctions between public health and healthcare services. So it will be interesting to observe that.

Dr. Aubry, I apologize for you being lost in cyberspace there, but your slides are still cued up. We lost you at the impact on delivery systems, with demand rising, the expert panel suggested other alternatives. That's where we were.

DR. AUBRY: All right. So I got cut off at that point?

DR. McCABE: Yes, nine slides from the end.

DR. AUBRY: All right, let's go to that. This is impact on delivery systems. Again, most of the users of Health Tech's information are the delivery systems trying to make some assessment of what's likely to happen in the next two to five years. This slide basically deals with the genetic counselor shortage, which is likely to continue, and basically the panel suggested other means of substitution for this to alleviate that shortage: group sessions, overall counseling services, other types of media. Brochures, videos, CD-ROMs, pre-test counseling, and direct-to-consumer advertising will also challenge the traditional role of the genetic counselor. Increased demand will be met with a growing role for commercial ventures and the potential of

electronic-patient interaction. So there's likely to be some attempt to fill the void here, unless the workforce of genetic counselors can increase.

Then beyond five years is the next slide. The panel thought that software programs and other electronic interfaces will be developed to carry out initial services and then post-test interpretation, and this might create an additional barrier for the underserved and uninsured population depending on access to care, providers, and means of electronic information exchange. So this is likely to be another example of the digital divide.

The next slide, beyond five years. As demand for genetic test interpretation grows and reimbursement issues are resolved, if they are resolved, other disciplines will move into the field. Again, an attempt to alleviate the chronic shortage of genetic counselors. Primary care physicians are not really currently equipped to provide this service, although many patients, of course, go to their primary care physician. That is also another workforce challenge, to have coordination with primary care physicians and other professionals and other types of allied services to coordinate care. It could be an area of education and training for primary care physicians, but they're somewhat under siege from all they have to do now.

The next slide, health insurance coverage implications. Health insurance coverage will continue to be an issue. Health insurers will continue to assess individual genetic tests as they become available, like BRCA1 and 2, as was assessed by the Blue Cross/Blue Shield Association and other groups, basically to determine whether there is enough evidence for improvement in health outcomes related to the new test, whether it changes management to improve the patient's outcome, and it's likely that these tests will have a fairly high bar of evidence to follow in order to gain coverage. Preimplantation genetic diagnosis will continue to be costly and not covered by health insurance plans as a benefit exclusion or not medically necessary over the next two to five years. The medical necessity, of course, is the cornerstone

of how health insurers, or Medicare for that matter, determines whether something is payable as a benefit under the plan. However, PGD will be a relatively large growth area of genetic testing, with patients seeking IVF services to specifically use PGD technologies. So we felt that this would be a growth area despite lack of insurance coverage.

The next bullet and the next slide have been covered, so I'd like to skip to DTC marketing and patient as consumer. This is an area we spent some time on. There's a possibility that developers involved in genetic medicine will compensate either the patient or the facility for testing services to encourage access to their patented therapies. As new proprietary treatments that are patented develop, it's likely that there will be some alternative sources of funding for genetic tests to determine eligibility for those services, and direct-to-consumer advertising will have a very large impact on the development and diffusion of emerging genetic tests. The best sort of analogy is the pharmaceutical industry, which has demonstrated DTC advertising as already very significant over the last three or four years, very successful, very significant return on investment. Through media, marketing and the Internet, patients will become increasingly aware of genetic testing and may choose to purchase these services for reasons other than medical necessity. In this situation the patient acts as a consumer, choosing to pay for products and services that may have little clinical benefit and create patient confusion and concerns. Of course, that confusion is then taken to primary care physicians who may not be well equipped to answer all the questions or coordinate services for that particular patient.

Next slide. While patients have turned to IVF when conventional methods of pregnancy have not worked, more patients will turn to IVF to access PGD specifically. Although these are costly and excluded, consumers will actively seek this option to directly access PGD. We touched on this on an earlier slide, but this will serve as a substitute for prenatal testing.

There were some other areas that we looked at in the report, including workforce, IT and

communications, regulations and standards, but this is sort of a sampling of some of the areas that we thought we'd highlight for this presentation. So that's the end of my presentation, I guess in two parts. Dr. McCabe, you were also at the panel, so I don't know if you want to make any comments on it as well, but I'd be happy to answer any questions during the Q&A session.

DR. McCABE: Yes, I actually did, while we were in the break when you were cut off, talk to both Dr. Koenig, who was part of the early process, and then myself, who was part of that day in San Francisco, discussed a bit of the process. If you could stay with us for the discussion, we were beginning to have a discussion. We have, though, comments from the public. But I just want to ask and be sure that that's true.

DR. AUBRY: Okay.

DR. McCABE: If anyone from the public in the audience wishes to make a comment, please register outside so they can let us know. But as of about 10 minutes ago, we did not have any desires from anyone to speak. If you do, please register and we will make time for you. Otherwise, we will continue this discussion until 4:15.

DR. TUCKSON: Yes, two questions, and one is sort of for Sarah in a way, the first one, and that is that I was a little surprised by the Frost & Sullivan estimates for how much of a business this is. I've been hearing numbers like it will be a $2 billion business in a couple of years, and I don't know whether it's because you sub-segmented the overall market by just categories, like prenatal, genetic, predisposition, so forth and so on. But I'd be curious what your answer is. At the end of the day, Sarah, I still think it's time for us to have a shared understanding of the number of tests that are out there, that we think are out there at least, and what the economics are. It's sort of like where we started. Were we going to refresh that database at some point?

MS. CARR: Well, I think the data that Manoj gave on -- the best data we have is from GeneTests, and that's a voluntary directory, but it's the best we can do, and that was current data I think from last week, right?

MR. KENKARE: Correct. Just to add to what you mentioned, we are trying to update the support from this year, 2002, because no one knows how many tests are out there. What we're planning to do is also to understand, talking to each and every lab perhaps, and trying to find out what kind of problems they face, and also trying to find out how many tests are done every day. It's a difficult job, but we're planning on working on it and making sure it's accounted for.

DR. TUCKSON: When you mentioned these categories of tests that you used for these definitions, these primary segments, is that meant to say or to imply, in terms of how you've lumped them, that there are some segments you did not cover?

MR. KENKARE: Yes, there are some segments which we didn't cover.

DR. TUCKSON: Okay. The second question is --

DR. McCABE: Before you do that, I would just ask if you were willing, as you prepare those data, because we've been relying on GeneTests and it sounds like you're going to do a more thorough look at this, if you would be willing to share those data with us. That would be very helpful.

MR. KENKARE: Absolutely. Whenever we start working on it, we'll certainly work with the Committee members and, of course, Dr. McCabe and Sarah.

DR. McCABE: And I would ask that you include newborn screening in that, because that

accounts for 4 million tests or 4 million babies with multiple tests per baby every year. So it still is probably -- it is the highest segment of the market. But since it's done in the public health arena, it's usually not looked at as part of the market, and this was true in the Health Tech discussions. It was very clear that that was a huge segment. In fact, in the two- to five-year range, it was probably going to continue to dwarf everything else. Is that true, Dr. Aubry? Am I remembering correctly?

DR. AUBRY: Yes, that's correct.

DR. LLOYD-PURYEAR: Can I say something? I was just going to say that to you, lumped prenatal screening with newborn screening or newborn screening with prenatal screening and made the statement that it's not cost effective and it costs a great deal. Actually, our understanding from any of the reports that we have read is that newborn screening is very cost effective and actually is a money-maker for the public health laboratories. So I think they need to be separated. You shouldn't be lumping them together.

MR. KENKARE: Absolutely. That's what we plan to do, because this report was done in 1999-2000, and it was an emerging market --

DR. LLOYD-PURYEAR: Newborn screening is not an emerging market.

MR. KENKARE: In 1999-2000 it was just emerging, because we've documented all the labs, and from the manufacturers' point of view, that's what we've been told.

DR. LLOYD-PURYEAR: Newborn screening has been going on for 40 years.

MR. KENKARE: I know. From the manufacturers' point of view, we look at the

manufacturing point of view, and that's what we discuss all the time.

DR. McCABE: You're looking at kits versus services.

MR. KENKARE: Yes, that's right.

DR. McCABE: I apologize, Dr. Tuckson, for having interrupted you.

DR. TUCKSON: No, that's great. Mr. Chairman, you never need to apologize to me. I'd like to understand from the Canadian team, and from Frost & Sullivan, you both mentioned – and I may be overreading this, but Frost & Sullivan, you have a slide that says "High Impact Challenges, Change to Product Driven Market." Ontario, you have a slide that say, "Intended Purpose of Proposed Service," not just a test but a service. Am I implying that both of you are saying that the way the world is moving is that we're moving away from a discrete thing called a test to a product or to a service, whereas the test is part of a package of something else, or am I overreading you?

DR. SUMMERS: I think for us, it's the difference between a publicly funded and market driven healthcare system. We can't think of a test in isolation, and the cost of the test is irrelevant, really, even if it's $4,000 Canadian, compared to the long-term, downstream care. That's why we're talking in that context.

DR. BROWMAN: I think the difference is how we view this when we see a patient as a unit of cost versus a unit of revenue, and I think that's the key difference. From our point of view in a publicly funded healthcare system, you have the responsibility to provide a service, of which the test is a part. Where a test is a unit of revenue, it may be that the private sector may find that providing the service around the test might be profitable, and so some might think of doing

that where others might think it's a question of choosing your businesses.

DR. TUCKSON: And what about Frost? How were you looking at it?

MR. KENKARE: We were looking at it from the manufacturers' standpoint, from the product as a profitable unit, and we're looking at the number of tests and kits and what the future is going to be like.

DR. TUCKSON: So you're looking at it only as the product is still the test.

MR. KENKARE: Correct.

DR. TUCKSON: That's helpful. Thank you. I think this Ontario thing is a little bit of a challenge from the earlier discussion that we talked about around government in the United States, and that is, again, what are we trying to accomplish? One way you could put this thing on is we must try to control or to protect every single test, which is important. But at the end of the day, the larger purposes of government is that we're trying to make sure that either we don't harm people, which is the most small thing, Muin, but the bigger thing is that you're trying to help people to be healthy, and that this thing, this test needs to be evaluated in that context. So informed consent, education of the doc around the use of the test -- it isn't the one microtest. It is how do you use this in a diagnostically intelligent way to give better healthcare outcomes. I don't think that we're ruled out from thinking like you simply because of the dynamics of our business. Anyway, Dr. Greene, I just sort of throw that out there for you as well.

DR. McCABE: I think it's also important to think about the Frost & Sullivan model in the context of newborn screening, something that we've been learning about in the genetics public health arena. There, until probably a decade ago, newborn screening was thought of as the test.

Still, if one is looking at the business side, the private side of newborn screening, it is perceived only as the test. But it's very clear that newborn screening is a system, with all the pre-analytic and post-analytic pieces being essential for the generation of benefit from that system. So eventually, hopefully, we will defragment the genetic services arena, too, and reincorporate the test back into the service, as the Canadians are able to do. But given the organization of medicine in this country, it will probably stay fragmented because I would argue, at least right now, the profit is in the test, and so the services are not profitable, and that's why the tests are separated out.

DR. TUCKSON: But I wonder, Wade, whether you imply that maybe some of this packaging of the test and service together, is that implied when you talk about the software programs and other electronic interfaces as part of the overall process of preimplantation genetic diagnosis, along with in vitro fertilization?

DR. AUBRY: Yes. I think that that's basically linking the information about the test, the pre-test and the post-test counseling, if you will, in whatever forms, through a genetic counselor or some other way, as part of the package of the test. I might also mention that I was involved in the Blue Cross/Blue Shield Association technology assessment on BRCA1 and 2, and if you read that decision, it basically included the counseling as part of the test as well. So even looking at it in a technology assessment way, there's clearly a package. It's not just the test itself. Does that answer your question?

DR. McCABE: Thank you.

DR. TUCKSON: Yes, thank you much.

DR. McCABE: I have four people in the queue. I'd ask you to be brief because we need to

then move on to a new topic at 4:15.

DR. BURKE: I just want to get back to where does the demand come from and the possibility that as you create new products, you really are pushed to create new demand, and also reflect a bit on Barbara's comment about the role of advertising, which as we know has a powerful role. I was interested to note, for example, that the role of marketing played a very big role in the failure of healthcare reform, for example. I think we might need to raise the question, under the heading of oversight of genetic tests, that advertising messages are a concern. I'm getting back to a theme that Barbara has raised many times. It's clear that there are advertising messages that, in fact, illustrate the effort of product producers to generate demand where there really isn't all that much interest on the part of, for example, public health or primary care personnel, or necessarily even patients. I think we have to understand that those advertising messages occur in the context of a background of media hype about genetics that I think has been pretty well discussed and elaborated upon by many speakers, and that that in turn may be fed by misinterpretation of statements that scientists make in order to inform the public and fellow scientists about progress in genomic research. There's been extraordinary progress, but sequencing the genome is still a long way from having a test that's useful for improving health outcomes. So I guess my question is, both from an ethical and from a prudent use of resources perspective, should we be concerned about how people get information about tests, should we be concerned about market forces trying very hard to create demands for products that investors have invested in, kind of independent of their healthcare outcome effects?

DR. McCABE: Who are you directing that to?

DR. BURKE: I'm directing it to all of the panel.

DR. McCABE: Anyone?

MR. KENKARE: I can start. As mentioned earlier, communication and dissemination of information is critical in this industry today. If you're working for Frost & Sullivan, we get calls every day from companies, start-up companies who are trying to invest in this industry, and it's very critical that the message that goes out to the general public as a whole and all the patients is that they should be wary about what's out there and what's the validity of the tests out there. It's very important, because companies are going out, investment banking firms, VCs are trying to invest in this area, and unless they're aware of what kind of information is out there, how the test can be used, how the patient can be educated about it, it's very important that we look at this before we jump into any conclusions of investments in the industry.

MR. FOLLOWWILL: I've also had several conversations over the last year with big pharma clients who have approached us, and my sense is there's a tremendous discomfort level with the whole DTC approach on the part of big pharma, because in a way, it's bypassing the practitioner, which is very problematic for big pharma. I think, obviously, it's the trend within the business, but my sense is, within the big pharma companies, there is as much discomfort as what I'm sensing around the table. So I think this is a very important area where, again, the conversation needs to be broadened beyond this circle to the big pharma and to say information flow here is absolutely critical, and it's not just about supply side forces trying to create demand or hoping to create demand. There's a much bigger thing going on here.

DR. McCABE: I would comment to our colleagues from Canada also, we had discussed in previous meetings that in Canada an individual can order a test upon themselves, it's not requisite that they go through a physician, whereas in many states in this country, they need to go through a physician. So one of the things that we have heard about -- we don't know the volume but we've been told it's occurring – is that individuals who wish to do anonymous testing are sending samples off to Canadian laboratories so that they can receive the results directly and not have them go to their physician's medical record.

DR. SUMMERS: That is true, but they generally have to go through a physician in Canada in order to get such testing done. I've had a number of people come up from the U.S. for Huntington's testing, for example, because they're worried about their HMO. I think the whole issue of direct-to-consumer testing is a big concern for Canada because that could easily boost healthcare costs with absolutely no control, and I'm hoping you guys will have some control over this.

DR. McCABE: Yes, Dr. Browman?

DR. BROWMAN: I think the key to this whole discussion is the appropriateness of use. Inappropriate use of the information may, in fact, be good business but bad public policy. There isn't a harmonization there, and I think what we should be focusing on is public education around appropriateness of use. I wanted to comment, Dr. McCabe, when you said that perhaps services would not be marketed because they don't generate revenue. But counseling services may actually improve appropriateness of use and save a lot of dollars.

DR. McCABE: Thank you. We have a number of people in the queue now, but I'll ask you to be very, very brief in your comments or questions.

DR. PENCHASZADEH: Much of what I was trying to say was put up by Wylie and the comments that I just heard from our Canadian colleagues. The only point that I would like simply to say is that there is something that is called conflict of interest that we know as clinicians or researchers. When I hear the phrase "educating the public," I would put it in quotes, particularly when it comes from the market that needs to convince the public to use particular products that may or may not have any bearing to their health outcomes, as Dr. Aubry has mentioned in one of his slides here. The other last comment is -- well, that is essentially what I wanted to say.

DR. McCABE: Thank you.

MS. BOLDT: I'll pass.

DR. McCABE: Thank you.

DR. GREENE: This s a pretty direct follow-up question to earlier discussion, and it's to Ontario. I'm still a little unclear about services. I wondered, by genetic services, do you include only the activities that are directly and immediately related to a test, or does that include more broadly follow-on such as colonoscopy for a person who has positive tests for predisposition or formula and management for a child with PKU? Depending upon your answer to that question, I would ask SACGT, keeping in mind earlier comments about the division between the parts of our healthcare system, what implications does that answer have for this Committee's recommendations?

DR. SUMMERS: Basically, we feel the service is all the way along. So if a person needs colonoscopy as a result of their genetic testing, that is part of the service. Now, the service may have moved from genetics to a different service, but nevertheless it should be seen as a package.

DR. McCABE: Thank you.

DR. LEWIS: I just want to comment on the education piece and the consumer and clinician issue, because to me it's not an adversarial or an either/or. In the ideal world, it's a partnership. Hopefully part of what we're teaching people is not only to look at what they see on television but to be able to critically analyze that information and not have it just create demand. I think that if we say that it is either the consumer or the provider, that's leaving the road that we're

making a mistake, that the critical piece is that it be a partnership.

DR. McCABE: Thank you.

DR. CHARACHE: A comment and then a question for Mr. Kenkare. The comment is that I don't know if this group knows, but one of the states in which people can self-order is Georgia. Between CDC and our hotel last week was a storefront whose name was Any Test Provided, and a huge billboard which advertised a different company that did the same thing. The question has to do with your comments, that the data you're collected is tuned towards the manufacturer. I think there are two manufacturers here, commercial groups. One is the kit manufacturer, and the other is the laboratory that does services. My question is are you differentiating between those two? Are you collecting data on the laboratories and their usage, or only on the opportunities for manufactured products?

MR. KENKARE: We're going to do for them both, for labs and manufacturers.

DR. McCABE: And the last comment or question in this section, Muin.

DR. KHOURY: Thank you. I just had a question for clarification to our Canadian colleagues. I like the work you've done tremendously. This toolkit evaluation template, if things go through the way you expect them to go through and they're blessed by the government, are you envisioning -- I think you had a slide up where you had the advisory committee and then expert panels, and then you had horizon scanning somewhere on the right. Can you elaborate more on how that process will go through and how you can apply something like this to which test, how many per year? I mean, have you thought about the implementation of this, or is this a bit premature right now?

DR. BROWMAN: The model is patterned after a model that exists in the Ontario cancer system, where there is an advisory group like this, and it's around new cancer drugs. It has a group of expert panels that it can turn to, and it will try and anticipate what new drugs are becoming available before they get approved federally. That is a multi-stakeholder advisory panel that has been successful in anticipating new drugs becoming available in 13 out of 14 cases in the past two years. In every case, an expert panel was able to develop a systematic review and recommendations around appropriateness of use of the drug as it was becoming commercially available. We're not sure that that track record is going to hold up, but there is a process of that sort in place. The process has been published in a journal called the Journal of Clinical Oncology, and that's one of the papers. Pater, P-A-T-E-R, is the first author, and it describes how this process works.

DR. McCABE: I'll ask Sarah and her staff to get a copy of that out to the members of the Committee.

Did you have a comment, Steve?

DR. GUTMAN: No, I just had a question. What is the relationship between the work that you do and the work done by Health Canada?

DR. SUMMERS: Health Canada is the federal government. So like I said before, we're basically working separately, although there are so few geneticists in Canada, there are so many links, we know what each other are doing and report back and forth. But Health Canada basically has an advisory kind of role, whereas the provincial government has a chance to actually implement recommendations.

DR. BROWMAN: I'm wondering if I could add one point along that line. In Canada, we do

have basically 11 different health systems in the provinces, but there is something called the Conference of Deputy Ministers, where the Deputy Ministers of Health meet twice a year to compare notes and look at what's happening. So there is a communications mechanism, although it's not clear that they have authority to do anything on a national scale.

DR. McCABE: Thank you. Dr. Aubry, do you have any final comments?

DR. AUBRY: No. Thank you for having me by phone.

DR. McCABE: Thank you very much for joining us, and thank you to the other members of the panel as well. I already commented to Dr. Browman and Dr. Summers that we've been quite impressed with what you've accomplished in the Province of Ontario, and we would like to stay in touch with you and perhaps invite you back at some point in the future. Thank you very much. And please, likewise from Frost & Sullivan. If there are work products that you can share with us that would be helpful to us, we'd very much appreciate them. Thank you.

With that, we'll now hear from Dr. Charache, liaison between SACGT and the Clinical Laboratory Improvement Advisory Committee. Dr. Charache will give us a brief update on CLIAC activities and the outcome of its last meeting on January 30-31 of this year. Dr. Charache, if you would, please.

DR. CHARACHE: The CLIAC meeting this time was perhaps, even according to its standards, unusually comprehensive and pithy, perhaps in part because the September 12th meeting had to be canceled. I'm just going to hit the highlights that pertained to issues that may be of interest to this group on several points, and these are the topics for which I have slides, essentially one per topic, with the exception of Quality Institute, which I've elaborated on a little further. The ones that are starred are new data, and I'm just going to speak more quickly on the other two. I

will add one other topic which came up in part because of the considerations that we just heard from the Ontario group and the Canada process.

We're not going to go into detail on waived testing because we covered this in the November meeting. What I wanted to indicate is that this has remained a very prominent issue of concern to CLIAC, and as a result of that a letter had been prepared which we spent some time in polishing for Secretary Thompson on this subject. It's a very comprehensive letter, five pages or four and a half pages, which outlines those factors which CLIAC believes are important in terms of deciding whether a test should be categorized as waived or not. A lot of it pertains to those issues we covered in November, specifically the data that we've all heard on poor practices in laboratories in which there is no CLIA oversight and that there needs to be consideration of medical, social, and public health overhead in decisions that are made to release tests on a waivered level. Of particular concern, as an example, was the influenza test, which had major public health issues, as well as therapeutic ones, for a test that was waived, and these particular issues we felt needed to be further considered.

We heard from Dr. Gutman about new processes that are under development at FDA, new strategies for premarket test review. This is necessary in part because of the requirements of FDAMA, the FDA Modernization Act, to make all premarket review processes less burdensome, and we recognize the challenge with some of the techniques that are being assessed to make the process as simple as possible, to get rid of the Mickey Mouse, while not compromising the ability to identify and address problems that are meaningful. There are some issues here that we're looking forward to hearing more about, and we have, of course, a great deal of confidence in the people who you all know now who represent FDA in going through this very difficult mine field in a key area.

The Quality Institute I'm going to comment on a little bit. Periodically, CDC has established

what's called a Quality Institute, and it has looked at specific issues and problems that need to be addressed in a comprehensive way. The proposal was put forward for developing a quality institute at this time to look at the entire picture of laboratory testing in a comprehensive way, looking at issues such as cost and public advertising and all aspects of it, not simply test performance alone. It seemed to be a very important concept and structure in the minds of CLIAC, and the few slides I'm showing you on this are Dr. Joe Boone's slides, who is here and presented it for CLIAC in a very helpful manner.

The three steps that are being proposed are, first, to have a conference to develop a framework for a national report on health laboratory systems. The second is to prepare a report which defines the laboratory system and a set of quality indicators for the nation's system. Finally, to create an ongoing quality institute that can help monitor and be responsive to changes in this area.

The vision includes ongoing data collection and analysis, Web-based access, a distributed structure, and framed performance standards which would be developed in the course of this initiative. Now, there are a lot of questions, and I've listed these questions, as you can see, in the handout of issues to be addressed. But one of the first ones is who is this report going to be directed toward and for what purpose, and what should be included in the report? It's clear it would include demographics, human and fiscal resources, coordination of efforts, training and technology, research, policy and ethics standards, and utilization. So this will be a very comprehensive look at the entire picture.

Finally, questions to be addressed, and these are starting questions. What indicators of quality in healthcare outcomes should be included? What are the key organizations that should participate in this effort? Who could and who would provide data? This is a key problem which we've all been struggling with. Finally, what structure and process should be used to

develop the report?

CLIAC voted strong support for this initiative. We felt that it was timely, it was relevant, and it was extremely important in looking at the entire healthcare picture.

The last two slides that I have here refer to issues that have come up during the course of discussion, and both of them have relevance to this body. This one that I'd like to outline was raised during the public comment period by Phil Bongiorno of the College of American Pathology, CAP. He called to our attention in letter format -- I'm sorry, that's the next one. This one is the issue of the laboratory director. This is an issue that has come up as a result of an effort led by CMS to perhaps make more permissive the ability to become a director of a clinical laboratory. At the present time, any physician who has had appropriate training can become a laboratory director. Any laboratory director can direct up to five laboratories. If you have a doctorate degree in a scientific discipline, at the present time you can only become a laboratory director, which gives you all the privileges that a physician director has, if you have been certified, if you have passed boards, and there's a list of boards which qualify for saying that you have gained enough knowledge of clinical medicine in your area or your discipline to be able to advise on when a test should be performed, how the results should be interpreted. There is a new track that has been proposed -- this is the III track -- which now says that any earned doctorate in a chemical, physical, biologic or clinical laboratory science, who has six years of laboratory training or experience, including two years of experience directing or supervising high-complexity testing, can become a laboratory director. CLIAC felt that, particularly given the responsibilities which we're suggesting that a laboratory director ought to have and that are part of, as an example, 14 requirements for performance of a laboratory director and are a cornerstone of many of the recommendations on the genetics testing working group that's now being formulated, we felt that that level of knowledge base would not be achieved by someone who had a doctor of science, particularly since this doesn't specify that

his experience has to be in a clinical discipline or a clinical laboratory of any kind. It was commented that someone with a doctoral degree in astrophysics would apply if his high-complexity testing could be in a research lab and not necessarily with clinical experience. So CLIAC feels very strongly that it's going to be key that the personnel requirements be maintained to apply to those who have had training which is appropriate for patient care testing.

As an added concern, this wording, which we had always read as meaning that you had to have a Ph.D., doesn't say that. It says you need a doctorate. CMS has recently decided that includes a pharmacist who has a doctor of pharmacy. We're obviously concerned about that, because it doesn't mean any laboratory skills. So we're concerned about any effort to downgrade the requirements for knowledge base of those who are at the top, and therefore setting the tone for a clinical laboratory.

The final slide is the one I started to talk about. This is something called to our attention by CAP. This pertains to a new HIPAA requirement. This requirement says that even if someone like CAP or joint commission or a small number of other groups are given deemed status to act as a CLIA certifying body, they have to have a different type of legally binding contract with any laboratory that they want to survey. So if we have a laboratory that has to be surveyed by CAP or by joint commission, they have to have a legal agreement, drawn up presumably by lawyers, between that laboratory and the credentialing body. The credentialing body has to be considered a business associate rather than a healthcare oversight agency with deemed status. We're concerned about this particularly for issues such as genetic testing, where you can have a little lab that's already worried about getting CLIA-certified having to pay for somebody to draw up such a contract so they can be certified under CLIA. We had not seen the documents ourselves, and therefore ask that this be validated in order to be sure that we wanted to respond. But it's likely that there will be a letter on this subject pertaining to the need to have deemed agencies deemed and not considered business associates.

I've commented, then, on these five issues. The final one that I'm just going to mention is that there is an area that we discussed very extensively in which we are like Canada, which is to say that all states act independently, and that has to do with the public health laboratories in each state. We heard a lot about bioterrorism and the fact that this pointed out that many of our state labs need to be upgraded. Each laboratory is funded by its own state, and they vary all over the map in terms of their qualifications and skills. There are some which don't even have Internet capacity. There are others that are leaders in the field. We have drafted a letter which emphasizes the need to upgrade and standardize these facilities, and I think it also helps explain the divergent types of perinatal testing/newborn screening that goes on in the different states, some of which may not even have sickle cell testing and others have very comprehensive approaches. That's it.

DR. McCABE: Thank you.

MS. CARR: I have two questions. Dr. Charache, can you clarify what the Quality Institute is all about? Is it going to focus on laboratories doing genetic testing specifically?

DR. CHARACHE: No. The Quality Institute is all testing, but I think the genetic testing has served as a pilot to help crystallize thinking about a lot of testing, because it has ramifications and it actually sets models for thoughts and ideas. This is for all testing that pertains to patient care decision making.

MS. CARR: Thank you. And also, do you understand, the Committee here, why the HIPAA regulation does this? I mean, what's driving it? Is it a privacy issue?

DR. CHARACHE: I think what's driving this, and I can ask Dr. Boone to elaborate if I'm not clear or I don't have it correctly, is the understanding that we -- the issues have just been

discussed. We can't consider an individual test or an individual laboratory producing information in isolation. It all has to be put into perspective of the overall structure and the milieu in which we're now operating, and it's to look at it comprehensively and how the regulations should fit together and what should be being done and how to standardize issues that are currently very diffuse and difficult to understand. Dr. Boone, would you comment?

DR. McCABE: Joe, do you have anything you want to add? If you could come to the mike, please.

DR. BOONE: I just want to say that I think we had several broad, cross-cutting issues, and I think when we mention the Quality Institute, everybody probably on the CLIAC Committee had a different view of what we were talking about, but what's sort of emerging is that we feel like we need to focus on patient safety concerns and to try to make the laboratory a true partner in the patient safety concerns that people have. So it's really a cross-cutting kind of activity that would encompass all types of testing, not just genetic testing, but the whole spectrum of testing, and would include both the pre and post kinds of issues, and the partners that the laboratory has to work with on a daily basis both in public health and in the private sector.

DR. McCABE: Thank you. Any other questions or comments for Dr. Charache?

DR. LLOYD-PURYEAR: I have a comment, or a question, rather. Going back to the concept that I'm familiar with that the newborn screening system is a system and not a test, will the Quality Institute be addressing issues of follow-up, long-term care? Can you elaborate?

DR. BOONE: Actually, we're very early in the planning process for this. We haven't even put together a steering committee yet to develop the topics and the speakers for the program for that conference. So it's a little bit premature for me to tell you exactly what we're going to be doing

at that conference. But at least in theory, we want to try to deal with testing as a system and not as an independent entity. So the answer, if we actually did talk about newborn screening, obviously, we'd have to talk about the system and not talk just about the testing process.

DR. McCABE: Any other questions or comments? Thank you very much, Dr. Charache. At this point, we were going to hear from Mary Davidson, co-chair of the Rare Disease Work Group. There were a number of recommendations that had come out of the roundtable discussion in November, and we had asked Ms. Davidson to report on the status of the further development of those recommendations. Unfortunately, Mary is ill with the flu today and can't be with us, so we will not be able to hear that report.

So we will proceed with the next item of business, and one of the important issues that we have discussed in the past is the extent to which laboratories conducting testing for rare diseases, many of which are done in academic institutions as part of a research protocol, will be capable of complying with increased oversight of genetic tests. In our oversight report, for example, we recommended that technical assistance be made available to laboratories performing tests for orphan diseases or mutations to help them meet the CLIA certification requirement. Last August, as part of discussions of the Rare Disease Work Group, we learned that the American College of Medical Genetics was planning to conduct a survey of laboratories to both provide information to them about CLIA regulations and to gather data about their current CLIA certification status. The ACMG and the American Society of Human Genetics jointly sponsored the survey, which has now been completed. Dr. Michael Watson, executive director of the American College of Medical Genetics and co-chair of the Rare Disease Work Group, is going to present those data today and show us the outcome of that survey. Dr. Watson, thank you for being here, and please proceed.

DR. WATSON: This is actually an easy meeting to come to, since I'm across the street. I can

actually give you a really fast update on the Rare Disease Subcommittee. We are still moving forward on the white paper. We had a conference call about a week and a half or so ago, and are moving still towards having drafts available for the Committee at -- is it the May meeting? Yes. At the May meeting.

So now, I'll move into this survey we attempted. I must say that I'm going to correct a few things on some of these slides as I go along because I literally got this data yesterday, and I wasn't home yesterday, so I started to review it this morning and pulled out some sort of key perspectives, I think, from the data, but we'll try to put additional perspectives together and send you something to reflect those.

So we sent this out blindly to the membership of the American Society of Human Genetics and the American College of Medical Genetics on a Web form, which was intended to be an anonymous process, since we were essentially asking people to tell us that, yes, they were violating a Federal regulation and doing testing in what should have been a CLIA-licensed laboratory setting. As it turned out, people interpreted our request in many ways, and as I looked at the responses, it's clear that they're all research laboratories, some CLIA-certified, some not, but rarely do they reflect on classical areas of testing that are well-established in our laboratories. Sort of the three general parameters around which people sort of identified themselves were either as people working in non-genetics or genetics testing laboratories, either CLIA-licensed or not CLIA-licensed, and either physicians or non-physicians directing those laboratories.

Now, we had responses from almost 100 laboratories, and we really looked most closely, at least for what I'm going to show you today, at all the laboratories that were not CLIA-certified, because one of the interests that the College and the Society had was in identifying those laboratories, trying to profile them, and get a sense of what kind of assistance they need to

become compliant or to at least understand that there is something to be compliant with, because it was clear that not everybody even appreciated that there was something to be compliant with.

Among those 99 labs were 35 that were not CLIA-licensed and there were eight additional labs that described themselves as non-genetic testing laboratories and in the low complexity typical area of testing.

Now, I have to figure out how to strip certain information off of the surveys, because even though we had no way of identifying people, it was clear that based on some of the individual tests they did, I knew who they were because they were one of only one or two people, and based on how they said they did the test, I knew exactly who they were. So they would write a little note that said, "I'm not going to tell you who I am, but you can probably guess," and then they'd sign their name. Which was one of the ways by which everyone would figure out who they were if they didn't really know the testing field well. So I'll strip that and make some of their comments available to you later.

So what kinds of tests were being done in these laboratories? It turns out that actually the vast majority of them were doing very complex kinds of testing, which to me is not surprising. When something becomes straightforward, a straightforward hybridization-based assay, the clinical sector moves in pretty rapidly and establishes a test at a fee-for-service level.
So interestingly, there's a lot of sequencing and a lot of scanning methods applied to rare conditions and to common conditions for which the patient had not been identified to have one of those things that are commonly tested for. So scanning for unknown sequence variation was not an uncommon finding. There was an enormous array of tests, some of which clearly would identify somebody because there is only one, but a lot of BRCA, testing for unknown mutations, and things of that kind.

There was also a subset of the tests that were being done that were clearly tests that are going to be very -- that may already be very high volume, but what distinguished them was the fact that they have very rapidly translated from discovery to use, and the research laboratory had established a pretty substantial clinical database on those patients and were in a somewhat stronger position, actually, then would the laboratory that picked it up for service immediately be, and those were areas that were really moving quickly. Now, of those laboratories, of the 35 that weren't CLIA-licensed, 12 of them were doing more than 50 cases per year, and that's about as high as we set our parameter, thinking that once you got to 100 a year, you presumably weren't really a research laboratory. So we knew of 12 doing more than 50, and most thought that providing specifics about their test might reveal them, so we have a lot of blanks within the survey itself.

So focusing on those 35 non-CLIA labs, 16 expressed that they were not knowledgeable of Federal laws that regulated clinical laboratories at all. Interestingly, 19 claimed to be knowledgeable, but were clearly in violation of those Federal laws that they claimed to be knowledgeable of, and went on to express what they felt to be some of the constraints to their getting licenses, and I'll touch on some of those towards the end of this.

We also had this subset of labs that may have had a CLIA license for low complexity, non-genetics areas of testing. Not many of those, and so we profiled them a little bit. Only one of those claimed not to be knowledgeable of Federal laws, and seven claimed to be knowledgeable of the CLIA licensing activities.

So among those same 35 now, 34 did absolutely no billing. They were presumably operating off of their research grants. Of those 34, four thought that if they didn't bill, it actually wasn't clinical testing, it was just research, even though they felt obligated to pass information on to their patients, and several actually commented that their IRBs provided them a mechanism to

get permission from the IRB to communicate that research-based information to their patients. Five of them felt that if their testing was paid for by a grant, it was therefore not clinical. So those are essentially the same kinds of people, but they're independent entities from the way they answered the questions. Forget the two bullets at the bottom. Those are carryovers from the prior slide. So among those eight labs, one didn't bill for testing. The majority of them obviously were billing for their service in a low complexity laboratory setting.

So as we began to look more carefully at those 35 labs that weren't licensed, why weren't they? Clearly, some weren't aware of the need for licensing, but as you look at this, it doesn't exactly match the numbers that said they weren't aware of it, because the vast majority said it was too difficult to get this license that they presumably were unaware of.

Another significant number said that if they didn't provide the testing, then patients would not have access to that service, and most of those people wrote phenomenally extended diatribes of their need to provide this service to people. I mean, they were quite heartfelt that if they didn't do these, that the patients wouldn't have access to them. I actually think that that's clearly true. It is very difficult to move new testing services into the reimbursement area in clinical laboratory settings right now, especially for rare conditions and especially for detection of unknown sequence variation that is complex to interpret and not well understood in the payer community.

This was actually kind of interesting to me. Actually, even among clinical laboratories run by Ph.D.s, they often don't know the extent to which their institutions cover them under their malpractice coverage. I know of a number of places where the day you walk out the door, you're no longer covered, and in genetics, your liability goes far longer than the day you walk out of that institution's door. So that's an issue that is very important, is really what kinds of malpractice covers the laboratories in genetic testing these days, but of these non-CLIA-

licensed laboratories, when we asked them if they were covered under their institution's malpractice coverage, partly in the interest of educating them and making them think about whether or not that's something they ought to be concerned about, five said no, they weren't and understood that they weren't covered under their malpractice coverage. I don't know if they appreciated what that actually meant, which in this world means when somebody makes a laboratory error, you sue everybody, and presumably it's the guy with the most money who is really the target, and most of the lower people get off because they're covered under that larger body. But as it turns out, these people probably aren't covered to any great extent and are at some risk. Eleven actually didn't even know if they were covered or not in their institution's malpractice. Eight of the labs thought that their research labs were covered because they were practicing medicine, and I think that's an important thing to think about. These were all physician-run research laboratories, they considered what they were doing to be important, and they considered that their exemptions from FDA and other regulatory types of oversight was more than adequate to protect them while they were practicing medicine in the best interests of their patients, and I'm not sure that's not entirely true.

Now, some of the comments that came from the laboratories, and these were actually what they were anticipating doing, five of those 35 labs indicated that they were beginning to work with their clinical laboratories. They hadn't worked out everything yet, but they had intentions of establishing a tighter connection with their institutional laboratories. They'll recognize significant trouble in doing that if their laboratory tests were not likely to be profitable in that clinical laboratory setting.

Three labs indicated that they were going to pursue licensing, and a smaller number -- I think two or three – indicated that they would welcome resources that would help them identify laboratories that were CLIA-licensed and were willing to take on research types of tests and move them into a clinical laboratory environment.

So obviously, from the perspective of the College and the Society, I think I actually knew what the answers to much of this would be, having run a lab for a long time and searched for services for difficult-to-find types of tests, but we really wanted to get a sense from the community of what kinds of things we could do to help them become compliant and actually practice better in their laboratories. Eighteen of the non-CLIA laboratories indicated that they needed some guidance with the development of protocol books. That's out of 34 total from all those 99 that we got. So most of the assistance is clearly in these non-licensed laboratories where they need help with just developing the basic protocol book. Nineteen thought they could use guidance to develop their quality assurance programs to ensure that their testing is done accurately. Eleven wanted help finding clinical labs that would be willing to take on their new tests, and a dozen thought that workshops at various meeting types of settings would be a useful mechanism for them to better understand what are the issues that a clinical laboratory brings to testing that may not be apparent to a research laboratory.

So as I pondered all this stuff -- that's actually the last slide going over the data, of which there obviously isn't a great deal -- I don't know that I learned a lot, but I think it confirmed a lot of what I suspected. I think clearly we're in an area where we're moving from little or no regulation to minimal regulation, and I don't know that that is going to have a significant level of control over laboratories that are operating at any level within the system. As we think about some of the issues of really what sorts of things are needed, I think it seems clear, at least from having sat through the nature of the responses we're getting from HHS, that there isn't going to be a lot of government control and I don't see a reflection of much interest in genetic testing at this point. That may change as there becomes an industry with a large financial base, as has been expressed by some of the consultants this afternoon, but I think at the rate we're going, that's going to come after the problem hits, and our interest right now is to avoid the problem. So we're actually focusing on a few areas where we think we can make the most difference, given that regulation is unlikely to be it in the short term.

I think the College is truly focusing in on infrastructure, looking at how we can build networks of providers. We're looking at whether or not we can get much more active in developing guidance documents that target all areas of the system, from the primary care provider to the specialist, to help them understand who to work with and how to work through specific genetic conditions in a triage type of perspective. Then we're looking a lot more carefully at information, and clearly I think that's been reflected from the consultants, is the need to bring our information technology to bear on the problems to, at the very least, make the best, most accurate information available on a curated basis, so at least we have places where people can keep up with what's going on if regulation isn't going to rein a lot of the laboratory activities in. We clearly make a difference by focusing the provision of information to help people do the best job they can. That may sound a bit pessimistic and cynical, but I tend to think of where I can focus efforts to make a positive difference in areas where we actually have an impact, and regulation tends not to be one of the places where we have an impact. Thank you.

DR. McCABE: Thank you, Mike. We'll now open this topic for discussion, and we can range more broadly than just Mike's presentation to the Rare Disease Work Group. If you'd join us at the table, Mike, please.

DR. WATSON: Sure.

DR. McCABE: But also I'd like people to think about next steps for the Rare Disease Work Group.

DR. BOUGHMAN: Since I had the privilege from the American Society of Human Genetics' point of view of being a part of this, I also got the volumes of data back. Mike did a very nice job of pulling the numbers together, but if you realize the genesis of some of the questions and the discussions that we have had here, I found a few of the comments that came back from

these laboratories as certainly confirming some of the ideas that were floated by the people around this table. But I came away from this actually not maybe even impressed -- at least, I was not unimpressed -- that with an e-mail to our membership, we did get 99 responses from laboratories willing to try to fill out a survey that was trying to accomplish several different tasks at the same time, and I think there would be a willingness out there if we could get some more focused questions that we wanted information back on that would be useful to this Committee in its deliberations. I think that we learned that we would get some reasonable response.

A couple of the comments that I would like to share, at least in part, one from a CLIA-licensed laboratory that made a comment about the laboratory inspectors from CLIA and the challenge in and the gaps between the way the CLIA inspectors and the things that they were looking for and the issues that geneticists felt were most important in the laboratory and the disconnect between those, and we've talked about that around this table before, but that in fact was one of the responses. Another one was about a situation that we have talked about here as well, where all positive results are confirmed in a CLIA-certified lab, all negative results are provided as uninformative unless a known mutation has been detected in that family, and in that situation the negatives could be confirmed in a CLIA-approved laboratory and then shared with the patients.

Cost, of course, was a real issue, and we had some pretty articulate comments about feeling obliged to do these tests and provide, in these very rare disorders, results to the patients, but in fact if it's a research lab focused on one and only one disease, that those were real challenges. Lots of different ways of saying that.

But one of the other comments that I would like to share came up more than once, and that actually will lead into some of the IRB and informed consent discussions for tomorrow, where

several of the labs say there has been increasingly detailed oversight by IRBs and that in fact it is through the increased oversight by IRB that the laboratory is understanding the need to move to CLIA certification and the use of that test as a clinical test. Another one said we're performing research, not offering a test, but since we need physician collaborators and they want the results, they get them and then pass them on to the patients. This group has in fact had discussions with their attorneys and the IRB, and they have developed a consent document that tries to get at the major issue here, but still are seeing the gap between those stages that we in fact had identified before.

So in summary, I would just say that I thought the numbers were useful, but in fact in reading through some of these comments, I felt that the discussions that we've had over the last several months in fact do reflect the reality and the challenges that our colleagues out there are feeling in the need to move this research into application as quickly as possible.

DR. McCABE: Joann, do you and Mike have any feel for the denominator here? I'm sure it went out to the membership of both groups, which is overlapping, and many of whom are clinical geneticists or researchers not doing human-related research. So is there any guesstimate of the denominator?

DR. WATSON: I would actually think that the Society's denominator is closer than the College. I mean, you can probably subtract the College's numbers from the Society and have a closer number, because most of our members are board-certified laboratory directors, and therefore are operating in a CLIA environment. We do have clinicians who operate in a research laboratory environment, and I could identify them pretty clearly from one of the categories that we asked them to identify themselves by. I actually think that from my academic experience of 20 years, I think the reality is that, certainly in the major academic medical centers I've been in, everybody is a geneticist. I mean, molecular biology is the tool in

medical centers and I would guess that, at least from my own experience, there's far more of this that goes on outside of people that associate themselves with the genetics community. So I'm not sure how much more we might learn. I'm not surprised what we learned from the genetics community, which is that it's largely very rare tests that aren't available in a clinical laboratory setting that we're dealing with. I think it's probably a very different scenario in other specialties and other areas of academic medicine that don't traditionally associate themselves with the genetics organizations.

MS. YOST: Can you give us an idea of what the response rate was?

DR. WATSON: The Society has 5,600 members, I believe. Eight-thousand? Ten? Eight-thousand? Subtract our 1,000 and --

MS. YOST: I'm just trying to get an idea of what the response rate was.

DR. WATSON: Low.

MS. YOST: The other question that comes along with that is do you feel or do you have any idea whether the proportions are also representative, where you have 99 laboratories responding and, of those, 35 are non-CLIA. Do you think that's representative or do you think that maybe you just kind of got --

DR. WATSON: We had a significant percentage of people who said that they were afraid to respond because it would reveal them.

DR. BOUGHMAN: I think we missed on both ends of that category. I think there would be many laboratories that are comprehensive laboratories that would fall under Mike's definition

with the large laboratory that does a lot of genetic testing and they didn't see the relevance of this survey itself, and there were those that recognized that their research in one disorder or a subset of mutations in that one disorder would identify them, reveal them, but I don't know whether that's 10 or 100 others. I'm not sure that this is 100 out of 5,000 potential responses of the group we were trying to get at. I would say it would be a few hundred, so that our response rate was not outrageously low, given that it was a one-shot e-mail, then with a click onto the Website, and answer the questionnaire.

DR. WATSON: I agree. I'd be surprised if you could double the College's numbers for those who are really only research-oriented because clearly population-type people who are a large contingent within the Society are not involved in this sort of laboratory testing.

DR. McCABE: Another way you could estimate the denominator would be to look at GeneTests, and we saw that number earlier.

DR. BOUGHMAN: Right.

DR. McCABE: It's in the 800, 900 range, and then recognize what has been stated, and I think is true, and that is that neurologists, non-geneticist neurologists, non-geneticist other subspecialists are doing some of those tests. So you could probably estimate in the 350 to 500 range would be very possible.

DR. WATSON: I know in the course of recently drafting a guideline on the genetics evaluation of hearing loss, we went back through GeneTests and looked at all the genetic testing laboratories for hearing loss genes, and a significant proportion of them called themselves research labs, but are not. I mean, they are doing a clinical test, and even though they call themselves research and may be operating under a grant, I think that's one of the idiosyncrasies

of GeneTests.

MS. YOST: My guess is just about all of them are real clinical labs.

DR. WATSON: Yes.

MS. YOST: My concern is that a lot of the difficulty that these folks have in understanding that they need to be enrolled and compliant with the CLIA requirements is perception, and I guess I would be very, very interested in having, without identifiers or any of -- you know, I don't have a clue who does what test, but I am interested in the comments that you received, the specific comments, to help us get past those perceptions and that anxiety level, because my idea is that if we could provide some of these things that these folks said they would like to have as far as technical assistance with no penalty attached, could we get them to come out of the woodwork? Because the goal here is the quality testing, not to create an additional burden or cost to these facilities, and so we need to find some innovative approaches to reach them and to get past that anxiety level, because that's what keeps them away from even exploring the concepts. So many of the things that they use in their research to validate their tests can be used to meet CLIA, and if people can really realize that and understand that it's not as complex as it sounds on the surface -- just because you have 100 pages of regulation doesn't mean it's going to cost $8 million and take you 20 years to meet the requirements. It doesn't. We have living proof of that, and so I guess we need to get past that to try and get to these folks in some easy way with no strings.

DR. BOUGHMAN: I would think, certainly from the American Society of Human Genetics' point of view and the responses that we got, we have enough interest out there to move forward in at least some sort of workshop format or whatever, and would start addressing these issues. Before we had even this amount of information, I wasn't sure if we threw the party whether

anybody would come, but I believe that there are people out there who would be interested in assistance and some guidance in getting from where they are now to being CLIA-approved.

DR. McCABE: Go ahead, Mike.

DR. WATSON: I do think there's a flip side to that, though, which is something I still don't myself understand, and that is where is CLIA willing to make allowances for a laboratory that doesn't meet the clinical laboratory standards? I know a lot of places in CLIA where it would scare the living daylights out of me to cut corners and there are places where I think one might be able to cut corners to make them make it easier to get a CLIA license, and there are certain kinds of testing I think for which that might be true, though I wouldn't want to see a lab doing 1,000 tests a year in a research laboratory setting. So I think if we work together we can probably figure out what it is we're going to educate people about.

MS. YOST: You do it by priority. You do what's most important to meet, and you work it through in a sequence. I mean, that's the whole way we implemented the program. Number 1, everything is educational. It's not punitive. Secondly, you focus on the personnel doing the testing, because that's really the important thing. If they have the appropriate training, you're halfway there, and then the other is the quality control. Once they understand those concepts, then you can go into more complex types of things, but I think if you can get those two concepts across -- and they're pretty straightforward because everybody I think has good intentions of providing good quality testing. Maybe they just don't always realize what's necessary to get from Point A to Point B, but it's not as complex.

DR. McCABE: That would seem like something that could be one of the things we could ask the Rare Disease Work Group to look at, would be to work with Ms. Yost and look at how we might develop implementation strategies, educational strategies, as well as prioritization. The

other thing that I might ask you to do, Judy, along with that is to look at the states that have requirements that are over and above CLIA.

MS. YOST: Right.

DR. McCABE: Because, for example, I live in one such state, and I'm required to be CLIA-approved in my state. I'm required to have a medical technician who would be in my lab, and the people who have done that by and large have medical technicians who come into the lab and serve as lab managers, just so there's a body in the laboratory with that status, but in fact they are not prepared. They haven't been trained to carry out the testing and they're at a much higher salary than the people who actually do the testing. So it's also important to look at individual states and what the requirements are, because they can be a barrier to implementation as well, the state rules that may not make a whole lot of sense.

MS. YOST: I don't have any authority over state rules.

DR. McCABE: No, I know, but it would be nice to --

MS. YOST: But I have a duty to consider that.

DR. McCABE: -- know which states have additional requirements because we would need to --

MS. YOST: I think we're talking two.

DR. McCABE: New York and California? Okay.

DR. WATSON: And as Pat Charache said, there's also a bottom which has to be set, and I'm

not sure it's set right yet.

MS. YOST: No, definitely not, but it's a moving target. There's no question. But I mean, if we stay away from the paper requirements and talk about things that are practical in the assurance of quality and looking at the whole system, as opposed to just individual standards, I think you can really reach people and they can really understand more clearly what they have to do to meet CLIA.

DR. McCABE: Let me recognize Elizabeth Thomson. I think this is the first time you've sat on the Committee representing the National Human Genome Research Institute and NIH, and for anyone who doesn't know Elizabeth, she is director of the ELSI Program in NHGRI.

MS. THOMSON: Well, I was going to say Sarah invited me to the table, but I am no Dr. Collins. But I do actually have a couple of comments on this whole CLIA issue, and I've known and worked with Judy for a good part of 10 years on this issue, and I would hope that the College and the Society would really come up with a plan to bring the labs into compliance. We've worked together on our cancer genetic testing labs and also in getting our NIH research labs, some of which weren't, early on, certified by CLIA, and you have to get your investigators over being afraid of worries about punitive actions, and to this point, I have seen none. I mean, I was stunned to learn that there are about 200,000 labs in the United States, and so our group of 30 or 100 labs that need attention is nothing compared to what they have to work with.

The other thing that stunned me when I first learned about CLIA is low volume testing labs are those that do under 2,000 lab tests, and some of our labs are doing 10 or 20. So I would think doing education and really setting the expectation that over the next several years they should plan to come into compliance.

DR. McCABE: And I think we heard at the last meeting about the opportunity to partner, which is another way of doing this, and a way that Pat Charache has talked about in the Hopkins model. We certainly heard about that from the University of Chicago model as well last time.

MS. YOST: I think that's absolutely critical in this case, particularly where you have this type of environment where there is some anxiety about the whole thing. Where you're working with peers, you're much more comfortable, and we're very comfortable with setting up some sort of formal or informal partnership to accomplish that. Again, that's not a problem. We do it in cytology now for the same reason.

DR. McCABE: Right.

DR. KOENIG: I just have a brief follow-up on the IRB issue for both Mike and for Joann, and in Mike's presentation, I seemed to get the impression that you were saying that in some cases these labs felt that their IRBs were telling them that they must disclose results, and then you read comments that were on the other side, and I just want to get more of a sense of what kinds of issues you think the IRB/Informed Consent Group needs to address in the future and what light this sheds on our work.

DR. WATSON: It covered the full gamut. I mean, there were a number of laboratories that said they just won't let me give information out, and there were I'd say a minority that expressed this opinion from their IRB that for certain results they had to give them out and that they could find a mechanism to work with them to do that.

DR. BURKE: I wanted to say that I thought the data that you presented was amazingly interesting and the process interesting, and that although it would be very interesting to have

numerators and denominators, I'm not sure that's the most important thing, and I'm in part just following up on Joann's comments. I really favor a workshop that promotes the educational process and helps people to understand, but I would push for an iterative approach that starts basically with a qualitative research model. That is, I think it's really important to create the relationship, whether it's by e-mail or convening a workshop or interviewing people or some combination, that allows for a very detailed debriefing of what is in their mind when they're feeling that they can't be CLIA-certified, and to what extent are they aware, for example, of state regulations that they think bar them that are separate from CLIA, to what extent they may have misapprehensions about punitive issues, or, and this is the qualitative model, to what extent there may be other rationales that didn't emerge in your comments that may be in people's thinking. I think this is a golden opportunity to figure out what are the barriers, both perceived and real, before figuring out what kind of educational model or workshop model is going to help bring people into the fold.

DR. WATSON: Yes, I agree. I mean, clearly, as a non-regulatory body, our interest was in trying to find out what mechanisms of education and training would help people better comply.

DR. CHARACHE: I think we agree that the approach that's required here is education and that one of the challenges is to find out who we need to educate. I'd like to put on the table that to me the key group that needs education is the IRB, because the first thing we learned when Hopkins wanted to look into this was that our IRB had no idea that when you returned a result to a patient or his family or healthcare provider, it meant patient care, and we after two years of -- well, eventually Hopkins makes the right decision. We now have a check box on our applications for review which asks if you're going to return results and, if so, if you're a CLIA-approved lab or not. So we were able to capture the group that needed to be educated. I don't know who should do this, but it seems to me it would be very helpful to send a questionnaire to the IRBs of the major academic institutions and ask them if they have laboratories doing

genetic testing who return information for patient care purposes. They always say that they do when they do, and then ask them how many of them are CLIA-approved. I think we have to teach the IRBs that this is necessary, but do it with an educational approach to the questionnaire, so that we are not doing it in a punitive or restrictive manner.

DR. McCABE: One of the other things I think will be very educational to both the IRBs and the research community, and perhaps, Elizabeth, you could clarify this, but I have heard that NIH has a rule that is being opposed now that if you are doing any testing, any patient testing, under an NIH grant, you're not permitted to return the results back to the patient if you're not in a CLIA-approved laboratory. I haven't seen the rule, but it certainly has achieved the status of urban myth in the research community.

DR. McCABE: If there is any basis to this, that will be a rapid education of both the investigators and the IRBs.

MS. THOMSON: I don't know if it's become a rule, but certainly if it got in my hands, I would -- I mean, some program people do understand about CLIA and will insist that extramural labs have CLIA approval, but I don't think it's a written rule.

DR. WATSON: I don't either. I know that the Task Force made -- that was one of its very specific recommendations, that NIH have a box with all your other compliances that required a lab to say whether they had that certification or not, but I don't think it is.

MS. THOMSON: One more follow-up comment to this whole issue, and that is, I mean, I've actually gotten calls from young Ph.D.s whose IRBs insist that they give back results, and the fellows who call me, they're like, "I don't want to give back. I'm not a doctor. I'm not doing clinical care," and their IRB is insisting that they do so, and I just explain to him and ask him if

he has a CLIA certification, and he says no, and I then just tell him to tell his IRB he can't and if they have any questions, they should call.

DR. GREENE: This is an issue that was also taken up by NBAC in their human biologic materials report and addressed by HHS in their response to NBAC's report, and I'm not sure if it's being addressed by the NHRPAC, but it seems like it might be something that could be. You know, any survey of IRBs might be something jointly undertaken with that body.

DR. McCABE: That's a very good idea. Also, it might be something for the IRB Work Group to work with the Rare Disease Work Group to take this on.

DR. KOENIG: This is definitely an issue that's very high on our radar screen as we move away from thinking about informed consent in the clinical context to the transition. So, absolutely. This is really critical.

DR. McCABE: And I'll take this opportunity to also mention that with Barbara leaving SACGT, as was recognized this morning, we've asked Victor to take on the responsibility of co-chair for that subcommittee or work group, but we're very pleased that Barbara's going to continue working on the group as well.

MS. CARR: Also, one of the other members of the work group is Barbara Handelin, who's affiliated or on the board of PRIM&R, and PRIM&R and ARENA are associated, and perhaps we could ask Barbara if she would relay some questions for the board to consider asking the IRB community. I mean, that might be the most effective way, because NHRPAC, like this Committee, will have trouble asking more than nine people any questions.

MS. THOMSON: Actually, Sarah, I'm not sure a survey is needed. I think we know that the

IRBs are inconsistent and, sure, you can get the data if you want. I wonder if it wouldn't be better to just see if you can get a place on the agenda.

DR. McCABE: But the issue might be, you know, through what was attempted with ASHG/ACMG, was to educate through the medium of a survey, and that might be a possibility with IRBs as well.

DR. GREENE: I think education through a survey obviously can be very effective, but I neglected to point out that another reason for working closely with NHRPAC is this is not an issue that's isolated for genetics. That's part of the reason NBAC took it up. It has everything to do with finding an antibody against hepatitis C and are you at risk for liver disease. So I think we wouldn't want to engage in genetic exceptionalism too much.

DR. KOENIG: Just to second that, for example, basic research using neuroimaging that finds results -- I mean, this is a ubiquitous research problem, research ethics problem.

DR. McCABE: Again, I've said this many times before, we're charged with focusing on genetics, so we don't intend to be genetics exceptionalists. It's just that's what our mission is, is to focus on genetics, and if we can help lead the way in other areas of medicine, so be it.

DR. CHARACHE: Just two thoughts. First, I want to reemphasize that I look upon this survey in terms of the exact questions that are asked as being critical, because it shouldn't be a threatening thing to receive. It should be an educational one with an outflow track for getting further information. Secondly, I think it's important to emphasize not only that the questionnaire did not address groups like -- I mean, we have people in ophthalmology and psychiatry, as well as neurology and so on. So we have a big population out there that we have to reach, and I think this is one reason for considering the IRB approach. But we also have the

whole tumor-associated acquired mutations, per the charge to this Committee, so I think it really is a fairly broad issue that would have to be defined.

DR. McCABE: Yes. One mechanism that works very well in this sort of situation is to declare an amnesty. So to formally declare that one is not being punitive, but then putting an end date on that, so that at the termination of that period of time, then there will be consequences, and that period should be a period of years probably to roll out the education. But I have seen this work in other issues where there was concern about punitive response. Other questions or comments?

DR. McCABE: So we've given the Rare Disease Work Group some additional work, but perhaps in collaboration with the IRB Work Group, and we'll look forward to a report at the May meeting. If there are no other comments at this time, we're going to recess until 8:30 tomorrow morning. I want to remind everyone that we will be in the Congressional Ballroom tomorrow. So a different room, and it's all the way down the other end of the building. It's where we met the last time.

The other thing is that Barbara Koenig has asked that I remind all of you that tomorrow we're going to have to come to some consensus on the informed consent report, and it's very important, therefore, that you review that, at least the recommendations that are at the end of the report. Those are on pages 28 to 31 under Tab 6. So please review that.

Then to remind the members of the Committee that we will be meeting in the hotel lobby at 6:50 tonight for those of you who are joining us for dinner. Thank you very much, and we're in recess until 8:30. We're starting a half hour earlier tomorrow than we did today, 8:30 tomorrow morning.

(Whereupon, at 5:27 p.m., the meeting was recessed, to reconvene at 8:30 a.m. on Thursday,

February 14, 2002.)